WEAVE SPRINT . PAPER IV

The dementias

Every dementia a psychiatrist must recognise and tell apart: Alzheimer's disease from its genetics to the anti-amyloid antibodies, the Lewy-body disorders with their dangerous neuroleptic sensitivity, the vascular and frontotemporal syndromes, the treatable causes that reward a systematic workup, and the depressive pseudodementia that mimics them all; then the assessment from bedside cognition to the fluid biomarkers, and the pharmacology of cognition and of the behavioural symptoms, with the antipsychotic mortality risk weighed before it is ever prescribed.

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Concept / rule Key number Trap

PAPER IV

Dementias and neurocognitive disorders

Three bands . one complete notes document

The major dementias, from Alzheimer's to the frontotemporal syndromes

1 · Dementia for the psychiatrist: what this chapter owns, and what it points to

The marks are earned by organising uncertainty, not by unloading a catalogue of causes. Cognitive decline reaches psychiatry through many doors: forgetfulness, altered judgement, language difficulty, behavioural change, loss of occupational competence, caregiver distress, an abnormal investigation, or a crisis of safety. These presentations do not arrive already sorted into syndrome, cause and consequence. The clinician must construct that order.

The organising task is to keep several questions separate while allowing their answers to inform each other. Is there convincing change from the person's previous level? What kind of cognitive and behavioural pattern is present? How has it unfolded? What has happened to everyday function? Which process best explains the pattern, and what else may be amplifying it? What evidence would alter confidence? What action is required now? The chapter's **diagnostic architecture** is built around these questions. Disease-specific sections supply the criteria, investigations and treatments; this orientation supplies the map into which those details belong.

1.1 Begin with levels of statement

A cognitive complaint, a demonstrated cognitive syndrome and an etiological diagnosis are not interchangeable statements. A complaint describes an experience or observation. A syndrome statement integrates evidence of change, the affected domains, behaviour and functional effect. An etiological statement proposes the disease process or combination of processes responsible. A safe answer makes clear which level is established, which is inferred and which remains uncertain.

This separation matters because the evidence needed at each level differs. A patient may report severe difficulty without showing the expected pattern on assessment. Another patient may deny change despite persuasive collateral evidence and altered performance. A striking investigation may support a proposed pathology but cannot, by itself, describe the person's functional state. Conversely, a convincing syndrome does not automatically identify its biological cause. The formal definitions and classification of neurocognitive disorders are taught in their dedicated section; here the essential orientation is that labels must not outrun evidence.

Complaint	Syndrome	Phenotype	Cause
THE ENTRY	THE LEVEL	THE PATTERN	THE INFERENCE

The idea of **syndrome level** protects both examination writing and practice. It prevents a symptom such as forgetting names from being treated as a disorder, and it prevents a broad term such as dementia from being offered when the question asks for a cause. It also allows

proportionate uncertainty. The clinician can be confident that meaningful decline is present while remaining appropriately cautious about its exact origin. That is not diagnostic weakness. It is accurate calibration.

RULE **State complaint, syndrome, phenotype and cause at the level the evidence can support.** Each is a different claim. Strong reasoning links them explicitly instead of collapsing them into a premature label.

1.2 Read every case through intersecting axes

A long differential becomes manageable when the presentation is placed on a small set of clinical axes. Baseline asks what the person could previously do. Pattern asks which cognitive, behavioural and neurological functions have changed together. Course asks how the change emerged and evolved. Function asks what the person can still manage independently and what others have quietly taken over. Context asks which medical, psychiatric, medication-related, sensory and social factors distort performance. Safety asks what may cause harm before diagnostic certainty is complete.

The **cognitive phenotype** is the recognisable configuration produced by relative deficits, preserved capacities, associated behaviour and neurological signs. It is more informative than the statement that cognition is "poor." The detailed profiles of the major dementia syndromes belong in their disease sections. At the orientation level, remember that similar overall impairment can arise from different patterns, and similar complaints can reflect different mechanisms. Phenotype guides the differential; it does not replace etiological proof.

CLINICAL AXIS	ORIENTING QUESTION	WHAT IT PREVENTS	WHERE DEPTH FOLLOWS
Baseline	What has changed from the person's established abilities?	Equating low performance with acquired decline	Clinical approach and young-onset presentations
Pattern	Which cognitive, behavioural and neurological features travel together?	Assuming every dementia is primarily amnestic	Major disease-family sections
Course	How did the change begin, fluctuate and progress?	Ignoring urgency or superimposed illness	Treatable and rapidly evolving presentations
Function	Which real-world tasks have changed, and why?	Letting a test score substitute for daily-life evidence	Definitions, assessment and care planning
Context	What could mimic, worsen or conceal the syndrome?	False either-or thinking about psychiatric and neurological causes	Systematic workup and differential diagnosis
Evidence	Which findings support, weaken or redirect the formulation?	Allowing a scan or biomarker to become the diagnosis	Assessment, imaging and fluid biomarkers
Safety	What requires action even while uncertainty remains?	Postponing care until every label is settled	Behavioural management, caregiver support and future care

Tempo deserves special attention because it changes the meaning of the same symptom. A chronic progressive narrative, a fluctuating presentation, a stepwise course and a rapidly evolving decline open different diagnostic routes. The dedicated sections teach those routes in full. This orientation uses tempo only as a sorting axis: establish it from dated examples and collateral history, then ask whether the proposed disease process genuinely fits it.

1.3 See the chapter as a sequence of decisions

The chapter is easiest to retain when its sections are read as answers to successive clinical decisions. The definitional framework determines what kind of syndrome is being described. The clinical approach establishes how history, collateral information, examination and investigations are assembled. The major disease-family sections then show how distinct phenotypes, pathologies and management questions modify that common approach. The treatable, rapidly evolving and borderline presentations guard against premature closure. Assessment and biomarker sections show how evidence is strengthened. Pharmacological and psychosocial sections translate diagnosis into care.

CHAPTER TERRITORY	QUESTION IT ANSWERS	HOW TO USE IT
Conceptual framework	What counts as a neurocognitive syndrome, and how is severity expressed?	Use it to frame the opening of an answer
Clinical approach	How is change established and patterned?	Use it to structure history, collateral evidence and examination
Major disease families	Which phenotype and pathology best explain the presentation?	Use disease-specific criteria only after the syndrome is clear
Treatable and rapid presentations	What must not be missed or dismissed as inevitable degeneration?	Use tempo and context to determine urgency
Assessment and biomarkers	What evidence can support or challenge the working formulation?	Order and interpret tests as answers to clinical questions
Treatment and care	What should change for the patient and caregiver?	Link each intervention to a target and monitoring plan
Application	Can the knowledge survive a vignette, viva or long answer?	Return to the same reasoning sequence under pressure

This structure prevents fragmented recall: an unranked list of diseases, tests and drugs, or detailed disease knowledge without a decision about what the current case requires. Reading the chapter as a pathway turns stored facts into clinical action. It also prevents overreach. A biomarker section does not make biomarkers the starting point, and a medication section does not make prescribing the whole of care.

GOOD TO REMEMBER

Before revising a disease section, write the question that section answers. After revising it, state what evidence would make you choose that diagnosis over its nearest competitors and what finding would make you reopen the case. This converts descriptive knowledge into usable discrimination without forcing false certainty.

1.4 Keep causes, contributors and neighbours distinct

Cognitive impairment rarely respects the boundaries of a textbook. A patient may have a primary neurodegenerative or vascular process, a psychiatric state that worsens performance, medical illness that reduces reserve, medication effects, sensory barriers and a caregiving environment that magnifies disability. A coherent formulation separates the process thought to generate the syndrome from factors that contribute to its expression. It also remains open to **mixed causation** when independent evidence supports multiple meaningful processes.

Neighbouring disciplines need clean boundaries. Delirium and the broader post-stroke cognitive spectrum are taught in the Stroke, TBI, delirium and focal brain syndromes notes. Endocrine, metabolic and nutritional diseases are taught in the Endocrine and metabolic psychiatry notes. Movement-disorder neuropsychiatry, inherited neurological disease and autoimmune

encephalitis are taught in the Neuropsychiatry of systemic and neurological disease notes. This chapter returns to them only through the dementia lens: when they mimic, contribute to, coexist with or alter the assessment of a cognitive syndrome.

The same principle applies to developmental baseline. Intellectual disability as a developmental condition belongs in the Intellectual disability and autism spectrum disorder notes. A dementia chapter asks a different question: whether there has been acquired decline from that individual's own established level. Low baseline performance and acquired deterioration must not be treated as synonyms. The quality of the longitudinal account becomes especially important when conventional test assumptions fit poorly.

TRAP **Do not write a miscellaneous "reversible causes" list and assume the differential is complete.** A contributor may worsen a dementia without causing it, a treatable disorder may coexist with degeneration, and an apparently familiar dementia label may conceal an urgent superimposed process.

A useful causal statement therefore has layers. It names the leading disease process only when justified, identifies active contributors, acknowledges plausible alternatives, and states what evidence would separate them. The aim is not to place every abnormality into the causal chain. It is to explain the observed pattern with the least distortion while preserving clinically important uncertainty.

1.5 Build evidence by convergence

No isolated source of evidence has universal priority. The patient's account shows subjective experience, goals and fears. Collateral history shows change, compensation and risk in ordinary life. Mental state examination identifies psychiatric phenomena that may affect presentation. Cognitive examination samples domains and error types. Neurological examination identifies associated signs. Laboratory studies investigate selected contributors. Imaging and fluid biomarkers may support or challenge a proposed biological process. Their value comes from convergence around a coherent clinical question.

General administration and scoring of cognitive instruments belong in the Psychometry, Assessment and Descriptive Psychopathology notes. The physics of imaging modalities belongs in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. The cerebrospinal-fluid examination procedure belongs in the Neurology foundations for psychiatrists notes. Within this chapter, these tools are considered for their dementia-specific role: what they add to phenotype, differential diagnosis, etiological confidence, treatment selection or follow-up.

Diagnostic discordance is not an inconvenience to be edited out. A history may suggest decline while brief testing appears reassuring. Cognitive performance may appear poor while function and trajectory remain inconsistent with the proposed syndrome. Imaging may show abnormalities that do not match the clinical pattern. A biomarker may increase confidence in a pathology without explaining the whole presentation. Discordance should trigger review of

baseline, language, education, sensory function, effort, context, timing, comorbidity and the possibility of multiple processes.

PITFALL

A referral label can become invisible evidence. Once the notes say “dementia,” every repeated question is read as confirmation and every inconsistency as denial. Reconstruct the history from examples, establish the trajectory independently, and ask what observation would make the inherited label less likely.

Evidence must be interpreted in relation to purpose. Screening, etiological support and monitoring ask different questions. A result can be technically valid yet clinically misapplied. The orienting habit is to state the question before choosing the evidence.

1.6 Place function, safety and caregiving beside cognition

Neurocognitive disorders are lived in households, workplaces and communities, not only in testing rooms. Functional inquiry should therefore move beyond a generic statement that activities are impaired. Ask what changed, whether the task was previously familiar, which cognitive difficulty disrupts it, what physical or social barriers contribute, and who now compensates. Family assistance may preserve outward performance while concealing the extent of support required. Equally, inability caused by physical illness, poverty, restricted opportunity or unfamiliarity should not be mislabelled as cognitive loss.

The **care ecology** includes the patient, caregiver, household, available services, finances, language, transport and the practical distribution of responsibility. It shapes what can be assessed, what can be implemented and what risk can be contained. Caregiver distress is not merely an outcome measure. It may signal unsafe supervision, misunderstanding of behaviour, conflict, sleep loss, financial strain or a plan that has become impossible to sustain. The dedicated caregiving and end-of-life section develops this territory in full.

IN INDIA

Assessment should fit the person's language, literacy, educational opportunity, occupation and household role. Family involvement can provide rich longitudinal evidence and practical support, but “the family will manage” is not a care plan. Clarify who will supervise medication, money, travel, meals and appointments; what happens when that person is unavailable; and whether access, cost or distance makes the proposed investigation or follow-up unrealistic.

Safety reasoning runs alongside diagnosis. The relevant domains include medication errors, financial vulnerability, getting lost, unsafe use of transport or appliances, falls, self-neglect, aggression, exploitation and caregiver collapse. The purpose is not to strip autonomy when risk appears. It is to understand the specific hazard, the person's decision-making ability for the relevant choice, available supports and the least restrictive workable response. Legal particulars should be checked against current applicable law rather than recalled from general textbook memory.

1.7 Let formulation drive treatment

Treatment becomes coherent when it follows the formulation. Begin with **LOCUS**: decide whether the current combination of medical stability, behavioural disturbance, diagnostic urgency, supervision and risk can be managed in the usual setting or needs a more supported setting. Then define **FOCUS**: the immediate symptom, risk, contributor or functional problem that treatment is meant to change, followed by the broader goals of preserving ability, reducing distress, supporting the caregiver and planning ahead. Finally choose **MODUS**: pharmacological, psychological, behavioural, environmental, rehabilitative, social, procedural and palliative approaches as appropriate.

The pharmacological sections teach cognitive enhancers, behavioural prescribing and disease-modifying therapy with their dementia-specific indications and safeguards. General antipsychotic pharmacology belongs in the Schizophrenia: management, antipsychotics and adverse effects notes. This separation matters because a drug cannot be transferred from another indication by familiarity alone. In a dementia answer, every prescription needs a target, an expected form of benefit, a harm-monitoring plan and a reason to continue, modify or stop.

Non-pharmacological care is not an appendix added after medicines. Communication, environmental adaptation, meaningful activity, sensory correction, sleep routine, caregiver education, behavioural analysis, rehabilitation and practical support may determine whether a plan succeeds. Use the same logic as for medication: identify the target, choose a feasible intervention and review the outcome.

- Link each intervention to a stated clinical or functional target rather than to the diagnosis in the abstract.
- Separate treatment of the underlying disease process from treatment of contributors, complications and caregiver strain.
- Make feasibility part of efficacy by considering supervision, cost, travel, language and follow-up capacity.
- Review benefit and harm in terms meaningful to the patient and caregiver, not only through a test score.
- Revise the plan when function, behaviour, medical state, support or goals change.

Current disease-specific guidance should be consulted in the relevant management sections rather than reconstructed from memory. An orientation cannot safely substitute for formal eligibility criteria, dosing, monitoring schedules or statutory requirements. Its task is to show where those particulars belong and how they serve a wider clinical plan.

1.8 Use the master map under examination pressure

When the vignette becomes crowded, frame it before you solve it. The mnemonic below is not a diagnostic criterion and does not replace disease-specific knowledge. It is a retrieval scaffold that preserves the order of reasoning. Each element points to material developed elsewhere in the

chapter, allowing the candidate to retrieve detail without turning the answer into an unstructured list.

MNEMONIC

FRAME

Function and former baseline: establish meaningful change in real life. **R**ate and route: describe onset, tempo and trajectory. **A**ffected pattern: identify the cognitive, behavioural and neurological phenotype. **M**imics, modifiers and mixtures: separate cause from contributors and neighbours. **E**vidence and evolving care: integrate collateral history, examination and targeted tests, then connect formulation to LOCUS, FOCUS, MODUS and longitudinal review.

In a long answer, open by stating the clinical construct in plain professional language. Classify only to the degree required, then move through presentation, course, functional change, associated features, examination, targeted investigations, differential diagnosis and management. In a vignette, begin with the most discriminating evidence rather than repeating every fact in the stem. In a viva, make uncertainty audible: state the leading formulation, the evidence supporting it, the strongest alternative and what would resolve the difference.

The chapter should leave the reader with a **longitudinal formulation**, not a static label. Diagnosis may become more or less secure as trajectory, function, examination, treatment response and biomarkers accumulate. Care goals also change. The clinician's responsibility is to revise openly without losing continuity: retain what remains supported, discard what no longer fits, and explain the practical consequence of the revision to the patient and caregiver.

The boundary map remains important during revision. General psychometry, imaging physics, cerebrospinal-fluid procedure, antipsychotic pharmacology, intellectual disability, delirium, systemic and neurological neuropsychiatry, and endocrine or metabolic disease retain their own chapter homes. Cross-reference them when needed, but keep the dementia answer centred on acquired cognitive decline, its phenotype, cause, functional consequences and care.

Frame every case by former function, rate of change, affected pattern, mimics and modifiers, converging evidence, and the care consequences of the formulation.

2 · Dementia: definition, classification and the neurocognitive-disorder framework

The diagnostic centre of gravity is decline plus disability. Dementia is not simply poor memory, a low cognitive-screen score, or any cognitive complaint in later life. It is an acquired syndrome in which decline from a previous level of ability is established, the affected cognitive domains are identified, and the consequences for everyday functioning are judged. The examination marks lie in stating that architecture clearly, then showing that the modern manuals draw its boundaries differently.

The contemporary framework also prevents a common conceptual error: the syndrome is not an aetiology. After establishing severity, the clinician must still specify the likely cause and recognise

that the cognitive phenotype may be cortical, subcortical, or mixed. This section therefore moves from definition to diagnostic threshold, then to practical classification. Disease-specific criteria, investigations and management belong to their respective sections.

DECLINE	DOMAIN	FUNCTION	CAUSE
FROM BASELINE	PROFILE	INDEPENDENCE	AETIOLOGY

2.1 From dementia to the neurocognitive-disorder framework

The older term dementia remains clinically familiar and is still used in the international classification. In the **DSM-5-TR major and mild neurocognitive disorder framework**, major neurocognitive disorder maps broadly onto dementia, while mild neurocognitive disorder maps broadly onto mild cognitive impairment. “Broadly” matters. These are conceptual correspondences, not permission to treat every historical use of the older labels as diagnostically identical.

The umbrella term has a wider scope than dementia. It can describe acquired cognitive impairment across the lifespan, including impairment associated with brain injury or infection, rather than implying a disorder restricted to later life. This wording also directs attention away from memory alone. A person may present because of executive, language, perceptual-motor, attentional, or social-cognitive decline, and the syndrome can still sit within this framework.

RULE **Define the syndrome before naming the disease.** Establish acquired decline, map the cognitive domains, determine whether independence is lost, exclude a delirium-only presentation and a better mental-disorder explanation, and only then add the aetiological formulation.

“Dementia” is therefore best retained as a clinically useful syndromic term rather than used as shorthand for irreversible degeneration. Some causes are degenerative, but others are vascular, neurological, endocrine, nutritional, infectious, metabolic, traumatic, or exposure-related. The classification should keep syndrome, severity and cause on separate lines because each answers a different question.

2.2 Major neurocognitive disorder: the diagnostic architecture

The DSM formulation begins with evidence of significant cognitive decline from the person's previous level in **one or more** cognitive domains. Evidence has a clinical component and an objective component: concern may come from the person, a knowledgeable informant, or the clinician, while substantial impairment should preferably be documented by standardised neuropsychological testing or, when that is unavailable, another quantified clinical assessment. Neither component should be treated as decorative. A test score without a credible decline history may misclassify limited education, language mismatch or longstanding low ability; a complaint without objective corroboration may reflect another process.

The named domain map contains **six** areas: complex attention, executive function, learning and memory, language, perceptual-motor function, and social cognition. The list is diagnostically liberating because memory impairment is not mandatory in every phenotype. It is also clinically

demanding: a routine interview that samples only orientation and recall can miss an executive, visuospatial, language-led or social-cognitive syndrome.

MNEMONIC

Decline - domains - daily function - differential

Use this sequence when constructing the definition. First establish decline from baseline; then identify the affected domains; next decide what has happened to independent daily function; finally check delirium and alternative mental-disorder explanations.

The decisive next question is whether cognitive deficits interfere with independence in everyday activities. At the **major functional threshold**, the person needs assistance with complex instrumental activities such as managing bills or medications. The criterion is about capacity, not merely whether another person happens to perform a task. A family may have always managed finances, or may take over tasks prematurely; conversely, a person may remain technically independent only because routines have narrowed and risks are being concealed. Functional enquiry must reconstruct what the person previously did, what now fails, how much support is required, and whether the failure is attributable to cognition.

The remaining **delirium and mental-disorder exclusions** are equally important. The deficits must not occur exclusively during delirium and must not be better explained by another mental disorder. This does not mean dementia and delirium cannot coexist, or that a patient with a mood or psychotic disorder cannot also develop cognitive disease. It means that the clinician must not assign the cognitive syndrome when the entire presentation is sufficiently explained by the competing condition.

GOOD TO REMEMBER

Ask for examples of failed tasks rather than asking only, “Is the patient independent?” Medication errors, missed payments, unsafe travel and abandoned household sequences reveal cognitive disability more reliably than a global yes-or-no answer.

2.3 Mild versus major: function is the hinge

Mild neurocognitive disorder also requires decline from a previous level within the same domain set, supported by concern and modest objective impairment. The separating feature is that the cognitive deficits do not remove the capacity for independence. Complex instrumental activities remain preserved, although they may require greater effort, compensatory strategies or accommodation. Thus “mild” refers to functional impact within this diagnostic framework, not to how distressing the symptoms feel, how abnormal a score looks, or how serious the underlying disease may eventually become.

AXIS	MILD NEUROCOGNITIVE DISORDER	MAJOR NEUROCOGNITIVE DISORDER
Magnitude of decline	Modest decline with modest objective impairment	Significant decline with substantial objective impairment
Cognitive breadth	Any named cognitive domain may be affected	Any named cognitive domain may be affected
Independence	Capacity remains intact	Deficits interfere with independence
Complex instrumental tasks	Preserved, but may need extra effort, strategy or accommodation	Assistance is required at least for complex instrumental tasks
Core clinical question	How is independence being maintained?	Which cognitive failures now require another person's help?

Severity within major neurocognitive disorder is also functionally specified. Mild severity means difficulty with instrumental activities such as housework or money management; moderate severity means difficulty with basic activities such as feeding or dressing; severe illness means full dependence **functional severity specifiers**. Do not confuse "mild major neurocognitive disorder" with mild neurocognitive disorder. The former has crossed the loss-of-independence threshold; the latter has not.

PITFALL

Do not equate family supervision with demonstrated dependence. Clarify whether help is necessary because cognition has failed, merely convenient, culturally customary, or prompted by physical disability. Functional staging is invalid if the cause of assistance is not established.

2.4 ICD framework and the cross-system examination trap

The international classification uses a similar clinical logic but a different domain threshold. Under **ICD-11**, dementia is characterised by marked impairment in **two or more** cognitive domains, severe enough to cause significant impairment in important areas of functioning. Mild neurocognitive disorder may involve similar domains, but its deficits are not severe enough to cause significant functional impairment. Memory is affected in most forms of dementia, yet impairment is not restricted to memory; executive functioning, attention, language, social cognition and judgement, psychomotor speed, and visuoperceptual or visuospatial functioning may be involved.

TRAP **Do not harmonise the domain count across manuals.** The DSM criterion uses the lower domain threshold stated above, whereas the ICD dementia requirement uses the stricter multiple-domain threshold. State the system before stating the threshold.

The international framework separates dementia from normal ageing by magnitude relative to age expectations and by functional impact. Appropriately normed standardised assessment can help establish whether performance deviates from expected ageing. Clinically relevant difficulty

that remains consistent with normal ageing should not be inflated into dementia merely because the patient is worried or slower than before.

The delirium boundary is temporal and phenomenological. Delirium produces a precipitous, transient and fluctuating global neurocognitive disturbance with confusion, whereas dementia is more often gradual, progressive and expressed through impairment of particular cognitive skills. Dementia increases vulnerability to delirium, so a person with established dementia who develops an acute disturbance of attention, orientation and awareness requires an additional delirium diagnosis rather than having the change attributed to "worsening dementia." Delirium itself is taught in the Stroke, TBI, delirium and focal brain syndromes notes.

Severity extension codes are available in the international system and are appended to the aetiological dementia code, including none, mild, moderate and severe categories **ICD severity extensions**. The available source does not establish the functional thresholds defining those levels, so the DSM functional definitions should not be copied into the international system by assumption.

2.5 Classification by cause: a map for differential diagnosis

Once the syndrome has been established, classification by cause prevents the vague and unsafe endpoint of "dementia, unspecified." A useful aetiological map groups causes as neurodegenerative, vascular, other neurological, endocrine, nutritional, infectious, metabolic, traumatic, and exposure-related **aetiological classification**. This is not a claim that every disease within a group behaves alike. It is a search structure that keeps the clinician from considering only the common degenerative disorders.

- **Degenerative and vascular:** consider a primary neurodegenerative process, vascular injury, or a mixed contribution.
- **Neurological and structural:** consider disorders that disrupt brain tissue, white matter, circulation or cerebrospinal-fluid dynamics.
- **Systemic states and acquired insults:** consider endocrine, nutritional, metabolic and infectious causes, together with trauma and relevant exposures.

An alternative map divides causes into inherited and acquired groups. The acquired branch can then be subdivided into primary degenerative, vascular, infective, inflammatory, neoplastic and traumatic causes. These systems are complementary. The first is broad and practical for an initial differential; the second makes inheritance and acquired brain disease explicit. Neither replaces a patient-specific formulation based on tempo, neurological findings, systemic clues, functional trajectory and the cognitive phenotype.

The historical **ICD-10** account remains worth recognising because older questions and records may use it. It retained a syndromic approach, provided general dementia criteria and criteria for **four** specific types, and required decline in activities of daily living. It must be labelled as the earlier classification rather than presented as current international wording.

For disease-level accounts of several categories in the aetiological map, follow the relevant cross-references. The endocrine, metabolic and nutritional diseases themselves are covered in the Endocrine and metabolic psychiatry notes. Inherited and other neurological diseases outside the dementia lens are covered in the Neuropsychiatry of systemic and neurological disease notes. The present purpose is to keep these causes visible in the dementia differential, not to reproduce their disease teaching.

2.6 Cortical and subcortical cognitive phenotypes

A second classification asks where network disruption is most strongly expressed. The distinction between **cortical and subcortical dementia** is anatomical and functional: in the cortical pattern, pathology directly affects cerebral cortical systems; in the subcortical pattern, the major cognitive impact is understood as loss of the normal regulatory influence of subcortical structures on the cortex, particularly prefrontal systems. This distinction is useful because it predicts the pattern of failure more than the global amount of impairment.

Alzheimer disease is the cortical prototype: early disturbance prominently involves episodic memory, language and visuospatial ability, while attention and frontal-executive functions are relatively preserved early. By contrast, **Huntington disease and progressive supranuclear palsy** exemplify the subcortical pattern, in which attentional control and executive function are disproportionately impaired and thinking is slowed.

CLINICAL AXIS	CORTICAL-PREDOMINANT PATTERN	SUBCORTICAL-PREDOMINANT PATTERN
Dominant cognitive failure	Memory, language and visuospatial systems	Attention, executive control and cognitive activation
Speed	Slowing is less prominent early in the prototype	Bradyphrenia is characteristic
Memory mechanism	Severe episodic amnesia may appear early in the prototype	Poor attention and encoding, with a prominent retrieval deficit
Recall versus recognition	Interpret within the broader amnestic pattern	Recognition is typically better than spontaneous recall
Focal cortical signs	Aphasia, apraxia or agnosia may occur	These are relatively absent early
Behaviour and mood	Less prominent early in the prototype	Change in mood, personality and social conduct is common

The memory contrast deserves emphasis. In a subcortical pattern, inefficient attention and encoding combine with impaired retrieval, so the patient may produce little spontaneously yet recognise more when choices or cues are supplied. This differs from the marked early episodic amnesia of the cortical prototype, but it remains a bedside clue rather than a stand-alone aetiological test. Depression, fatigue, education, language, motor slowing and test conditions can also alter apparent retrieval efficiency.

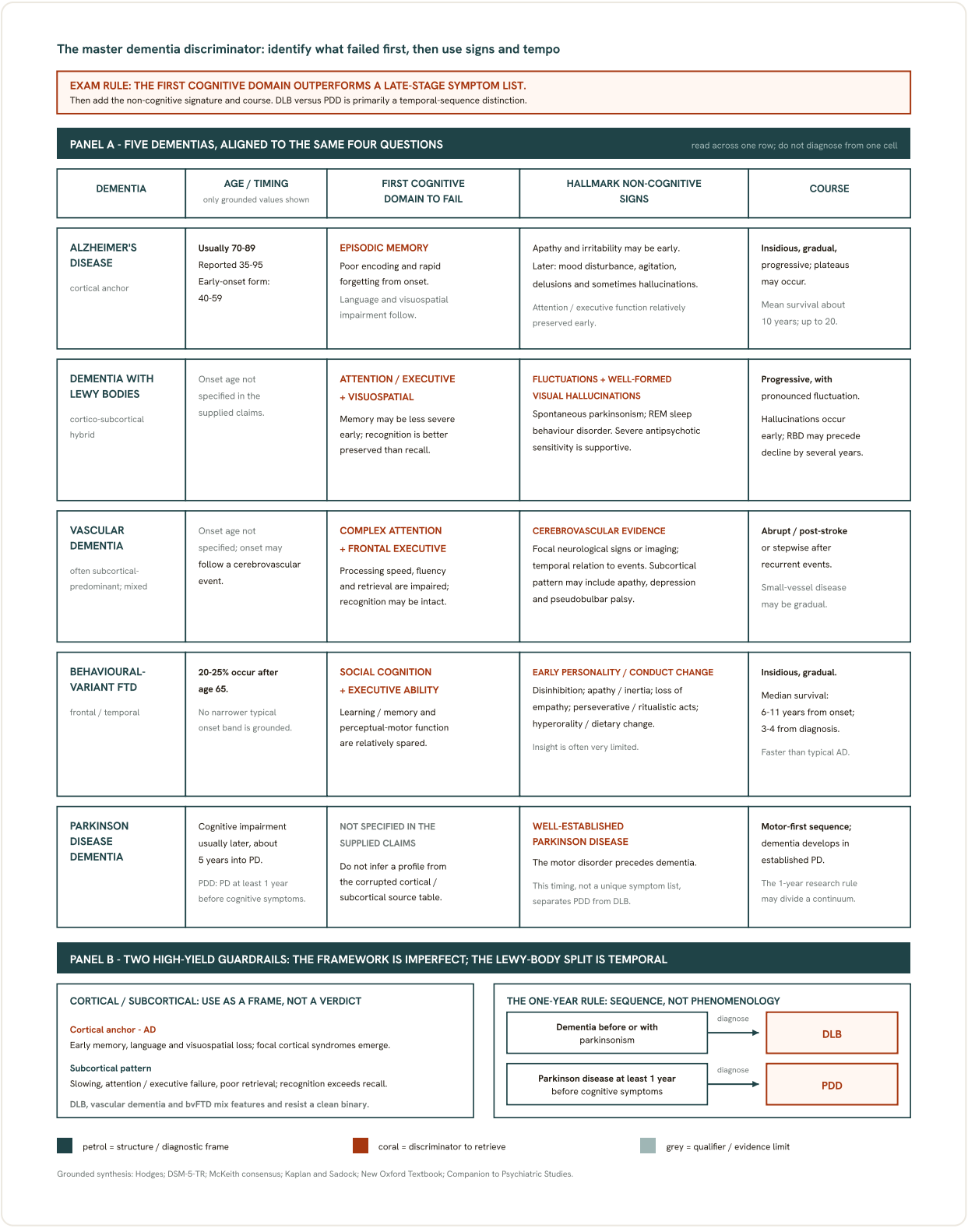

Fig 32.1 Master dementia discriminator: compare age or timing, the first cognitive domain to fail, hallmark non-cognitive signs and course across Alzheimer's disease, dementia with Lewy bodies, vascular dementia, behavioural-variant frontotemporal dementia and Parkinson disease dementia; the cortical/subcortical frame is useful but imperfect, and DLB versus PDD is separated principally by temporal sequence.

The accompanying figure extends phenotype-based discrimination across the major dementia syndromes. Use it after defining the neurocognitive syndrome, not as a shortcut that converts a striking feature into a diagnosis. The profile must be reconciled with onset, course, functional change, neurological examination and the broader differential.

2.7 Why the cortical-subcortical dichotomy is a heuristic

Real disorders do not respect a binary diagram. Vascular dementia often has a subcortical-predominant profile because of lacunar and diffuse white-matter pathology, yet focal cortical damage may coexist. **Dementia with Lewy bodies** combines poor attention and executive ability with cortical dysfunction implicating posterior cortical systems. Behavioural frontotemporal dementia may combine marked personality and social-conduct change with recognisable cortical features. These are mixed cortical-subcortical profiles rather than clean occupants of either pole.

A broader account therefore allows a cortico-subcortical hybrid category. The term is valuable when it stops forced classification; it becomes unhelpful if it is treated as a final diagnosis. Anatomical phenotype and aetiology are different axes. A mixed profile may arise because a disease affects several networks, because pathology has advanced, or because pathological processes coexist.

- Use the dichotomy to organise the bedside cognitive phenotype.
- Do not use it to exclude a disease merely because a feature falls on the other side.
- Reassess the profile over time, while keeping aetiological, functional-severity and anatomical classifications separate in the formulation.

2.8 A formulation that remains clinically useful

A complete formulation should answer a sequence of linked questions. Is there credible acquired decline? Which domains are affected? Is the impairment objectively supported? Has capacity for independent everyday activity been lost? Is the disturbance exclusively delirious or better explained by another mental disorder? Which aetiological class and cognitive phenotype best fit? This sequence turns “memory complaint” into a defensible syndrome statement without pretending that classification alone establishes cause.

Baseline reconstruction is the quiet skill behind all of these decisions. Education, occupation, language, sensory ability, motor impairment, household roles and opportunities for independent activity shape both test performance and the visibility of decline. The clinician should therefore triangulate the person's account, collateral history, observed performance and records of real-world tasks. Disagreement among these sources is information, not noise: the person may lack awareness, an informant may overstate impairment, or a structured clinic encounter may conceal failure that appears only in complex daily life. The aim is not to reward a persuasive narrative but to establish a coherent change from that individual's own baseline.

A useful written statement separates certainty at each level. The cognitive syndrome may be well established while the cause remains provisional; conversely, a known neurological disease does not by itself prove that current functional loss is cognitive. Record the dominant domains, the effect on independence, the temporal course, relevant exclusions and the leading aetiological class. This makes later revision possible without rewriting the history and prevents the disease label from swallowing the syndrome description.

The same sequence also prevents predictable errors. Normal ageing is not dementia without functional and normative evidence. Mild neurocognitive disorder is not simply an early synonym for major disorder. Major disorder is not defined by memory failure alone. A subcortical profile is not synonymous with a particular disease, and a cortical profile is not proof of the cortical prototype. Finally, an acute attentional disturbance in a person with dementia is not automatically progression; superimposed delirium must be considered.

Memorise the hierarchy: establish decline, map domains, judge independence, exclude delirium-only and better mental-disorder explanations, then classify severity, phenotype and aetiology.

3 · The clinical approach to cognitive decline, including young-onset dementia

Why it matters clinically. Cognitive decline is not diagnosed by a low score alone. The clinician must establish that there has been a change from the person's previous level, define the affected cognitive and behavioural phenotype, determine its tempo, and show how it has altered everyday function. The marks lie in turning an imprecise complaint such as "forgetfulness" into a coherent syndrome while keeping psychiatric, neurological, medical, substance-related and contextual explanations in view.

The assessment is therefore an exercise in triangulation. The patient contributes subjective experience, symptoms and goals; an informant contributes longitudinal observation; examination and cognitive assessment test the emerging hypothesis; and functional evidence shows whether the change matters in real life. Discordance between these sources is information, not noise. It may reflect impaired awareness, over- or under-reporting by an informant, language or educational mismatch, an acute superimposed illness, or a phenotype that a brief screen samples poorly.

RULE **Build the syndrome before naming the disease.** First establish change, tempo, cognitive-behavioural pattern and functional consequence; only then rank aetiologies and select investigations.

STORY	PROFILE	FUNCTION	CONTEXT
CHANGE AND TEMPO	DOMAINS AFFECTED	REAL-LIFE CONSEQUENCE	CAUSE AND MODIFIERS

3.1 Begin with change, not with a label

The opening task is to decide what has changed and whose concern brought the patient to assessment. Clarify the first noticed difficulty, the circumstances in which it appeared, and whether the patient, family, employer or another observer recognised it first. Ask for concrete episodes rather than global judgments. "He is forgetful" is weak evidence; a description of repeated missed obligations despite established routines is clinically interpretable. Equally, an isolated error during stress, sleep loss or illness should not be inflated into a progressive syndrome without longitudinal support.

An accurate account cannot be expected from the **patient alone**, because impaired memory and awareness can make a patient-only history incomplete. The core temporal axes are onset, course and duration. Establish whether onset appeared insidious or sudden; whether the course is gradual, stepwise, episodic or fluctuating; whether change is progressive, static or partly reversible; and whether worsening relates to a medical event, medication change or altered environment. These distinctions do not by themselves diagnose a cause, but they reorganise the differential and determine urgency.

Define the **premorbid baseline** with the same care. Schooling, occupation, language, literacy, habitual division of household tasks, sensory limitations and longstanding personality determine what counts as decline. A person who never managed money cannot be judged impaired because a relative now manages it; conversely, loss of a highly practised but cognitively demanding skill may be meaningful even when basic self-care remains intact. The relevant comparison is the patient with their own earlier functioning, not the patient with an imagined average.

GOOD TO REMEMBER

Ask the informant for the earliest unequivocal change and for a recent concrete example. This often separates a longitudinal decline from a vague family impression and anchors every later question to a real baseline.

3.2 Structure the interview to preserve each account

A useful **staged interview** begins with patient and informant together, continues with the informant alone, and ends with the patient being examined alone. The joint phase identifies the presenting concern and allows observation of interaction. The private informant phase permits discussion of decline, risk, behavioural change and caregiver strain without humiliating or provoking the patient. The private patient phase protects confidentiality, allows direct mental-state assessment and reduces cueing or correction by relatives.

This sequence is not a licence to treat the informant as automatically correct. Record who observed each event, how often they see the patient, whether they benefit from a particular account, and whether family conflict may colour the history. When accounts diverge, document the divergence explicitly. A patient may minimise because of impaired awareness or fear of losing independence; an informant may magnify ordinary errors because of anxiety, exhaustion or a sudden change in expectations. The clinician's task is to test each account against examples, chronology and function.

MNEMONIC

STORY BEFORE SCORE

Secure the **story of change**, its **tempo**, the **observed examples**, the resulting **real-life loss** and the patient's **own account** before interpreting a screening result.

Interview technique matters. Use short, concrete questions, allow time for retrieval, check hearing and comprehension, and avoid turning the encounter into a public test of competence.

Ask permission before sensitive questions where possible. Preserve the patient's dignity while still obtaining a candid collateral account. If no informant attends, seek consent to contact someone who knows the patient's previous and current functioning; meanwhile, state clearly that diagnostic confidence is limited by the absent longitudinal history.

3.3 Take a domain-led cognitive history

The history should follow a **domain map** and must not reduce cognition to memory. Probe each domain through everyday examples, then ask when the problem began, how it has evolved, what compensations are used and what consequence followed. A domain-led approach identifies non-amnestic presentations, exposes uneven profiles and prevents a fluent patient from being declared cognitively intact merely because social conversation is preserved.

DOMAIN	TARGETED ENQUIRY	INTERPRETIVE PURPOSE
Attention and concentration	Slips, absent-mindedness, losing track, or failure when distractions compete	Distinguishes sustained inefficiency from a narrowly described memory complaint
Memory	Recent events, retained personal knowledge, remote information, repetition and benefit from reminders	Separates acquisition, storage and retrieval complaints at the level possible in history
Language	Word finding, naming familiar people, comprehension, reading and writing	Detects language-led decline that may distort apparently "global" testing
Executive function	Planning, organising, solving unfamiliar problems, handling medicines or finances and completing multistep tasks	Shows whether complex goal-directed activity has deteriorated
Calculation	Errors in transactions, bills, change or previously familiar arithmetic	Links a cognitive complaint to practical competence
Spatial and perceptual ability	Route finding, recognising faces or objects and navigating familiar surroundings	Identifies impairment that may present as getting lost or misidentification
Praxis	Using familiar tools, dressing, feeding and carrying out learned sequences despite adequate movement	Distinguishes loss of learned action from weakness or poor effort
Social cognition	Judgment, tact, empathy, inhibition, personality and conduct	Captures behavioural presentations that memory-first questioning misses

Do not accept a domain as impaired merely because the patient says "yes" to a broad question. Establish a before-and-after contrast and obtain an example with ecological validity. Ask whether the error is new, whether it recurs, whether prompts help, and whether the task failed because of cognition, mood, motivation, vision, hearing, language, motor disability or unfamiliarity. The

same observed failure can arise through different cognitive routes; history narrows the mechanism without pretending to replace formal assessment.

3.4 Establish function, safety and behavioural change

Functional status converts symptoms into clinical significance. Ask not only whether a task is completed but how it is completed, with what errors, prompting, supervision, compensatory effort and risk. Driving, money management, medication use and activity planning are particularly informative because they require integration of several abilities. Extend the enquiry to self-care, shopping, housework, work, hobbies and social participation. Structured living-skills measures and functional staging scales can support severity assessment, but they do not replace a contextual account.

- For each important activity, document independence, assistance, supervision and complete dependence in plain language.
- Separate cognitive failure from physical incapacity, lack of opportunity, family takeover and culturally assigned roles.
- Ask what has become unsafe, what remains preserved and what support already prevents harm.

Behavioural and psychological change belongs in the initial history, not in an afterthought. Enquire about altered personality, mood, psychotic experiences, apathy, agitation, anxiety, disinhibition, repetitive motor behaviour, sleep, eating and sexual behaviour. The **Neuropsychiatric Inventory** offers a systematic way to capture the recognised disturbance groups, including delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, night-time disturbance and appetite or eating change. A structured inventory improves coverage; clinical interpretation still requires context, frequency, impact and a search for precipitants.

> **PITFALL**
> Do not call preserved washing and dressing "preserved function" and stop. Complex activities often fail earlier, and relatives may conceal decline by quietly taking over finances, medicines, travel or appointments.

3.5 Use background and context as aetiological evidence

A careful **aetiological background** can redirect the entire formulation. Previous affective illness, vascular disease and prescribed or recreational drug exposure may explain, mimic or contribute to cognitive impairment. Relate each potential factor to the timeline rather than compiling an undifferentiated problem list. Ask whether cognition worsened after an event or exposure, improved when it resolved, or followed a parallel course. Association is not proof, but temporal linkage increases or decreases plausibility.

Broaden this into a **contextual history**: relevant medical and neurological illness, cerebrovascular events and risk, head injury, infection risk, psychiatric illness, alcohol and other substance use, family history of dementia or neurological disease, education and occupational or

chemical exposure. Depression deserves particular attention because it can produce cognitive impairment and may coexist with or precede a dementing illness. Its full differentiation from dementia is addressed elsewhere in this chapter; here, the key is to avoid forcing mood and neurocognitive explanations into an either-or choice.

Family history should be constructed across generations where possible. Record the type of impairment, age pattern in qualitative terms, neurological or systemic accompaniments, and whether diagnoses were verified or merely remembered. Do not convert "an elderly relative was forgetful" into evidence of a familial syndrome. Equally, do not dismiss a cluster of early or unusual neurological presentations because relatives used non-medical language. Family structure, adoption, estrangement and premature death can make an apparently negative history uninformative.

The social history is part of measurement. Language, education, literacy, occupation, migration, sensory impairment and familiarity with test materials affect performance. Poverty, isolation, caregiver availability and access to records shape what can be established and what support is feasible. These factors neither prove nor disprove neurocognitive disease. They determine how confidently observed performance can be interpreted and whether apparent loss reflects decline, deprivation of opportunity or mismatch between the assessment and the person.

3.6 Examine and test the hypothesis, not the patient's worth

Bedside cognitive assessment is hypothesis testing. Select tasks that sample the suspected domains, interpret them against language, education, sensory and motor capacity, and note the manner of performance as well as the final score. Error type, strategy, cueing response, perseveration, fatigue and inconsistency may be more informative than a total. Administration and scoring of general cognitive instruments belong in the Psychometry, Assessment and Descriptive Psychopathology notes; disease-specific cognitive profiles are covered in the dedicated assessment section of this chapter.

A teaching vignette illustrates why **collateral history** can outrank a screen when significant aphasia makes commonly used bedside instruments unreliable. The lesson is not that testing is useless in aphasia. It is that a score cannot answer a question the instrument is no longer able to sample validly. Establish premorbid and pre-event function, describe which responses remain interpretable, and seek domain-appropriate assessment rather than converting language failure into a global cognitive diagnosis.

TRAP **"Low cognitive score equals dementia."** A score is evidence within a formulation. It can be lowered by language, education, sensory loss, motor impairment, mood, acute illness or poor engagement, and it can miss a focal or behaviour-led decline.

The examination should also test competing explanations suggested by the history, but a comprehensive neurological examination, neuroimaging principles and fluid examination procedures belong to their respective specialist sections. Refer to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes for imaging modalities and to the Neurology foundations for psychiatrists notes for the general cerebrospinal-fluid

procedure. The present task is to make investigation question-led: every test should address a ranked possibility, urgency or management consequence.

3.7 Young-onset dementia requires a wider diagnostic aperture

Young-onset dementia begins before **65 years**. Alzheimer disease remains the commonest single cause, accounting for **30-40%** of cases in the cited clinical series. **Frontotemporal lobar degeneration** is a close second, while vascular and inherited neurological causes assume greater relative prominence. This differs from later-life dementia, where the usual degenerative and vascular disorders together account for **at least 80%** of cases. The practical message is not that common diseases disappear in younger people. It is that the residual differential is broader, rarer and more often genetically determined or potentially treatable.

All people with a younger-onset presentation require detailed investigation, and the likelihood of an unusual disorder rises as onset becomes younger. “Detailed” means that the diagnostic question must be reopened rather than simply applying a later-life template more intensely. Recheck whether the dominant change is memory, language, behaviour, executive control, movement, seizures, systemic illness or a mixed syndrome; reconstruct the pedigree; verify tempo; and review exposures and prior neurological events. The exact investigation panel belongs to the systematic workup sections and should be chosen from the phenotype rather than ordered as an unexamined bundle.

Red flags include progression beyond **approximately three MMSE points/year**, a family history containing neurological or systemic features outside the common patterns, and distinctive feature combinations. Limb apraxia with myoclonus and alien-limb phenomena suggests a corticobasal pattern; dysarthria, dysphagia and personality change suggest a frontal syndrome with motor-neurone-disease overlap. These combinations are signposts for specialist investigation, not substitutes for diagnosis.

- Escalate urgency when decline is rapid, fluctuating in an unexplained way, or accompanied by new neurological or systemic features.
- Escalate breadth when the phenotype is unusual, the family pattern is striking, or routine explanations do not fit the chronology.
- Escalate genetic care when the history suggests inheritance, because testing affects relatives as well as the patient.

Developmental context also matters. Dementia in children and young adults is rare and is often associated with lysosomal storage disease. In Down syndrome, dementia occurs in **about 50% or more** of affected people and generally emerges later in adult life. Assessment must demonstrate decline from the individual’s established developmental baseline rather than infer dementia from pre-existing disability. Intellectual disability and the developmental syndrome itself are addressed in the Intellectual disability and autism spectrum disorder notes.

Some inherited neurological and metabolic conditions enter the younger-onset differential but are not taught here. Huntington disease belongs in the Neuropsychiatry of systemic and

neurological disease notes. Wilson's disease and inherited metabolic or storage disorders belong in the Endocrine and metabolic psychiatry notes. Naming these routes matters because a generic "dementia screen" is not an adequate endpoint for a younger patient with an atypical phenotype.

3.8 Synthesize the assessment into a defensible formulation

The final product is not a catalogue of abnormalities. It is a concise formulation that states the evidence for decline, the dominant cognitive-behavioural phenotype, tempo, functional effect, associated psychiatric or neurological features, background contributors, safety concerns, and the degree of diagnostic confidence. Separate observed facts from informant report and from inference. State what remains uncertain and what evidence would change the ranking.

A practical synthesis proceeds in sequential passes. First describe the syndrome without an aetiological label: baseline, onset, course, domains, behaviour, function, awareness and associated features. Then rank likely causes and mimics, explain the evidence for and against each, and specify the investigation or follow-up needed to resolve uncertainty.

This structure protects against premature closure. It also allows the clinician to communicate uncertainty honestly without becoming vague. "Progressive cognitive decline" is insufficient if domains and function are unspecified; a confident disease label is unsafe if chronology and collateral evidence do not support it. When acute confusion is possible, the distinction from delirium must be addressed using the Stroke, TBI, delirium and focal brain syndromes notes. Potentially reversible causes require the systematic workup described in the dedicated section of this chapter, not an improvised memory-based list.

> In cognitive decline, the decisive sequence is: prove change, define phenotype and tempo, establish functional consequence, then investigate the cause.

4 · Alzheimer's disease: epidemiology, risk factors and genetics (APOE, APP, presenilins)

The marks lie in separating burden, risk and causation. **Alzheimer dementia** is common in later life, but an epidemiological association is not a diagnosis, a risk allele is not a deterministic mutation, and neuropathological change is not synonymous with clinical dementia. A strong answer therefore moves in a disciplined sequence: define whose prevalence is being quoted, show the steep relation with age, classify modifiable and non-modifiable risks, and then distinguish rare high-penetrance familial disease from the susceptibility architecture of the much larger sporadic group.

The epidemiology also teaches clinical humility. Prevalence depends on population, setting, diagnostic method and calendar period. Age, survival, vascular health, education and social conditions shape the observed burden. Genetics operates within that context rather than outside it. The pathology and amyloid cascade, clinical staging and diagnostic criteria, and treatment are developed in their own sections; here the task is to understand who develops disease, which exposures alter probability, and how the major genes differ in biological and counselling significance.

6.2 million	13.8 million	5.3%	34.6%
US, LIVING WITH AD DEMENTIA IN 2021	US PROJECTION FOR 2060	US, AGE 65 TO 74	US, OLDER THAN 85

4.1 Epidemiological frame: age dominates the curve

The most robust epidemiological pattern is the **age gradient**. In the United States estimate for 2021, prevalence was **5.3% at ages 65 to 74, 13.8% at ages 75 to 84, and 34.6% above age 85**. These are prevalence figures, not the probability that an individual will inevitably develop disease. They reflect accumulated incidence together with survival. They also explain why demographic ageing can enlarge the number of affected people even if age-specific risk does not change.

The same source estimated that 6.2 million United States residents aged 65 years or older were living with Alzheimer dementia in 2021. It projected 13.8 million people older than 65 years by 2060, including 6.7 million older than 85 years. The projection is best read as a service-planning warning: the subgroup with the greatest age-related burden will contribute heavily to future caseloads. It is not an India estimate and should not be transferred across populations as though geography and ascertainment were irrelevant.

DSM-5-TR provides a differently framed set of estimates. In high-income countries, neurocognitive disorder due to Alzheimer's disease rises from 5% to 10% among people aged 60 to 64 to at least 25% thereafter. Its United States estimate for 2016 was 5.4 million people of all ages, around 200,000 with onset before age 65; it also reported disease in 11% of people aged 65 or older and 32% of those aged 85 or older. These figures need not match a later estimate because the year, sampling frame and diagnostic method differ.

EPIDEMIOLOGICAL STATEMENT	WHAT IT LEGITIMATELY SUPPORTS	WHAT IT DOES NOT SUPPORT
Prevalence rises markedly with age	Age is the strongest population-level risk factor	Age alone establishes a diagnosis
A projected case count rises	Future service burden may increase as the population ages	Every individual has a rising deterministic risk
Two sources quote different prevalence figures	Methods, settings and calendar periods must be stated	One estimate can be silently substituted for the other
Clinical prevalence is measured	The number of people meeting a clinical case definition is estimated	Every person with pathological change has dementia
A subgroup has higher observed prevalence	Biology, survival, comorbidity and social exposure deserve analysis	The disparity is an intrinsic property of group identity

IN INDIA

No India-specific prevalence, incidence or national case-count estimate is available in the cited material for this topic. Use the international figures only with their stated population and year. Quoting a United States estimate as Indian prevalence is not approximation; it is a change of denominator, health system and ascertainment context.

4.2 Onset, sex and population disparities

Although Alzheimer disease is strongly age-related, onset is not confined to a single period. The recorded range extends from **age 35 to age 95**. DSM-5-TR states that symptoms usually begin at ages 70 through 89, while forms beginning at ages 40 through 59 are often, but not invariably, associated with known causative mutations. The useful inference is probabilistic: an unusually early presentation strengthens the reason to examine inheritance carefully, but age at onset by itself neither proves nor excludes a pathogenic mutation.

Observed prevalence is higher among women in the cited United States data: 12% of women older than 65 compared with 6% of men older than 65. The major explanation offered is women's longer lifespan, with possible biological and environmental or cultural contributions. The examination error is to convert prevalence difference into a simplistic sex-specific cause. Longer survival increases the time spent in the age bands where prevalence is greatest, and the remaining difference may reflect several interacting mechanisms.

The same caution applies to racial and ethnic disparities. Among United States residents older than 65, prevalence was 18.6% in Black Americans, 14% in Hispanic Americans and 10% in White Americans. The source attributes much of this difference to unequal burdens of cardiovascular disease and diabetes and to socioeconomic inequities. Group labels are therefore signals to investigate accumulated exposure, access, comorbidity and ascertainment, not biological shortcuts. A doctor-facing account should describe disparity without racial essentialism.

Depending on setting and diagnostic criteria, 60% to more than 90% of dementias are attributed to Alzheimer's disease. That breadth is itself informative: case mix changes across community, clinic and institutional settings, while diagnostic boundaries alter the numerator. Alzheimer disease may be the leading contributor without being the only cause in an individual. Mixed pathology is common clinically, but its detailed diagnosis and management belong elsewhere in the chapter.

4.3 Pathology without dementia: the denominator problem

A crucial conceptual distinction is that biological change may precede, or never produce, the clinical syndrome. As many as 70% of cognitively normal older adults show clear Alzheimer histopathological changes, and up to 30% meet full autopsy-confirmed neuropathological criteria. These observations do not make clinical assessment obsolete. They show that pathological burden, cognitive reserve, co-pathology and resilience influence whether tissue-level disease becomes manifest as functional cognitive decline.

RULE **Separate clinical prevalence from pathological prevalence.** Alzheimer-type change in a cognitively normal person is not equivalent to dementia, while dementia remains a clinical syndrome whose cause requires appropriate diagnostic evaluation.

This distinction also protects interpretation of biomarkers and genetic results. A marker that shifts probability cannot be read in isolation from cognition, function and longitudinal course. Conversely, normal performance at one encounter does not settle the lifetime biological question. The examiner is looking for this layered model: pathology can exist without current clinical impairment, risk can exist without pathology being demonstrated, and a clinical syndrome can have more than one pathological contributor.

The numerical contrast is best used to explain penetrance and expression rather than to claim that silent pathology is harmless. Some individuals may be earlier in a disease process; others may tolerate considerable burden without crossing a clinical threshold. The neuropathological lesions and biomarker interpretation are owned by their dedicated sections. Here the epidemiological lesson is that the denominator must match the question being asked: clinical cases, pathological cases and at-risk persons are different populations.

4.4 Modifiable and non-modifiable risk

Age is the strongest identified risk factor. Genetic predisposition is also substantial, with 60% to 80% of attributable risk assigned to genetic influence in the cited synthesis. Neither statement means that environment is negligible. A high heritable contribution describes variation in a population under its prevailing conditions; it does not tell an individual that outcome is fixed, and it does not make preventable exposures clinically irrelevant.

The 2020 report of the Lancet Commission estimated that **about 40% of dementias worldwide may be related to modifiable factors**. This estimate concerns dementia broadly, not Alzheimer disease alone, so its scope must be retained. The listed factors span the life course: less education; midlife hypertension and high cholesterol; cardiovascular or cerebrovascular disease; diabetes and obesity; depression across earlier and later life; sleep disturbance; traumatic brain injury; excessive alcohol use; smoking; anticholinergic medication burden; physical inactivity; air pollution; social isolation; and hearing impairment.

DSM-5-TR identifies low educational status, midlife hypertension, obesity, hearing loss, late-life smoking, depression, physical inactivity, social isolation and diabetes as Alzheimer-specific risk and prognostic factors. It also states that **clustering of vascular risk factors** increases risk. Traumatic brain injury, particularly in men, may increase risk, although the association remains controversial. This wording matters: a possible association should not be upgraded into settled causation.

- **Life-course accumulation:** education, vascular exposure, sensory loss and social context act over different periods rather than at one late-life moment.
- **Shared pathways:** several factors affect both vascular and neurodegenerative outcomes, so risk reduction need not depend on assigning a single future dementia subtype.

- **Clustering:** multiple vascular risks together carry more concern than an isolated label viewed without context.
- **Association is not destiny:** a risk factor changes probability; it does not establish present disease or guarantee future disease.
- **Scope discipline:** the broad dementia-attributable estimate and the Alzheimer-specific factor list should be presented as related but not identical constructs.

GOOD TO REMEMBER

Risk review is clinically useful even when causation cannot be assigned in one patient. Address vascular health, hearing, activity, mood, social connection, alcohol, smoking and medication burden because they affect present health and may also alter future cognitive risk. Do not promise that modifying one factor will prevent Alzheimer disease in that individual.

4.5 Genetic architecture: cause, susceptibility and background

The genetics become clear when divided into categories. **Familial Alzheimer disease** is described by Kaplan and Saddock as accounting for about **5%** of cases, with early onset, autosomal dominant inheritance and high penetrance. The remaining sporadic forms have a genetic contribution resembling that of other common neuropsychiatric disorders: many susceptibility variants interact with age and non-genetic exposures rather than acting as a single sufficient cause.

Twin evidence supports a meaningful but incomplete inherited contribution. Concordance in **monozygotic twin pairs** is about 50%. If genes were irrelevant, such concordance would be difficult to explain; if genes alone were sufficient for all disease, concordance would be complete. The gap between those possibilities points toward variable penetrance, polygenic background, environmental exposure, survival and stochastic biological processes.

MNEMONIC

Cause, Susceptibility, Context

Cause: rare dominant mutations with high penetrance. **S**usceptibility: common alleles that alter probability. **C**ontext: age, vascular and life-course exposures that influence whether risk becomes clinical disease.

TRAP **Do not quote one universal percentage for "familial Alzheimer disease".** The supplied texts use different boundaries: one gives about 5% for familial forms, while another describes clearly inherited early-onset disease as a smaller minority. State the source and definition, and do not pretend the discrepancy has been resolved.

The conflict is not merely editorial. "Familial" may mean any aggregation among relatives, or it may be reserved for a pedigree showing high-penetrance autosomal dominant transmission. "Early onset" is also not a synonym for "Mendelian": causative mutations are enriched in earlier presentations but are not present in every such patient. In an answer, define the category before

quoting its proportion and keep mutation-caused disease separate from common familial clustering.

4.6 The autosomal dominant genes: APP and the presenilins

The first identified cause of familial early-onset disease involved the **amyloid precursor protein gene (APP)** on chromosome 21. Pathogenic variants increase extracellular longer beta-amyloid fragments, including amyloid-beta 42. The high-yield link is therefore direct: the encoded precursor sits upstream of amyloid generation, and a mutation can shift processing toward the aggregation-prone product. The fuller amyloid cascade and neuropathological consequences belong in the dedicated pathology section.

Presenilin-1 and presenilin-2 are located on chromosome 14q24.3 and chromosome 1q, respectively. They are integral transmembrane proteins with at least seven transmembrane domains and function as aspartyl proteases in gamma-secretase cleavage of the precursor protein, generating beta-amyloid. Thus, these dominant genes converge on production or processing of the same molecular substrate even though their chromosomal locations differ.

GENETIC CATEGORY	LOCATION OR SCALE	BIOLOGICAL OR CLINICAL MEANING
APP	Chromosome 21	Dominant familial cause; pathogenic variants increase longer extracellular beta-amyloid fragments
PSEN1	Chromosome 14q24.3	Presenilin component of gamma-secretase processing
PSEN2	Chromosome 1q	Presenilin component of gamma-secretase processing
APOE	Chromosome 19q	Common late-onset susceptibility locus, not a deterministic dominant mutation
Genome-wide association loci	More than 40 confirmed risk genes	Common small-effect architecture converging on several biological pathways

Kaplan and Saddock's edition lists 185 PSEN1 mutations, 13 PSEN2 mutations and 24 APP mutations, virtually all transmitted as autosomal dominant, fully penetrant variants. These are edition-specific counts rather than timeless biological constants; mutation catalogues change as new variants are characterised. For examination purposes, the durable distinction matters more than memorising a potentially moving inventory: these genes can cause high-penetrance familial disease, whereas common susceptibility alleles modify risk.

4.7 APOE: the major susceptibility locus

The **apolipoprotein E gene (APOE)** lies on chromosome 19q. Its three recognised alleles are epsilon 2, epsilon 3 and epsilon 4, distinguished by amino acids at residues 112 and 158: epsilon 2 is Cys112/Cys158, epsilon 3 is Cys112/Arg158, and epsilon 4 is Arg112/Arg158. Epsilon 3 is

the most common allele in most populations. The structural detail is worth knowing, but its clinical meaning is the real examination target.

APOE epsilon 4 is enriched in late-onset disease. Its frequency is approximately 50% in familial late-onset Alzheimer disease and 40% in sporadic late-onset disease, compared with about 16% in controls. Across late-onset cases, 30% to 60% carry at least one epsilon 4 allele. Because many affected people do not carry it, and many carriers do not inevitably become affected, it is a susceptibility allele rather than a diagnostic marker or a Mendelian cause.

The dose-risk relation is strong but still probabilistic. **One copy raises risk about 4-fold**, while two copies raise it about 10-fold. Relative risk is not the same as absolute lifetime probability. The latter depends on background population risk, age, ancestry, competing mortality and other genetic and environmental influences. A result therefore cannot be translated into a certain personal forecast by repeating the fold-change alone.

PITFALL

Do not tell a patient that an APOE epsilon 4 result diagnoses Alzheimer disease or guarantees future dementia. It changes susceptibility. Interpretation requires the clinical phenotype, family history, purpose of testing and appropriate genetic counselling; the relative-risk figure alone is not an individual prognosis.

4.8 Beyond APOE: modifiers, pathways and genetic convergence

GAB2 illustrates gene-gene interaction. It was identified through genome-wide association as an additional risk allele among APOE epsilon 4 carriers, but not among affected non-carriers. Carrying both risk alleles was associated with an almost 25-fold greater risk than carrying neither. Mechanistically, GAB2 can modulate beta-amyloid production through interaction with GRB2, which physically interacts with APP and the presenilins. This is a modifier model, not a replacement for the distinction between causal mutations and susceptibility alleles.

The wider **polygenic risk architecture** includes more than 40 confirmed risk genes identified through genome-wide association studies. Unlike the dominant genes, each generally has a small effect, with an odds ratio below 1.2, and is relatively common in the population. Their biological convergence is more informative than any isolated locus: implicated pathways include immunity, lipid metabolism, tau binding and amyloid precursor protein metabolism. Common disease emerges from networks rather than one obligatory mutation.

The association between Down syndrome and Alzheimer disease is an important genetic bridge, but its gene-dosage mechanism, diagnostic classification and assessment of cognitive decline are taught in the dedicated Down-syndrome section. Intellectual disability as a developmental syndrome belongs in the Intellectual disability and autism spectrum disorder notes. This boundary matters because a shared molecular link does not make the baseline developmental condition and later cognitive decline interchangeable clinical constructs.

The complete genetic answer therefore ends with hierarchy. Rare dominant variants in the APP gene and presenilin genes can be highly penetrant causes. The APOE epsilon 4 allele is a major

common susceptibility factor with a copy-related increase in risk. Other common loci contribute smaller effects and reveal convergent biological pathways. Age and modifiable exposures remain clinically relevant throughout. None of these layers should be allowed to masquerade as another.

> Rare APP and presenilin mutations can cause autosomal dominant Alzheimer disease; APOE epsilon 4 modifies late-onset risk but is neither necessary nor sufficient for the disorder.

5 · Alzheimer's disease: neuropathology and the amyloid cascade

The scoring answer links lesion, location, sequence and mechanism. Alzheimer pathology is not merely a list of plaques, tangles and transmitter deficits. The lesions have different cellular compositions, begin in different regions and acquire different explanatory roles. A mature answer therefore separates the amyloid map from the tau map, relates both to neuronal and synaptic injury, and then treats the amyloid cascade as a mechanistic model rather than as a synonym for the microscopic diagnosis.

The practical value of this distinction is interpretive. A pathologic finding matters because of what it contains, where it occurs, how widely it has spread and what other processes accompany it. The same discipline prevents two common errors: assuming that every lesion has the same spatial progression, and treating one proposed causal chain as if it made the rest of the pathology redundant.

LESION	MAP	SYSTEM	MODEL
IDENTIFY THE STRUCTURE	FOLLOW ITS SPREAD	TRACE CIRCUIT LOSS	TEST THE CAUSAL CLAIM

5.1 The two signature lesions are not the same map

Amyloid plaques are the defining lesion in the standard neuropathologic account. They consist of insoluble deposits of fibrillar amyloid-beta, with dystrophic neurites, microglial cells and reactive astrocytes arranged around the deposit. **Neurofibrillary tangles**, by contrast, are intracellular inclusions. Their paired helical filaments contain aggregated, hyperphosphorylated microtubule-associated tau protein. Composition already gives the first conceptual separation: one lesion is organised around fibrillar amyloid-beta deposition, while the other reflects abnormal tau aggregation within neurons.

The second separation is topographic. Plaques first appear widely through the neocortex and are found later in the entorhinal cortex and hippocampus, followed by subcortical regions. Tangles begin in the entorhinal cortex, extend to the hippocampus and lateral temporal lobe, and only then become widespread through the neocortex. Thus, “early Alzheimer pathology” is incomplete unless the candidate states which lesion is being mapped.

AXIS	AMYLOID PLAQUE	NEUROFIBRILLARY TANGLE
Basic structure	Insoluble fibrillar amyloid-beta deposit with surrounding dystrophic neurites and glial reaction	Intracellular inclusion containing paired helical filaments of aggregated hyperphosphorylated tau
Earliest distribution	Neocortex	Entorhinal cortex
Subsequent spread	Entorhinal cortex and hippocampus, then subcortical regions	Hippocampus and lateral temporal lobe, then wider neocortex
Diagnostic caution	Defining lesion in this pathologic account	Not pathognomonic, because tangles are also the principal lesion in MAPT-related frontotemporal dementias

MNEMONIC

A-N, T-E

Amyloid begins in the **N**eocortex; **T**au begins in the **E**ntorhinal cortex. The letters prevent the classic reversal, while the full spread sequence still needs to be understood.

RULE **Always name the lesion before describing its spread.** Neocortex-first describes the plaque map; entorhinal-first describes the tangle map.

5.2 Gross progression and the regional burden of neuronal loss

Macroscopic progression does not become conspicuous at the same moment as microscopic disease. In early Alzheimer disease, the brain may look grossly normal, or atrophy may be confined to the hippocampus. One macroscopic clue to hippocampal volume loss is enlargement of the inferior horn of the lateral ventricle. This observation matters because a subtle gross specimen does not negate an active microscopic process.

With progression, the macroscopic pattern becomes more evident: cortical sulci widen and the ventricles enlarge. Atrophy is often particularly prominent in posterior temporal, parietal and frontal lobes. These findings express tissue loss at the organ level; they should not be used to collapse the distinct plaque and tangle sequences into a single map.

At the cellular level, **neuronal loss** is most marked in the entorhinal cortex and hippocampus. This regional emphasis helps explain why the medial temporal system is central to the pathologic narrative even though amyloid plaques are described as appearing first across neocortex. The lesion that appears first, the region with greatest neuronal loss and the structure most closely aligned with cognitive evolution need not be identical constructs.

Later disease also involves neurotransmitter systems. Cholinergic neurons in the nucleus basalis are lost, and brainstem noradrenergic and serotonergic neurons are affected. The pathology therefore expands from local tissue injury to disconnection of projection systems. This is the

bridge from morphologic description to neurochemical models: circuit failure is real, but it does not by itself identify the initiating event.

GOOD TO REMEMBER

When shown a gross specimen, describe what is visible before inferring cause: hippocampal atrophy and inferior-horn enlargement may be early clues; later, widened sulci, ventricular enlargement and distributed lobar atrophy become clearer.

5.3 Tau staging: an ordered account of neurofibrillary spread

Braak and Braak staging organises neurofibrillary change by its anatomic reach. The sequence is **stages I-II, transentorhinal; stages III-IV, limbic; and stages V-VI, isocortical or neocortical**. It is a staging system for neurofibrillary pathology, not a relabelling of the plaque sequence. Its educational value lies in converting a static slide into an evolving regional process and thereby supporting an anatomic understanding of changing cognitive deficits.

Photomicrographic comparisons make the burden dimension concrete. In **stage VI, plaques and tangles are extensive throughout the neuropil, whereas stage IV shows some tangles with substantially less neurofibrillary pathology in the neuropil**. The comparison preserves direction: the more advanced stage carries the heavier and more widespread pathologic burden. Isolated tangles in the entorhinal cortex without plaques can also be seen in normal ageing. Their presence alone cannot therefore be read as a complete Alzheimer pattern.

Two interpretive boundaries follow. First, staging is about distribution and burden, not merely whether a tangle can be found. Second, a tangle is not uniquely diagnostic of Alzheimer disease. MAPT-related frontotemporal dementias also have tangles as their principal lesion. The diagnosis therefore depends on the configuration of lesions and regions, not on a decontextualised microscopic label.

TRAP **Do not write that plaques and tangles both begin in the hippocampus.** The hippocampal and entorhinal emphasis in neuronal loss can seduce candidates into assigning the same starting point to both lesions.

5.4 Additional lesions and co-pathology

Real brains need not display a chemically pure single-protein disorder. **Alpha-synuclein co-pathology** may be detected in **up to 50%** of individuals with Alzheimer disease. It most commonly appears as thread-like deposits or intraneuronal Lewy bodies in the amygdala and transentorhinal cortex, although Lewy bodies may also occur in neocortex. The correct lesson is heterogeneity of pathologic burden, not automatic reassignment of the clinical diagnosis.

Other microscopic findings include **granulovacuolar degeneration and Hirano bodies**. They most commonly affect pyramidal neurons in the hippocampus and may occur in Alzheimer disease. These findings enrich the neuropathologic description but should remain subordinate to the central organisation of plaques, tangles, regional neuronal loss and projection-system involvement.

This layered view also improves clinicopathologic reasoning. A patient may have a dominant Alzheimer pattern with additional protein aggregation. Conversely, finding one ancillary lesion does not tell the examiner how much amyloid deposition, tau spread or neuronal loss is present. The disciplined report separates dominant pattern, stage and co-pathology instead of forcing every observation into an all-or-none label.

PITFALL

A pathology report that mentions Lewy bodies alongside Alzheimer lesions is not self-interpreting. Do not ignore the co-pathology, but do not replace the dominant diagnosis solely because an additional inclusion is present; distribution and overall burden remain essential.

5.5 The cholinergic account: strong neurochemical basis, limited causal reach

A transmitter deficit can explain impairment without explaining the whole disease. The **cholinergic hypothesis** rests on converging neuropathologic and neurochemical observations: a major decline in basal-forebrain cholinergic projections to cortex, reduced choline acetyltransferase activity and marked loss of cholinergic cell bodies in the nucleus basalis. Reductions in enzyme activity and nucleus-basalis integrity correlate with cortical neuritic plaque density, and cholinergic deficits correlate with poorer cognitive-test performance.

The model therefore has genuine explanatory force. It connects a defined projection system, a measurable neurochemical deficit, cortical pathology and cognitive performance. It also supplies a rational bridge between tissue pathology and symptomatic impairment. Yet correlation between circuit loss and cognitive deterioration does not, by itself, establish that cholinergic depletion initiated the entire disease process.

The later formulation is appropriately narrower: progressive loss of cholinergic neurons and falling acetylcholine levels contribute to cognitive deterioration, but cholinergic depletion alone is no longer regarded as sufficient to account for all Alzheimer symptoms. Nor is the cholinergic system the only network affected. Noradrenergic projections from the locus ceruleus to cortex and glutamate systems are also involved, alongside the serotonergic and other brainstem losses described in the neuropathology.

This is why the cholinergic account should not be set against every molecular process as an exclusive rival. It addresses an important level of the disease, namely transmitter and projection-system failure. Amyloid production and deposition, tau phosphorylation, inflammatory responses and neuroprotective processes address more fundamental questions about how neurodegeneration develops and propagates.

5.6 The amyloid cascade: from precursor processing to tissue injury

The amyloid cascade hypothesis proposes a causal sequence rather than simply naming a lesion. Faulty processing of amyloid precursor protein generates neurotoxic amyloid-beta fragments. These fragments are then placed upstream of neurodegeneration and other hallmarks of Alzheimer pathology, including phosphorylated tau aggregation and synaptic loss. The

strength of the model is its attempt to connect molecular processing, deposited protein, cellular reaction and downstream structural injury in one chain.

In the classical processing account, amyloid precursor protein is cleaved by alpha-, beta- and gamma-secretases. Alpha-secretase cleavage yields a nontoxic metabolite. The alternative sequence, beta-secretase followed by gamma-secretase, produces **amyloid-beta 42**, described as relatively insoluble. It fibrillises into diffuse plaques, provokes an inflammatory response and is neurotoxic. Proposed downstream effects include axonal breakdown, the formation of neuritic plaques and neurofibrillary-tangle formation in surviving neurons.

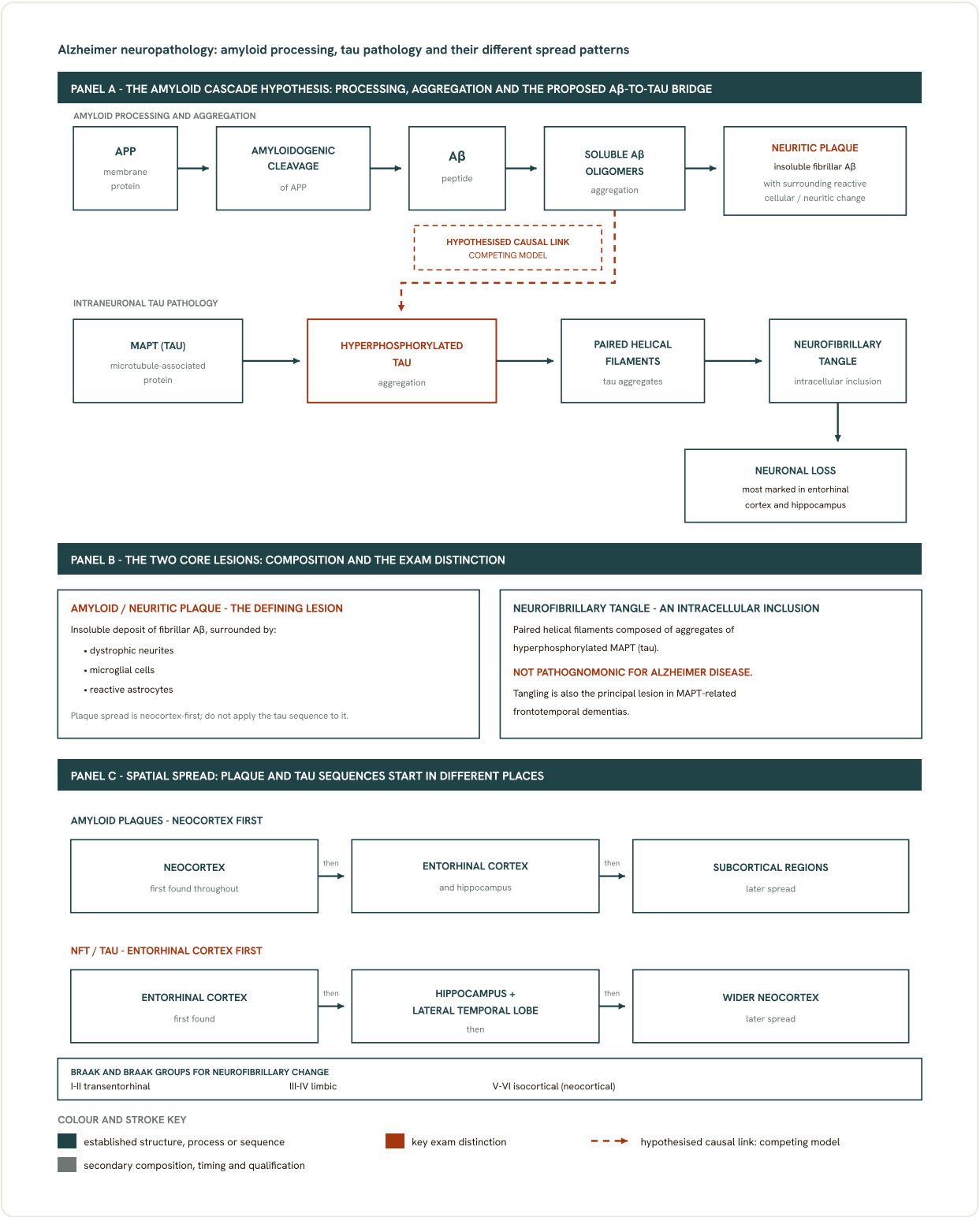

Fig 32.2 **Alzheimer neuropathology and the amyloid cascade hypothesis.** APP processing and Aβ aggregation are shown above tau hyperphosphorylation, paired helical filaments and neurofibrillary tangles. The lower panel keeps the neocortex-first amyloid plaque sequence separate from the entorhinal-first tau sequence. (Kaplan & Saddock's CTP 2024; Hodges, Cognitive Assessment for Clinicians.)

The accompanying figure should be read as a directional hypothesis. It begins with processing of the precursor protein, separates the nontoxic route from the amyloid-producing route, and follows the latter toward aggregation, inflammation and neuronal injury. Its arrows express proposed causal ordering. They do not mean that every downstream process is passive, that all

lesions share the same anatomic spread, or that pathology can be inferred from a single node in isolation.

The word “cascade” is useful precisely because it invites questions at each link. Is the relevant fragment generated? Does it remain soluble or aggregate? Does aggregation recruit glial and inflammatory responses? How are axonal and synaptic injury related to tau change? A high-quality account states the sequence, then examines the evidence and the limitations rather than repeating the pathway as settled dogma.

5.7 Why amyloid was placed upstream

Several observations are used to support an upstream role for amyloid precursor processing. They are best treated as converging lines of evidence, not as interchangeable proofs. Their relevance here is mechanistic; the broader epidemiology, penetrance and counselling implications belong to the dedicated section on Alzheimer epidemiology, risk factors and genetics.

- People with Down syndrome who survive past 40 years almost always develop Alzheimer disease in the cited account, linked to an extra copy of the APP gene.
- Rare inherited Alzheimer disease can result from mutations in APP, directly connecting altered precursor biology with disease.
- Presenilin interacts with gamma-secretase, while rare inherited disease is associated with presenilin 1 or presenilin 2 mutations.
- The epsilon-4 form of apolipoprotein E increases the rate of beta-amyloid production in the cited mechanistic account.

Taken together, these observations connect gene dosage, rare pathogenic variants, secretase-associated biology and a susceptibility-associated apolipoprotein form with amyloid production or processing. The inference is that amyloid biology is not merely an incidental end product of dying tissue. However, support for an upstream role does not establish that amyloid alone determines the pace, topography or clinical expression of late-onset disease.

The causal claim should therefore be stated with correct scope. Genetic observations strongly motivate the pathway, especially where precursor processing is directly altered. They do not license the candidate to substitute a genetics essay for neuropathology, nor to assume that every sporadic case follows a simple single-gene logic. Mechanistic relevance and population-level determinism are different questions.

5.8 Tau, inflammation and the limits of a pure cascade

The major challenge is not whether amyloid belongs in Alzheimer pathology; it plainly does. The challenge is whether a simple amyloid-first chain is sufficient to explain the disease. Clinical trials of immunotherapies directed at amyloid-beta 1-42 have failed in the evidence base summarised by the source. Possible explanations include intervention after the disease process had become too advanced and enrolment of participants who did not actually have amyloid pathology. These possibilities preserve the hypothesis from a premature dismissal, but they also expose how strongly trial interpretation depends on timing and biologic selection.

Late-onset Alzheimer disease is consequently better approached as complex. The molecular links within the cascade require fuller explanation, and associated processes, especially inflammation, need attention. The glial reaction around plaques and the inflammatory response provoked in the processing model are not decorative histology. They indicate that deposited protein interacts with surrounding tissue and that injury may be mediated through more than direct peptide toxicity.

Tau-mediated injury also has active mechanistic significance. Amyloid-beta contributes to hyperphosphorylation of microtubule-associated tau, promoting its aggregation into neurofibrillary tangles. Once established, tau pathology causes synapse loss and neuronal death independently of amyloid-beta effects. Tau is therefore not merely a passive stain recording prior amyloid injury; it can carry damaging consequences of its own.

The resulting model is neither a rejection of the cascade nor an excuse to label every process an independent hypothesis. Amyloid production and deposition, tau phosphorylation and aggregation, inflammation, synaptic loss, neuronal death and transmitter-system failure occupy related but distinguishable levels. A useful synthesis asks what each level explains and where causal certainty weakens.

EXPLANATORY LEVEL	WHAT THE EVIDENCE SUPPORTS	WHAT MUST NOT BE OVERCLAIMED
Cholinergic deficit	Projection loss, reduced choline acetyltransferase activity and association with cognitive performance	Cholinergic depletion alone does not account for the whole syndrome
Amyloid cascade	Faulty precursor processing is placed upstream of toxic fragments, neurodegeneration, phosphorylated tau aggregation and synaptic loss	A simple late-onset model is challenged by treatment failures, timing problems and biologic complexity
Tau process	Amyloid-beta promotes tau hyperphosphorylation and aggregation; tau can then drive synaptic and neuronal injury independently	Tau should not be reduced to a passive downstream marker
Multiple-system degeneration	Amyloid deposition, tau phosphorylation, inflammation and several transmitter systems are implicated	No single transmitter deficit should be mistaken for the complete pathogenesis

5.9 An integrated answer for pathology and pathogenesis

The final synthesis should move from observation to inference in a fixed order. Begin with the gross brain: it may be normal-looking early, may show hippocampal atrophy with inferior-horn enlargement, and later shows wider cortical and ventricular change. Move next to the core microscopic lesions, keeping plaque composition and neocortex-first spread separate from tangle

composition and entorhinal-first spread. Then add regional neuronal loss, neurotransmitter-system degeneration and the possibility of ancillary lesions or co-pathology.

Only after that description should pathogenesis be introduced. The cholinergic account explains a clinically important projection-system deficit but not the entire disease. The amyloid cascade places abnormal precursor processing and neurotoxic amyloid fragments upstream. Tau aggregation, inflammatory responses and synaptic injury then complicate any purely linear reading, especially because tau can cause further loss independently of amyloid-beta.

This structure also keeps adjacent chapter material in its proper place. Neuropathology does not require a detour into diagnostic criteria, biomarker cut-offs, imaging physics, current antibody regimens or symptomatic drug doses. Those subjects use the pathology developed here, but they answer different questions. The pathology section asks what is in the brain, where it spreads and how the proposed molecular sequence relates to the observed injury.

A concise conclusion can therefore be both balanced and decisive: Alzheimer disease has characteristic amyloid and tau pathology with different spatial trajectories, accompanied by selective neuronal and projection-system loss. The amyloid cascade offers a powerful upstream framework, supported by processing and genetic observations, but the mature model must accommodate active tau toxicity, inflammation, co-pathology and multisystem neurodegeneration.

> Memorise the separation: amyloid plaques begin in neocortex, neurofibrillary tangles begin in entorhinal cortex, and the amyloid cascade is a causal hypothesis that must be integrated with active tau injury, inflammation and transmitter-system loss.

6 · Alzheimer's disease: clinical staging, diagnostic criteria and management

Why it matters clinically. Alzheimer's disease is not recognised by a single forgotten appointment, a single low screening score, or an image interpreted in isolation. The examiner expects a coherent account that moves from the characteristic clinical trajectory to the neurocognitive syndrome, establishes the likely aetiology, grades diagnostic certainty, and then links the stage to a proportionate care plan. It separates preserved ability from expected progression.

The central idea is progression with changing cognitive and functional emphasis. Early disease may be dominated by an amnestic syndrome while ordinary self-care remains intact. Dementia becomes the appropriate syndrome label when cognitive decline interferes with independent functioning. Later, multiple cognitive domains, behaviour, mobility, continence, communication, and physical dependence become involved. Atypical presentations complicate recognition but do not abolish the need to demonstrate a compatible progressive course and exclude a better explanation.

Memory	Function	Course	Care
EARLY SIGNAL	SYNDROME BOUNDARY	DIAGNOSTIC WEIGHT	STAGE MATCHED

6.1 The clinical trajectory and the meaning of stage

A useful bedside model describes a predictable progression through **three stages**: mild cognitive impairment, mild-to-moderate dementia, and advanced dementia. The model is clinical rather than merely chronological. It asks which cognitive systems are failing, whether everyday independence is preserved, which neuropsychiatric and physical problems have appeared, and how much supervision is now required. It also corrects a common misconception: typical Alzheimer's disease does not begin as simultaneous global intellectual failure.

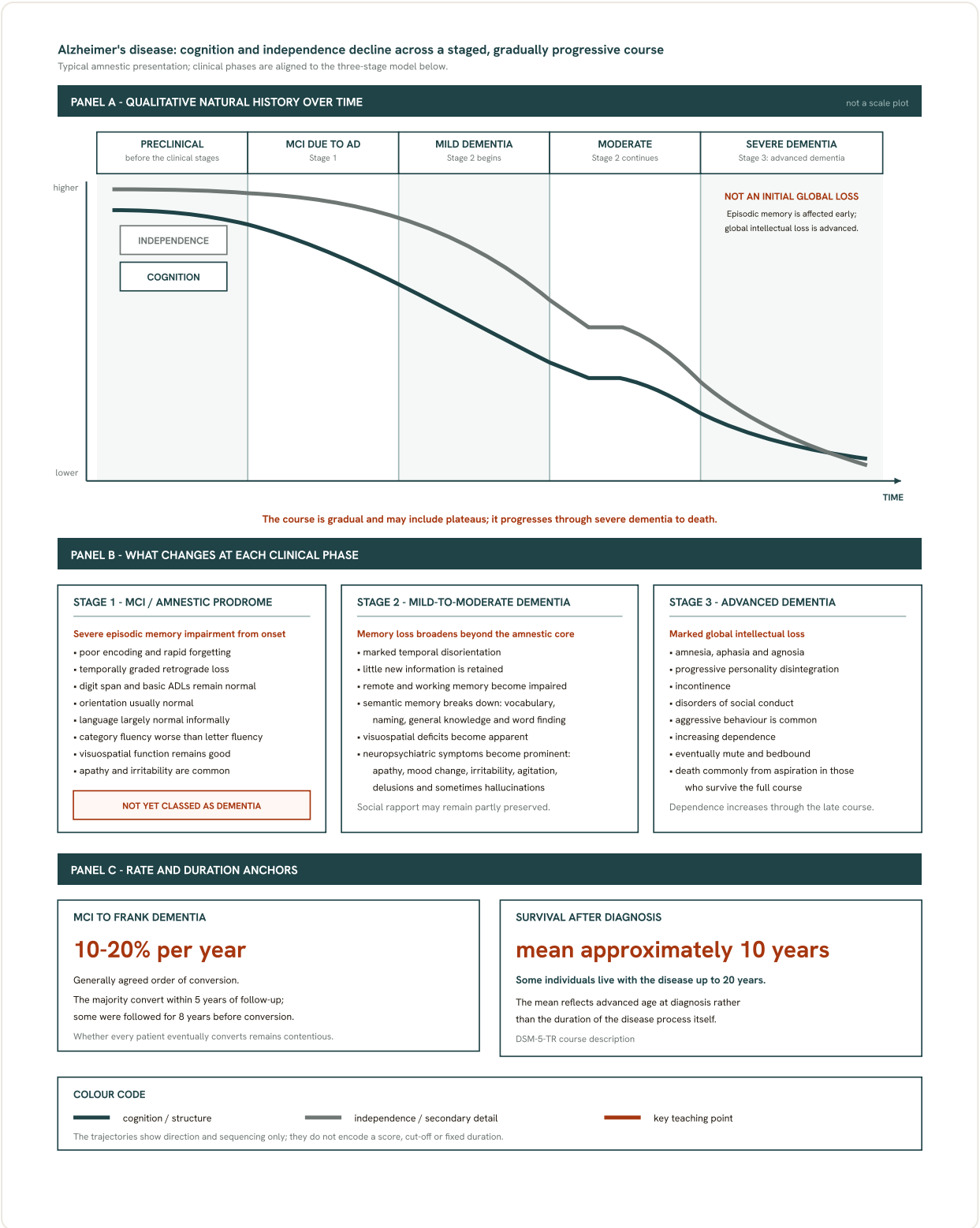

Fig 32.3 Natural history of typical Alzheimer's disease. Cognitive decline begins before major functional dependence, progresses from the amnestic MCI prodrome through mild-to-moderate dementia, and culminates in advanced global impairment and dependence.

The accompanying figure should be read as a continuum rather than a set of sealed compartments. Cognitive decline and functional loss do not move in perfect lockstep. A highly supported patient may appear functionally better than the underlying impairment suggests, while sensory loss, low education, physical illness, depression, or an unfamiliar testing context can make performance look worse. Staging therefore needs history from the patient and a

reliable informant, direct cognitive examination, and a functional account grounded in the person's usual roles.

RULE **Stage the person by cognition plus function, not by a score alone.** The clinically decisive question is whether decline has crossed from preserved independence into dependence, and which new risks that transition creates.

Preclinical biological change, symptomatic mild cognitive impairment, and dementia can be represented along a unified natural-history line, but they are not interchangeable diagnostic labels. Biological evidence can increase confidence about aetiology; it does not replace the clinical description of the person's current syndrome. Conversely, an apparently normal brief screen does not neutralise a convincing history of selective episodic-memory failure in the prodromal phase.

6.2 The staged clinical phenotype

CLINICAL STAGE	COGNITIVE PROFILE	FUNCTION AND BEHAVIOUR	INTERPRETIVE POINT
Stage 1: mild cognitive impairment	Severe episodic-memory impairment is present from the outset, with poor encoding, rapid forgetting, anterograde amnesia, and a temporally graded retrograde loss. Orientation is usually preserved. Informal language and visuospatial performance may remain largely satisfactory, although category fluency may be weaker than letter fluency.	Basic activities of daily living remain normal. Apathy and irritability may appear, but loss of functional independence is not yet sufficient for dementia.	A normal brief cognitive screen does not exclude this selective amnestic prodrome. General administration and scoring of cognitive screens belong in the Psychometry, Assessment and Descriptive Psychopathology notes.
Stage 2: mild-to-moderate dementia	Worsening memory and attention produce marked temporal disorientation and poor retention of new information. Remote and working memory become impaired. Semantic breakdown produces reduced vocabulary, word-finding difficulty, semantic paraphasias, impaired naming, and loss of general knowledge. Visuospatial deficits become evident.	Neuropsychiatric symptoms become more prominent, including apathy, mood disturbance, irritability, agitation, delusions, and sometimes hallucinations. Social rapport may remain partly preserved.	The syndrome is no longer a circumscribed memory complaint. Cognitive decline now compromises everyday functioning and spreads across domains.
Stage 3: advanced dementia	There is marked global loss, with amnesia, aphasia, and agnosia. Communication may ultimately be lost.	Personality disintegrates progressively. Incontinence, disordered social conduct, aggressive behaviour, immobility, and increasing dependence become prominent.	Management priorities shift toward comfort, prevention of avoidable suffering, carer support, and anticipatory planning.

The early memory disorder is not merely inefficient retrieval. Poor encoding and rapid forgetting mean that cues may provide limited rescue, and the patient cannot reliably retain the substance of a conversation. This explains repeated questions, missed arrangements, and loss of newly learned routes even when social manner, vocabulary, and simple attention look deceptively intact. As disease advances, failure of semantic knowledge, visuospatial processing, and executive control progressively changes both test performance and real-world competence.

GOOD TO REMEMBER

Ask for an example of lost independence, not only a list of cognitive symptoms. Errors in medication use, money management, navigation, cooking, communication, or occupational tasks often define the syndrome transition more clearly than a total screening score.

6.3 Atypical Alzheimer's disease and diagnostic flexibility

The amnestic presentation is the majority pattern, but Alzheimer's pathology can first become clinically visible through another network. The principal atypical variants include language-led and posterior cortical presentations. **Logopenic progressive aphasia** presents with word-finding hesitancy and pauses, phonological errors, and reduced digit or sentence span. Knowledge of word meaning is relatively intact, while apraxia of speech and agrammatism are absent. The language phenotype therefore reflects impaired access and phonological working memory rather than early loss of semantic knowledge or motor-speech programming.

Posterior cortical atrophy begins with higher visual and visuospatial difficulty. The patient may become lost in unfamiliar surroundings or struggle to reach and grasp accurately. Posterior cortical atrophy may be visible on structural imaging, while memory, language, and insight remain relatively preserved early. Severe progression may produce functional blindness. A rarer frontal-predominant presentation can feature apathy without the severe early amnesia expected in the typical form.

The practical lesson is not to force every patient into an amnestic template. A progressive focal cortical syndrome may still be due to Alzheimer's disease, but its first deficit should be documented precisely and competing neurodegenerative, vascular, structural, psychiatric, sensory, and systemic explanations considered. Imaging may support the anatomical pattern, while the physics and general interpretation of imaging modalities are covered in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

TRAP **"Memory is not the presenting complaint, so this cannot be Alzheimer's disease."** That statement misses language-led and posterior cortical presentations. State the dominant network syndrome first, then judge whether its course and aetiological evidence support Alzheimer's disease.

6.4 Conversion, progression and prognosis

For amnestic mild cognitive impairment, a generally accepted conversion estimate is **10-20% per year**. The majority who convert do so during longitudinal follow-up, although later conversion occurs and it remains contentious whether every patient will eventually develop dementia. This uncertainty matters when counselling. Mild cognitive impairment is a risk state and a clinical syndrome, not a promise of inevitable dementia in a particular individual.

Published conversion figures vary because clinical referral samples, community cohorts, definitions, ascertainment, and duration of follow-up differ. The correct interpretation is therefore not to transplant a study-specific proportion into an individual prognosis. Instead, communicate that risk is meaningfully increased, arrange longitudinal review, and reassess both

cognition and function. Change within the same person is usually more informative than a single isolated performance.

Once major or mild neurocognitive disorder due to Alzheimer's disease is established, the course is generally gradual and progressive, although plateaus may occur. Mean survival after diagnosis is approximately **10 years**, and some people live much longer. The estimate is shaped strongly by the advanced age at which diagnosis is often made and should not be presented as a countdown. In the late phase, patients may become mute and bedbound; among those who survive the full course, aspiration is the commonest terminal event.

Prognostic conversation should therefore be staged and revisited. Early discussion concerns uncertainty, preserved abilities, adaptation, safety, and future preferences. With increasing dependence, the focus expands to supervision, caregiver capacity, behavioural symptoms, swallowing and mobility problems, burdens of intervention, and goals of care. The point is preparedness without therapeutic nihilism: progression is expected, but suffering, unsafe care, and unsupported carers are not inevitable consequences that must simply be accepted.

6.5 Diagnostic architecture: syndrome, course, cause and exclusion

Diagnosis works best as a layered argument. First establish a major or mild neurocognitive syndrome and describe the domains affected. Next show an insidious onset and gradual progression. Then decide how strongly the clinical and available biological evidence attributes the syndrome to Alzheimer's disease. Finally, test whether vascular disease, another neurodegenerative disorder, substance effects, or another mental, neurological, or systemic disorder explains the presentation better.

MNEMONIC

Syndrome, Slope, Source, Substitutes

Syndrome identifies mild or major neurocognitive disorder; **Slope** establishes insidious progressive change; **Source** estimates the likelihood of Alzheimer's disease; **Substitutes** are competing or mixed explanations that must be actively examined.

This architecture prevents opposite errors. Premature aetiological closure labels an older patient with forgetfulness as having Alzheimer's disease before delirium, depression, medication effects, sensory limitations, or systemic illness have been considered. Endless exclusion without positive formulation lists normal investigations but never describes the characteristic course, cognitive profile, or functional consequence. The workup for reversible causes and rapidly progressive presentations is covered elsewhere in this chapter; delirium in full belongs in the Stroke, TBI, delirium and focal brain syndromes notes.

- Obtain a longitudinal history from the patient and a knowledgeable informant, anchored to change from previous ability.
- Describe affected cognitive domains and the consequences for instrumental and basic activities rather than relying on a global label.

- Look for atypical, focal, fluctuating, abrupt, stepwise, toxic, systemic, or neurological features that weaken a straightforward Alzheimer's formulation.
- State whether the evidence supports a pure aetiology, a mixed aetiology, or continuing diagnostic uncertainty.

PITFALL

Do not turn a biomarker or scan into the whole diagnosis. A positive biological signal addresses aetiology; the clinician must still define the current syndrome, functional impact, alternative contributors, capacity, risk, and care needs.

6.6 International diagnostic formulation

Under **ICD-11 6D80**, all diagnostic requirements for dementia must be met and the dementia must be presumed attributable to underlying Alzheimer disease. Attribution may draw on quantified clinical assessment or standardised cognitive or neuropsychological testing, neuroimaging, genetic testing, medical tests, family history, and clinical history. The neurological Alzheimer disease diagnosis is also assigned. This makes the distinction between the dementia syndrome and its underlying disease explicit.

The typical additional clinical description is gradual onset with progressive memory difficulty, word-finding difficulty, and mild functional impairment. The syndrome broadens as other brain regions are affected. Atypical forms express the function of the initially affected region, such as early visual-processing impairment in posterior cortical atrophy.

SUBTYPE	CLINICAL MEANING	USE
Early onset	Symptoms are present before **65 years**.	Early-onset dementia due to Alzheimer disease.
Late onset	Symptoms are present at or after the same age boundary.	Late-onset dementia due to Alzheimer disease.
Mixed with cerebrovascular disease	Alzheimer disease dementia co-exists with cerebrovascular disease.	Mixed vascular subtype.
Mixed with another nonvascular aetiology	Alzheimer disease dementia co-exists with another nonvascular aetiology.	Mixed nonvascular subtype.
Onset unknown or unspecified	Onset cannot be established reliably.	Use when onset cannot be classified more precisely.

In an examination answer, begin with the dementia syndrome, then give the presumed aetiology and the most defensible onset or mixed subtype. Do not use “mixed” as a synonym for uncertainty. It is a positive formulation that multiple pathological processes contribute materially to the cognitive syndrome.

6.7 Cross-mapping diagnostic certainty

The **DSM-5-TR** structure begins by requiring criteria for major or mild neurocognitive disorder. It then requires insidious onset and gradual progression across the affected cognitive domain or domains; major neurocognitive disorder requires impairment in at least **two domains**. The clinician next decides between probable and possible Alzheimer's disease and confirms that cerebrovascular disease, another neurodegenerative disease, substances, or another mental, neurological, or systemic disorder does not explain the disturbance better.

For major neurocognitive disorder, **probable Alzheimer's disease** is supported either by evidence of a causative mutation from family history or genetic testing, or by the complete clinical pattern: clear decline in memory and learning plus another cognitive domain, steady gradual progression without extended plateaus, and no evidence of mixed aetiology. If that standard is not met, the diagnosis is possible Alzheimer's disease.

For mild neurocognitive disorder, the certainty threshold is deliberately stricter. Probable Alzheimer's disease requires evidence of a causative mutation. Without such evidence, clear memory and learning decline, steady gradual progression without extended plateaus, and absence of mixed aetiology support **possible Alzheimer's disease**, not probable disease. The distinction reflects uncertainty about future progression at the mild stage and is a favourite source of reversed answers.

The **ICD-10-CM cross-map** in the diagnostic manual should follow the manual actually being used. Where examinations still use this older coding frame, do not substitute its coding logic for the primary international formulation. For major neurocognitive disorder due to probable or possible Alzheimer's disease, code Alzheimer disease first and then distinguish the presence or absence of behavioural disturbance; severity is recorded but not separately coded. Mild neurocognitive disorder due to Alzheimer's disease uses the mild-neurocognitive-disorder code without an additional Alzheimer disease code. The behavioural-disturbance suffixes are not reproduced here because the available source was corrupted at those characters.

6.8 Biomarker frameworks: what they add and what they do not

The approach to mild cognitive impairment due to Alzheimer's disease separates **Core Clinical Criteria**, intended for broad clinical use without highly specialised tests, from Clinical Research Criteria that incorporate biomarkers and are intended for research settings, academic centres, and clinical trials. Biomarkers are not part of the DSM mild-neurocognitive-disorder criteria described above. This is an important boundary between a clinical diagnostic manual and a research framework.

The **AT(N) framework** classifies biomarkers by the pathological process they represent. “A” denotes aggregated amyloid-beta measured through cerebrospinal-fluid amyloid measures or amyloid imaging. “T” denotes aggregated tau measured through phosphorylated tau in cerebrospinal fluid or tau imaging. “(N)” denotes neurodegeneration or neuronal injury assessed through anatomical imaging, glucose-metabolism imaging, or total tau in cerebrospinal fluid. Parentheses around N signal that neurodegeneration is not specific to Alzheimer's pathology.

Profiles are then interpreted biologically: absence of abnormal A, T, and N markers is a normal Alzheimer-biomarker profile; abnormal A alone indicates Alzheimer pathological change; abnormal A and T constitute Alzheimer's disease biologically, with N indicating whether measurable neurodegeneration is also present. An abnormal N marker without abnormal A suggests a non-Alzheimer pathological change, while abnormal A with abnormal N but normal T suggests Alzheimer pathological change with a suspected concomitant non-Alzheimer process.

This framework is intellectually useful because it separates amyloid pathology, tau pathology, and downstream injury instead of treating “a positive biomarker” as a unitary entity. Clinically, however, one must still answer what syndrome the patient has, whether functioning is impaired, whether comorbidity contributes, and whether a test result will change counselling or treatment. Cerebrospinal-fluid sampling procedure belongs in the Neurology foundations for psychiatrists notes, while dementia-specific biomarkers are examined separately in this chapter.

6.9 Management as a stage-matched care system

Management is wider than prescribing. Use a LOCUS, FOCUS, and MODUS formulation. LOCUS asks whether care can remain outpatient, requires urgent assessment, or needs inpatient management because of acute behavioural risk, delirium, medical instability, unsafe wandering, inability to meet basic needs, or collapse of the care arrangement. FOCUS identifies the immediate target and then the medium- and long-term aims. MODUS ensures that medication, psychological adaptation, environmental change, rehabilitation, social support, carer work, legal and financial planning, and palliative goals are considered together.

At every stage, disclose the formulation sensitively, assess decision-making capacity for the decision at hand, identify a reliable caregiver or support network, review driving and other safety-critical activities, simplify routines, and treat remediable contributors to distress or poor performance. Preserve autonomy where it remains safe. The care plan should anticipate the next likely transition rather than waiting for a crisis to reveal that supervision, respite, or a different living arrangement is already needed.

For cognitive symptoms, cholinesterase inhibitors and memantine are the established symptomatic drug classes, selected according to severity, tolerability, comorbidity, and the applicable regulatory framework. Their dosing, titration, adverse effects, interactions, licensing bands, and stopping decisions are taught in the dedicated cognitive-enhancer section rather than duplicated here.

Disease-modifying anti-amyloid therapy requires separate assessment, biological confirmation, and monitoring. Lecanemab, donanemab, and aducanumab differ in evidence, regulatory history, administration, monitoring burden, and risk. Those protocols, efficacy estimates, and amyloid-related imaging abnormalities belong in the dedicated anti-amyloid section. They should never displace symptomatic treatment, vascular and general health care, psychosocial intervention, or support for the caregiver.

Behavioural and psychological symptoms require a formulation before a prescription: identify pain, fear, overstimulation, unmet needs, communication failure, medication effects,

environmental triggers, and superimposed medical illness. Begin with targeted non-pharmacological and environmental measures whenever the situation allows. Antipsychotic use is exceptional, risk-based, time-limited, and reviewed. Dementia-specific prescribing, together with stroke and mortality risk and the wider management of behavioural symptoms, is covered in the dedicated behavioural-symptom section. General antipsychotic pharmacology belongs in the Schizophrenia: management, antipsychotics and adverse effects notes.

In advanced disease, FOCUS shifts toward comfort, dignity, prevention of avoidable injury, feeding and swallowing decisions, pressure care, communication through familiar routines, and support for family grief and burden. Palliative principles can coexist with active treatment of distress. The final care plan should be explicit about who will respond to deterioration, where care is preferred, which interventions remain proportionate, and how carers can obtain urgent help.

> Diagnose the syndrome, demonstrate the progressive course, grade the certainty of Alzheimer's aetiology, exclude a better or mixed explanation, and match the care plan to function and risk.

7 · Dementia with Lewy bodies: core and supportive features and the one-year rule

The marks lie in classification, not in recognition alone. A patient with cognitive decline, vivid visual experiences, changing attention, dream enactment and parkinsonism may suggest dementia with Lewy bodies immediately. The higher-quality answer goes further. It establishes the essential dementia syndrome, separates core clinical features from supportive findings, distinguishes indicative from supportive biomarkers, applies the probable or possible threshold correctly, and then uses the temporal sequence of cognitive and motor symptoms to distinguish dementia with Lewy bodies from dementia arising in established Parkinson disease.

The central discipline is to keep different diagnostic frameworks apart. The current consortium model gives REM sleep behaviour disorder the same core status as the other core clinical features. The **DSM-5-TR framework** retains an older split in which REM sleep behaviour disorder is suggestive rather than core. Each framework can appear in examinations and clinical records. A safe answer therefore names the framework before counting features.

50-75%	ALMOST 85%	60-92%	AS HIGH AS 77%
FLUCTUATING COGNITION	COMPLEX VISUAL HALLUCINATIONS	SPONTANEOUS PARKINSONISM MAY OCCUR	REM SLEEP BEHAVIOUR DISORDER

7.1 Start with the essential syndrome

The essential feature is dementia: progressive cognitive decline severe enough to interfere with usual social or occupational functioning. This requirement prevents a collection of characteristic symptoms from being mistaken for a dementia diagnosis when everyday independence is not meaningfully affected. The core features refine the aetiologic diagnosis only after the cognitive syndrome has been established.

The cognitive profile may not begin as a classic amnestic presentation. Prominent or persistent memory impairment may be absent early and usually becomes evident as the disorder progresses. Attention, executive function and visuospatial ability may be especially impaired. Clinically, this means that a patient who struggles with spatial judgement, planning, mental tracking or sustained attention may have disabling cognitive decline even when relatives do not initially describe repetitive forgetting as the dominant problem.

This profile also explains why a brief memory-focused history can miss the syndrome. The interview should reconstruct performance across tasks: navigating familiar spaces, organising multistep activities, following a conversation through variable alertness, judging visual relationships and adapting when a rule changes. Functional decline remains the anchor. A low test performance without corroborated decline is not interchangeable with dementia, while apparently adequate recall does not exclude a disorder whose early burden lies elsewhere.

RULE **Establish dementia before classifying the Lewy-body pattern.** Core features and biomarkers determine diagnostic probability only after progressive, functionally significant cognitive decline has been demonstrated.

7.2 The four core clinical features

The current McKeith 2017 **DLB Consortium model** recognises **four** core clinical features: fluctuating cognition, recurrent well-formed visual hallucinations, spontaneous parkinsonism and REM sleep behaviour disorder. The accompanying figure provides the visual spine. The candidate should be able not only to name these features, but also to identify what makes each one diagnostically characteristic.

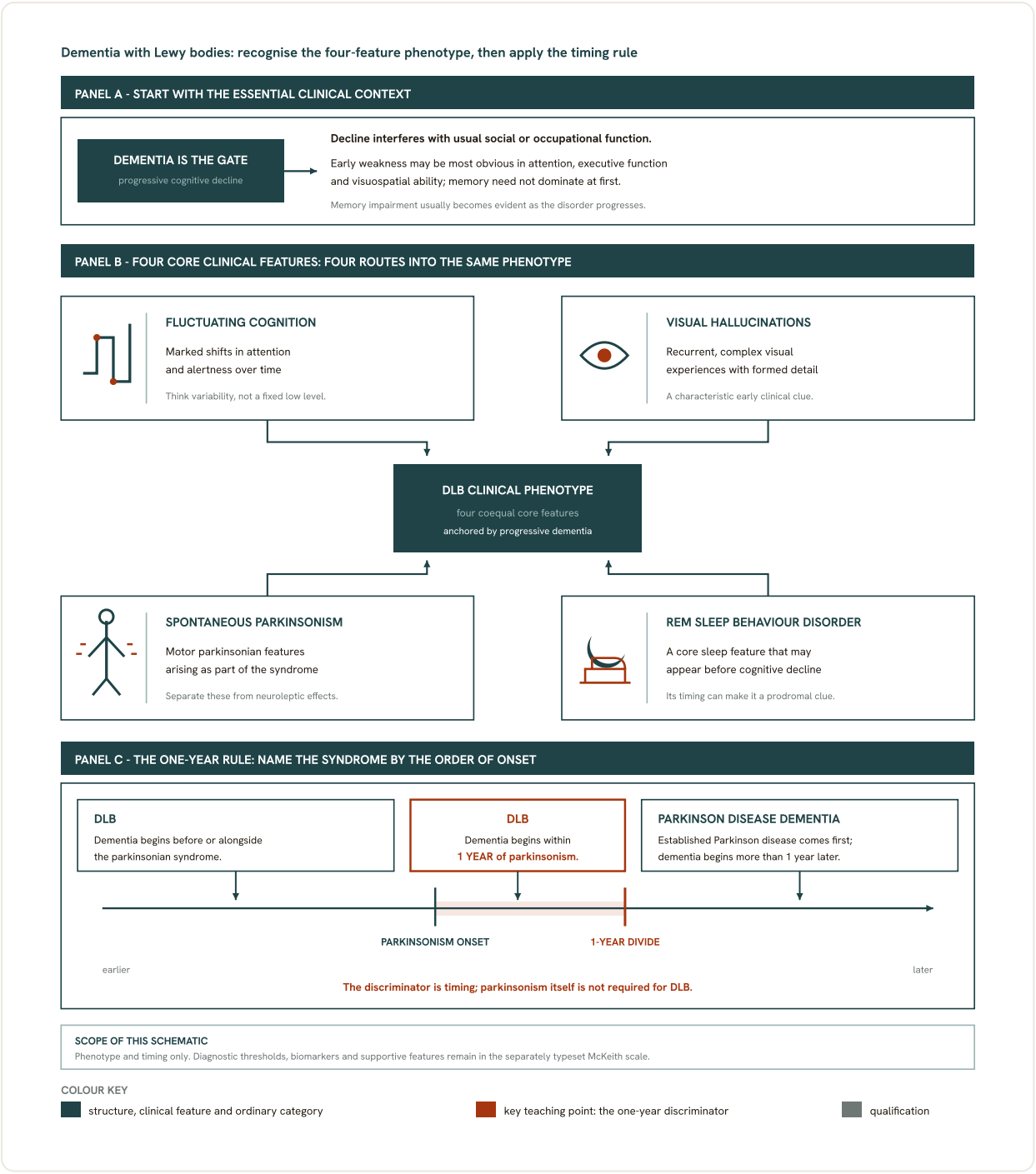

Fig 32.4 **Dementia with Lewy bodies: four core clinical features and the one-year rule.** Progressive dementia provides the clinical context; fluctuating cognition, formed recurrent visual hallucinations, spontaneous parkinsonism and REM sleep behaviour disorder form the core phenotype. The relative timing of dementia and parkinsonism separates dementia with Lewy bodies from Parkinson disease dementia. Adapted conceptually from the DLB Consortium fourth consensus report (McKeith et al., *Neurology* 2017;89:88-100).

Fluctuating cognition refers to pronounced variation in attention and alertness. It is not simply a good morning followed by a tired evening, nor the understandable variability produced by effort, anxiety or poor sleep. The diagnostically useful history describes conspicuous changes in engagement, coherence or responsiveness over time. Collateral history is crucial because the patient may not recognise the contrast, and the clinic encounter may capture either the clearer or the impaired state.

Recurrent complex visual hallucinations are typically vivid, colourful, well formed, three-dimensional and silent, often depicting people, children or animals. They are usually recognisable scenes or figures rather than vague visual distortion. Their recurrence, detail and early presence support the pattern. This phenomenology should be elicited neutrally: ask what the person sees, how formed the image is, whether it moves or speaks, how often it returns and how convinced the person is that it is present. In dementia with Lewy bodies these hallucinations tend to occur early, whereas hallucinations in Alzheimer disease are generally a later complication.

Spontaneous parkinsonism means motor parkinsonian features arising as part of the illness rather than as an adverse effect of dopamine-blocking treatment. The distinction is essential because neuroleptic-induced extrapyramidal signs can falsely create an apparently core feature. Parkinsonism is not mandatory: up to 25% of people with probable neurocognitive disorder with Lewy bodies may never develop extrapyramidal signs. Absence of the motor syndrome therefore does not cancel a diagnosis supported by the remaining clinical and biomarker pattern.

REM sleep behaviour disorder is dream enactment associated with loss of normal REM sleep atonia. It may precede cognitive decline and often begins several years before the dementia syndrome; it is likely to be a common prodromal feature. Ask the bed partner about purposeful or defensive movements during dreams, not merely restless sleep. When the history is uncertain, polysomnographic demonstration of REM sleep without atonia serves as an indicative biomarker rather than relying on description alone.

MNEMONIC

F-V-P-R

Fluctuating cognition, **V**isual hallucinations, spontaneous **P**arkinsonism and **R**EM sleep behaviour disorder form the current consortium core. The mnemonic is a recall frame; the marks come from describing the characteristic form of each feature.

7.3 Supportive clinical features: persuasive, but unweighted

Supportive clinical features strengthen pattern recognition and often dominate practical risk, but they carry no formal diagnostic weighting in the consortium algorithm. This distinction is easy to lose because some supportive findings are striking. They matter to assessment and care, yet they cannot be added together as if they were core features or indicative biomarkers.

- Severe sensitivity to antipsychotic agents, postural instability, repeated falls, syncope and other transient episodes of unresponsiveness are clinically consequential supportive features.
- Severe autonomic dysfunction broadens the history beyond cognition and movement; the symptom should be linked to functional risk rather than recorded as an isolated checklist item.
- Hypersomnia and hyposmia may support the overall syndrome but do not independently set its diagnostic probability.
- Hallucinations in other modalities, systematised delusions, apathy, anxiety and depression describe the neuropsychiatric breadth of the illness without acquiring core-feature status.

The absence of weighting does not mean absence of importance. Repeated falls, unresponsiveness and autonomic dysfunction can alter the urgency and setting of assessment. Antipsychotic sensitivity can change prescribing safety. The detailed management of neuroleptic sensitivity belongs to the dedicated section on dementia with Lewy bodies management, while general antipsychotic pharmacology belongs to the Schizophrenia: management, antipsychotics and adverse effects notes. Here, the diagnostic lesson is narrower: supportive findings enrich the phenotype but do not cross the threshold by arithmetic.

PITFALL

Do not count several supportive symptoms as equivalent to a core feature. A patient may have falls, autonomic symptoms, depression and delusions, yet the probable or possible category still depends on the specified combination of core features and indicative biomarkers.

7.4 Indicative and supportive biomarkers occupy different levels

Indicative biomarkers are reduced dopamine-transporter uptake in the basal ganglia on SPECT or PET, low cardiac uptake on iodine-labelled MIBG myocardial scintigraphy, and polysomnographic confirmation of REM sleep without atonia. They enter the probable or possible algorithm directly. They should be ordered to resolve a diagnostic question, not as decorative additions after the clinical pattern is already secure.

Dopamine-transporter imaging is especially useful when the motor examination does not clearly establish parkinsonism. In a meta-analysis of four studies involving 419 people, the cited SPECT method had **86.5% sensitivity and 93.6% specificity** for diagnosing dementia with Lewy bodies. The same source notes that the test is unnecessary once parkinsonism is well established clinically. This is a practical example of diagnostic restraint: a biomarker is most useful when it can materially change confidence, not merely repeat an obvious bedside finding.

For myocardial MIBG scintigraphy, a meta-analysis of eight studies involving 346 people reported 98% sensitivity and 94% specificity for differentiating dementia with Lewy bodies from other dementias. Such figures describe performance in the cited evidence base, not a substitute for examining the patient, checking competing explanations or applying the clinical criteria. Imaging physics and modality principles are covered in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

Supportive biomarkers include relative preservation of medial temporal structures on CT or MRI; generalised low perfusion or metabolism with reduced occipital activity, with or without a cingulate island sign on FDG-PET; and prominent posterior slow-wave EEG activity with periodic fluctuation in the pre-alpha or theta range. These findings support the pattern but carry no diagnostic weighting. The conceptual boundary mirrors the clinical one: “supportive” means coherent with the diagnosis, not numerically exchangeable with an indicative biomarker.

DIAGNOSTIC LAYER	WHAT BELONGS HERE	HOW IT IS USED
Essential syndrome	Progressive cognitive decline that interferes with social or occupational functioning	Required before probable or possible DLB is considered
Core clinical features	Fluctuation, recurrent well-formed visual hallucinations, spontaneous parkinsonism and REM sleep behaviour disorder	Directly determine diagnostic probability
Indicative biomarkers	Reduced basal-ganglia dopamine-transporter uptake, low myocardial MIBG uptake, or REM sleep without atonia	Directly enter the criteria in combination with the clinical pattern
Supportive clinical features	Sensitivity, falls, unresponsiveness, autonomic and sleep symptoms, other hallucinations, delusions and affective symptoms	No diagnostic weighting
Supportive biomarkers	Medial temporal preservation, occipital functional-imaging change, cingulate island sign or posterior slow-wave EEG activity	Support the pattern without diagnostic weighting
Factors against the diagnosis	Another physical or brain disorder sufficient to explain the picture, or parkinsonism first appearing only with severe dementia	Reduce diagnostic likelihood and force reconsideration

7.5 Converting evidence into probable or possible DLB

The consortium threshold is deliberately asymmetric. **Two** core clinical features are sufficient for probable dementia with Lewy bodies, whether or not an indicative biomarker is present. Probable DLB can also be diagnosed when one core clinical feature is accompanied by one or more indicative biomarkers. Indicative biomarkers alone cannot establish probable DLB. This last clause matters: strong biological support without a core clinical expression remains below the probable threshold.

One core clinical feature is sufficient for possible dementia with Lewy bodies when indicative biomarker evidence is absent. Possible DLB can also be diagnosed when one or more indicative biomarkers are present but no core clinical feature is present. The category is inherently less stable: some patients later fulfil probable DLB, while others evolve toward Alzheimer disease or another disorder. “Possible” should therefore prompt longitudinal review rather than false certainty.

The algorithm is easiest to apply in sequence. Count only core clinical features, then ask whether an indicative biomarker is present. Do not count supportive clinical findings, supportive biomarkers or the mere clinical impression of a “Lewy-like” illness. This ordering prevents

criterion inflation and keeps the probable category tied to either a sufficiently rich clinical phenotype or a clinical-biomarker convergence.

GOOD TO REMEMBER

When writing the diagnosis, show the evidence trail concisely: establish dementia, name the core feature or features, name any indicative biomarker, and then state probable or possible DLB. This makes a counting error visible before it reaches the conclusion.

7.6 The criteria-set trap: consortium versus the diagnostic manual

The consortium and DSM-5-TR frameworks use different taxonomies. In the consortium framework, REM sleep behaviour disorder is one of four core clinical features. In the manual framework, there are three core features: cognitive fluctuation, recurrent well-formed visual hallucinations and spontaneous parkinsonism arising after cognitive decline. REM sleep behaviour disorder and severe neuroleptic sensitivity are suggestive features there.

The resulting thresholds also differ in language. Under DSM-5-TR, probable disorder requires two core features, or one or more core features together with a suggestive feature; possible disorder requires only one core feature, or suggestive features without any core feature. Under the current consortium model, the probability calculation instead combines its four core clinical features with indicative biomarkers. The same patient can therefore be described through legitimate but non-identical structures.

TRAP **Do not answer "How many core features?" until the criteria set is named.** The current consortium report has four core clinical features; DSM-5-TR has three core features and places REM sleep behaviour disorder among suggestive features. Silently merging them creates a hybrid system that belongs to neither source.

This is also why "neuroleptic sensitivity is a core feature" is an unsafe unqualified statement. It is supportive in the consortium clinical list and suggestive in the manual framework, but not core in either of the supplied schemes. Conversely, REM sleep behaviour disorder changed status in the updated consortium approach while the manual framework retained its earlier position. Attribution, not memorised confidence, resolves the apparent contradiction.

7.7 The one-year rule: sequence, label and limitation

The distinction rests on when dementia emerges relative to the motor disorder. Dementia with Lewy bodies is diagnosed when dementia occurs before or concurrently with parkinsonism. Parkinson disease dementia is the term used when dementia occurs in the context of well-established Parkinson disease. For research comparisons, the existing **one-year rule** remains recommended. In ordinary clinical settings, the label most appropriate to the presentation may be used, and a broader term such as Lewy body disease can sometimes communicate the continuum more honestly.

The DSM-5-TR formulation states the other side of the boundary: for major neurocognitive disorder to be attributed to Parkinson disease, the Parkinson disease diagnosis must have been

present for **at least one year** before cognitive decline reaches the level of major neurocognitive disorder. Cognitive symptoms in neurocognitive disorder with Lewy bodies may begin before, with or even without parkinsonism. Thus, the rule is not "motor symptoms at any time means Parkinson disease dementia." It is a temporal convention anchored to established motor disease preceding the dementia syndrome.

CLINICAL SEQUENCE	PREFERRED LABEL	INTERPRETIVE POINT
Dementia before parkinsonism	Dementia with Lewy bodies	Cognitive syndrome leads the motor syndrome
Dementia and parkinsonism begin concurrently	Dementia with Lewy bodies	Concurrent onset remains on the DLB side of the convention
Established Parkinson disease precedes major cognitive decline by at least one year	Neurocognitive disorder due to Parkinson disease or Parkinson disease dementia	Motor disease clearly precedes the dementia syndrome
Clinical presentation does not fit a clean temporal split	Use the clinically appropriate term; Lewy body disease may be helpful	The strict interval is primarily retained for research distinction

The convention has acknowledged limitations. It may arbitrarily divide a continuum of presentations arising from underlying Lewy body disease, and it offers little treatment guidance by itself. An additional Parkinson disease expert-consensus view permits clinician choice between the two diagnoses when major neurocognitive disorder begins before or within twelve months of the motor diagnosis. The existence of this alternative is precisely why the candidate should state which convention is being applied rather than present the boundary as a biological discontinuity.

Parkinson disease neuropsychiatry without dementia, including psychosis outside the dementia syndrome, belongs to the Neuropsychiatry of systemic and neurological disease notes. The present distinction is limited to the dementia lens: clinical sequence determines nomenclature, while the broader motor and neuropsychiatric disorder requires its own assessment.

7.8 Differentiation from Alzheimer disease and diagnostic restraint

Alzheimer disease is the most common clinical misdiagnosis of dementia with Lewy bodies. The neuropsychological contrast is relative rather than absolute. Compared with Alzheimer disease, people with DLB may perform worse on attention, working memory, figure copying, spatial judgement and set shifting. Visuospatial and executive impairment are often greater, while episodic and verbal memory impairment may be less severe. Better recognition than free recall suggests a retrieval problem rather than complete loss of stored information.

The clinical features refine this profile. Early recurrent, detailed visual hallucinations, pronounced cognitive fluctuation, spontaneous parkinsonism and REM sleep behaviour disorder shift the pattern toward DLB. The presence of at least two early core features among fluctuation, prominent visual hallucinations and parkinsonism has high specificity for DLB in the cited account. Functional imaging may add reduced dopamine-transporter uptake in the basal ganglia

or occipital hypoperfusion or hypometabolism. A positive dopamine-transporter scan is not entirely exclusive to DLB, while associated occipital hypometabolism favours DLB over frontotemporal dementia.

Even a convincing clinical distinction does not imply mutually exclusive pathology. A person with a typical insidious amnestic Alzheimer presentation may have Lewy-body pathology at autopsy, and a patient may meet criteria for both disorders. The correct conclusion is therefore probabilistic: identify the dominant clinical syndrome, acknowledge convergent biomarker evidence and remain open to co-pathology. An isolated hallucination, scan result or extrapyramidal sign should not be allowed to erase the rest of the phenotype.

TRAP **Do not quote a prevalence estimate as though all sources measured the same population.** Clinically diagnosed DLB averages 4.2% of dementias in community studies and 7.5% in clinical samples in the cited population-framed estimates, whereas Lewy-body pathology at autopsy is reported in 20-35% of dementia cases in US and UK studies. Other textbooks give higher general clinical estimates. These are different denominators and ascertainment methods, not numbers to average.

The final examination answer should therefore preserve hierarchy and attribution. Begin with functionally significant progressive cognitive decline. Describe the current consortium core, then the supportive clinical features. Separate indicative biomarkers, which can change probable or possible status, from supportive biomarkers, which cannot. State the probability threshold. Flag the alternative manual taxonomy. Finally, apply the temporal rule to distinguish DLB from Parkinson disease dementia and note that the interval is a practical convention imposed on a clinical continuum.

Memorise the sequence: establish dementia; identify the four consortium core features; remember that supportive findings carry no weight; apply the rule that probable DLB requires two core features or one core plus an indicative biomarker; and recognise that established Parkinson disease preceding major cognitive decline by at least one year favours Parkinson disease dementia.

8 · Dementia with Lewy bodies: neuroleptic sensitivity, safe prescribing and management

The treatment paradox. Dementia with Lewy bodies combines cognitive, psychiatric, motor, sleep and autonomic problems, yet the drug most likely to be reached for during frightening hallucinations or agitation may cause the most dangerous deterioration. **Severe neuroleptic sensitivity** can present with an acute onset or marked worsening of parkinsonism and impaired consciousness after even a low dose of a first-generation or second-generation antipsychotic. Tolerance of a previous exposure does not exclude the diagnosis.

This is therefore not merely a psychosis-treatment topic. It is a diagnostic-safety and prescribing topic. **Up to 50%** of people with neurocognitive disorder with Lewy bodies may show severe neuroleptic sensitivity, so recognition of the syndrome changes the entire management plan. The

high-yield answer begins by deciding whether the experience requires drug treatment at all, removes reversible aggravators, uses cognitive-enhancing treatment as part of behavioural management, and reserves dopamine-blocking treatment for exceptional situations.

RULE **In suspected or established DLB, an antipsychotic is an exception, not the reflex response to a hallucination.** Treat the patient's distress and risk, not the mere presence of a perceptual symptom.

8.1 Management frame: LOCUS, FOCUS and MODUS

LOCUS determines how intensively the patient can be assessed and observed. Stable cognitive or behavioural symptoms usually belong in outpatient care with a reliable caregiver, medication reconciliation and planned review. Inpatient care is appropriate when behaviour cannot be safely contained, consciousness or mobility has deteriorated, oral intake is compromised, or close observation is required while potentially offending medicines are withdrawn. Emergency care is required for an abrupt severe reaction after antipsychotic exposure or for immediate danger that cannot be managed in the current setting.

FOCUS should be stated as an observable target rather than as "treat DLB." Acute targets are safety, severe distress, impaired consciousness and sudden motor worsening. Short-term targets include hallucinations that frighten the patient, delusional behaviour that creates danger, sleep-related injury, depressive symptoms, falls and caregiver exhaustion. Mid-term targets are cognition, daily function, mobility and a sustainable medication burden. Long-term targets are quality of life, participation, caregiver capability and avoidance of preventable iatrogenic decline.

MODUS includes environmental and social measures, caregiver education, cognitive and behavioural treatment, carefully selected medication, rehabilitation and, in narrowly selected severe presentations, a procedural treatment. The patient and caregiver should understand that symptoms may fluctuate, that a calm hallucination does not automatically need suppression, and that every new medicine must earn its place against sedation, postural symptoms, confusion, reduced mobility and polypharmacy.

The governing prescription style is **geriatric psychopharmacology**: initiate at a very low dose, titrate slowly, monitor periodically, reduce the dose at the earliest reasonable opportunity and minimise polypharmacy. In DLB this is not ceremonial caution. It is the practical response to unusually high sensitivity to drug-related adverse effects.

AVOID	START	TITRATE	REVIEW
ROUTINE BLOCKADE	VERY LOW	SLOWLY	EARLY

8.2 Recognising and responding to neuroleptic sensitivity

The core clinical pattern is temporal: a dopamine-blocking drug is introduced or increased, followed by a disproportionate acute deterioration in parkinsonism, mobility, alertness or consciousness. The response may occur despite a dose that appears modest by ordinary psychiatric practice. This makes the medication timeline as important as the mental-state

description. Ask what was given, why it was given, what changed afterwards, and whether the change was motor, cognitive, behavioural or global.

First-generation antipsychotics should generally be avoided. Substituting a second-generation agent does not erase the risk because tolerance may also be low and the evidence guiding such use is limited. If a severe reaction is suspected, withhold further exposure, move the patient to an appropriate medical LOCUS, assess consciousness and motor function, look for concurrent illness or medication effects, and provide supportive monitoring. Rechallenge should never be casual merely because psychotic symptoms persist.

CLINICAL QUESTION	INTERPRETATION	IMMEDIATE MANAGEMENT IMPLICATION
Is the hallucination distressing or dangerous?	A well-tolerated symptom may not justify drug risk	Observe, explain and adjust the environment
Was an antipsychotic recently introduced or increased?	Creates a direct temporal suspicion	Withhold further exposure and reassess urgently
Have parkinsonism and consciousness worsened together?	Strongly supports a severe sensitivity response	Escalate the LOCUS and monitor closely
Is another precipitant plausible?	Illness, pain, dehydration and medication burden may amplify symptoms	Search for and correct the precipitant
Did the patient previously tolerate an antipsychotic?	Prior tolerance does not rule out DLB	Keep the diagnosis and sensitivity warning active

PITFALL

Do not label abrupt post-prescription immobility and reduced responsiveness as "progressing dementia" without reconstructing the medication timeline. The error converts an adverse reaction into an excuse for further prescribing.

Altered awareness may also indicate delirium superimposed on dementia. Its full assessment and treatment belong in the Stroke, TBI, delirium and focal brain syndromes notes. General antipsychotic pharmacology and the broader extrapyramidal and metabolic adverse-effect teaching belong in the Schizophrenia: management, antipsychotics and adverse effects notes.

8.3 The sequence before any antipsychotic

Start with a formulation, not a prescription. Clarify whether the target is hallucination, delusion, agitation, fear, aggression, sleep disruption or caregiver distress. Establish whether the patient is suffering or at risk. Review pain, infection, constipation, urinary symptoms, hydration, sensory impairment, sleep disruption, unfamiliar surroundings and recent medication changes. These checks do not deny the neuropsychiatric symptom; they prevent a modifiable driver from being mistaken for an indication for dopamine blockade.

The recommended **therapeutic sequence** is clinically coherent. If distressing hallucinations or other neuropsychiatric symptoms occur in a person receiving anti-parkinsonian medication, first

consider whether that regimen can be reduced without unacceptable motor loss. Then consider a trial of an acetylcholinesterase inhibitor. Only if symptoms remain sufficiently severe should a low-dose dopamine antagonist enter the discussion, because these drugs are poorly tolerated and their supporting evidence is inadequate.

MNEMONIC

PAUSE before blockade

Pin down the target and precipitant; **A**ssess distress, danger and anti-parkinsonian medication; **U**se environmental and caregiver measures; **S**tart cognitive-enhancing treatment when indicated; **E**xceptionally consider an antipsychotic with explicit monitoring.

Non-drug care should be concrete. Improve lighting and visual cues, reduce confusing shadows and overstimulation, preserve familiar routines, check hearing and vision, and coach caregivers to acknowledge distress without arguing about the content of the experience. Increasing arousal and attention through social interaction or environmental novelty may lessen visual hallucinations and fluctuations. A written plan should state which behaviour warrants contact, which change warrants emergency review, and which medicines should not be given reflexively.

The purpose of sequencing is not therapeutic delay. It matches treatment intensity to symptom burden while preserving cognition, mobility and consciousness. When danger is immediate, containment and urgent assessment proceed in parallel; when danger is absent, time spent on formulation is often the safest intervention.

8.4 If an antipsychotic is unavoidable

An unavoidable prescription requires a documented indication: severe distress, dangerous behaviour or psychosis that has not responded to safer measures. Record the baseline motor state, alertness, postural symptoms, oral intake and functional ability; discuss the sensitivity risk with the caregiver; choose the least burdensome option supported by the available evidence; use the lowest practical exposure; and arrange early review. Continued treatment should depend on demonstrable benefit, not on the inertia of a discharge list.

Write the monitoring contract before exposure. It should contain:

- a named target behaviour, with concrete examples of the distress or danger being treated;
- a baseline description of movement, consciousness, posture, intake and the patient's usual fluctuation;
- caregiver instructions to report sudden immobility, reduced responsiveness, falls, excessive sedation or functional loss; and
- a prespecified review decision: continue only for clear benefit, otherwise reduce or withdraw promptly.

This contract prevents common distortions. A transient quietening caused by sedation must not be mistaken for treatment of psychosis, and a naturally fluctuating good period must not be

credited automatically to the drug. The relevant outcome is safer, less distressing behaviour without a disproportionate cost to consciousness, mobility, cognition or daily function.

The evidence is limited and sometimes internally uncomfortable:

AGENT	WHAT THE DLB EVIDENCE SAYS	PRESCRIBING INTERPRETATION
Quetiapine	An open study suggested benefit in some patients but somnolence and orthostatic hypotension caused discontinuation; a controlled study found tolerability without superiority to placebo	Tolerability in the controlled study does not establish efficacy
Risperidone	Poor tolerability, with worsening of cognition and neuropsychiatric symptoms reported	Does not offer a reassuring DLB profile
Olanzapine	Generally poorly tolerated, although a small trial found **5 mg/day** reduced hallucination and delusion severity	This is a dose-specific trial finding, not a general recommended DLB dose
Clozapine	No DLB-specific efficacy study; **6.25-50 mg/day** is extrapolated from psychosis in Parkinson disease dementia	Any consideration must acknowledge that the dose and efficacy inference are not derived from a DLB trial

The Parkinson-disease-psychosis-without-dementia algorithm, including detailed use of pimavanserin, belongs in the Neuropsychiatry of systemic and neurological disease notes. The distinction matters: importing an algorithm from a neighbouring disorder without declaring the extrapolation turns uncertainty into false authority.

TRAP **"Use an atypical antipsychotic because it is safer" is not an adequate DLB answer.** Second-generation status does not neutralise neuroleptic sensitivity; the answer must state avoidance, exceptional use, very low initiation, slow titration, explicit monitoring and early withdrawal when benefit is absent.

GOOD TO REMEMBER

Put "possible severe neuroleptic sensitivity" prominently in the case record and caregiver plan. A correct diagnosis that is invisible during an emergency admission does not protect the patient.

8.5 Cognition and behaviour: cholinesterase inhibitors and memantine

Cholinesterase inhibitors are the mainstay of DLB treatment, with the strongest evidence for donepezil and rivastigmine. Their value is broader than a cognitive-score change: beneficial effects have been reported for cognition, hallucinations, delusions, activities of daily living and global clinical status. Adverse effects include nausea, vomiting, anorexia and somnolence, with adverse events particularly prominent with rivastigmine; its patch may reduce some gastrointestinal difficulty associated with oral treatment. Evidence for galantamine is more limited.

The **NICE sequencing for DLB cognition** is a useful examination and clinical spine. Offer donepezil or rivastigmine in mild to moderate illness; consider galantamine only when both are not tolerated. Donepezil or rivastigmine may also be considered in severe illness. Consider memantine when acetylcholinesterase inhibitors are not tolerated or are contraindicated. The sequence identifies choice and place in therapy; it does not supply a DLB-specific dose in the evidence available here.

Trial evidence supports the hierarchy without making it absolute. Donepezil produced a pooled cognitive advantage of **nearly 2 MMSE points**, with maintained cognitive benefit and a greater likelihood of avoiding deterioration on global impression. Rivastigmine showed a smaller cognitive change that was not statistically significant. These data should support a monitored therapeutic trial, not substitute a score for the patient's function. Ask whether attention, engagement, hallucinations, self-care and caregiver burden have changed, and document tolerability alongside benefit.

Memantine has mixed evidence in DLB. Studies using mixed DLB and Parkinson disease dementia samples found small but statistically significant benefit in DLB subgroup analyses, while individual reports describe possible improvement in quality of life, global status, goal attainment, caregiver burden, attention and sleep behaviour. The correct conclusion is modest uncertainty: memantine has a defined place when cholinesterase inhibitors cannot be used, but it should not be presented as uniformly effective.

Before initiation, agree on target outcomes and a review method. During follow-up, separate adverse effects from disease fluctuation, and ask caregivers for examples rather than a global "better" or "worse." Formal cognitive instruments may support longitudinal observation, but their general administration and scoring belong in the Psychometry, Assessment and Descriptive Psychopathology notes.

A useful follow-up review triangulates the patient's account, caregiver observation and direct examination. Cognitive benefit may appear as steadier attention, more coherent conversation, greater participation in self-care or fewer distressing perceptual experiences rather than as a dramatic test-score change. Conversely, nausea, poor appetite, daytime sleepiness, worsening postural symptoms or reduced engagement may erase a modest benefit. Document both sides of the ledger. If the disease is fluctuating, repeat observation across ordinary settings before concluding that treatment has failed, unless an adverse effect demands earlier action.

8.6 Motor, sleep, autonomic and affective targets

DLB management is symptom-targeted because improving one domain can destabilise another. Anti-parkinsonian medication may aid mobility yet aggravate hallucinations; reducing it may ease psychosis yet impair movement. The practical method is negotiated prioritisation: identify which loss is currently most disabling, alter contributors sequentially where possible, and judge the whole patient rather than a single symptom scale. A **phase 2** placebo-controlled trial found that adjunctive zonisamide improved parkinsonism without worsening cognition or psychiatric

symptoms, but adverse effects increased with dosage, particularly weight loss and reduced appetite. No DLB-specific dose is supplied by that evidence.

REM sleep behaviour disorder requires an injury-prevention plan as well as medication consideration. Make the sleeping environment safer and ask about dream enactment, falls from bed, injury to the patient or bed partner, nocturnal confusion and daytime sedation. Rivastigmine or memantine may reduce episode frequency. Melatonin and low-dose clonazepam are recognised options, while clonazepam requires particular caution in older adults because it is long acting. The available DLB passages do not establish a specific dose for either agent.

For depression and anxiety, assess severity, suicide risk, medical contributors and medication burden, then use psychological, social and pharmacological options cautiously. **Citalopram** is the only antidepressant investigated in a controlled DLB trial; it showed no benefit and was poorly tolerated. Other controlled DLB trials of selective serotonin reuptake inhibitors or serotonin-noradrenaline reuptake inhibitors are lacking, and medicines with anticholinergic adverse effects should be avoided. Postural hypotension, urinary symptoms, restless legs and excessive daytime sleepiness should be treated as explicit targets rather than folded into "dementia." Each intervention must be checked for its effect on cognition, falls, alertness and interaction with the rest of the regimen.

This multidomain review is where polypharmacy grows unless someone owns the whole list. At every visit ask: What is each medicine targeting? Is benefit visible? Is the symptom still active? Can the dose be reduced or the drug stopped? The aim is not a medicine for every symptom; it is the smallest coherent regimen compatible with safety and function.

8.7 Psychological, social, rehabilitative and procedural care

Non-pharmacological care is not an appendix to drug treatment. Person-centred care, physical exercise, cognitive training, social interaction and cognitive behavioural approaches may help, although the evidence remains limited. Environmental novelty and purposeful interaction may improve arousal and attention and thereby reduce hallucinations or functional fluctuation. Occupational and physiotherapy input can translate these principles into safer mobility, preserved routine and meaningful activity.

Caregiver work has direct clinical value. Explain fluctuations, hallucinations and medication sensitivity; distinguish reassurance from confrontation; plan responses to nocturnal behaviour; reduce avoidable environmental confusion; and provide a route for urgent help. Review caregiver sleep, strain and ability to supervise medicines. Social planning should include fall risk, home safety, driving or other hazardous activities, adherence, advance preferences and the realistic capacity of the household. These discussions should be revisited as cognition and function change.

Transitions between home, emergency care and the ward are high-risk moments because the clinician who receives the patient may see agitation without knowing the usual motor state or the sensitivity history. Send a compact care summary with the diagnosis, baseline cognition and mobility, medicines that previously caused deterioration, current targets, caregiver contact and

agreed escalation plan. On admission, reconcile the actual medicines taken rather than copying an old list. At discharge, remove discontinued drugs from the active list, explain every remaining change to the caregiver and specify who will review efficacy and adverse effects. Continuity is itself a safety intervention when the syndrome fluctuates and multiple specialties are involved.

Procedural treatment is reserved for selected severe illness. Electroconvulsive therapy may be considered when severe depression and psychosis coexist, but the DLB evidence is limited to case reports and a small case series. Repetitive transcranial magnetic stimulation may also be helpful, with similarly limited certainty. The decision therefore requires a clear target syndrome, appraisal of medical and cognitive vulnerability, caregiver involvement and follow-up that tests whether meaningful benefit occurred.

> In DLB, protect the patient from iatrogenic dopamine blockade before treating distressing symptoms through a staged, target-based plan that preserves cognition, consciousness and mobility.

9 · Vascular dementia: subtypes, clinical features, criteria and the Hachinski score

Why it matters clinically. Vascular dementia is not a unitary stereotyped syndrome. It is a clinically defined neurocognitive disorder in which cerebrovascular disease is sufficient to explain the cognitive decline. The marks lie in showing that the candidate can connect phenotype, course and vascular evidence, rather than merely noticing vascular risk factors or an abnormal scan. Across major sources, vascular disease is the **second** most common cause of dementia after Alzheimer disease. Its importance therefore comes from frequency as well as diagnostic complexity.

The modern term **vascular neurocognitive disorder** includes major and mild syndromes, while the traditional term vascular dementia usually implies cognitive impairment severe enough to interfere substantially with independence. This section uses both where the source framework requires it. The broader vascular cognitive impairment spectrum, post-stroke cognitive syndromes and detailed strategic-infarct neuropsychiatry belong in the Stroke, TBI, delirium and focal brain syndromes notes. Here the task is narrower: recognise vascular dementia, classify its principal forms, describe its characteristic clinical profiles, apply diagnostic criteria and interpret the ischaemic scale without overclaiming what it proves.

RULE **Vascular disease must be explanatory, not merely present.** A diagnosis rests on a coherent relationship between cognitive decline and cerebrovascular disease, supported by the course, examination and appropriate imaging.

9.1 The diagnostic idea: syndrome plus sufficient vascular cause

A short sequence of questions organises the assessment. Is there a major or mild neurocognitive syndrome? Is cerebrovascular disease demonstrated clinically, on examination or on neuroimaging? Is that disease sufficient, in distribution and timing, to account for the cognitive

deficits? This sequence prevents the common shortcut of moving directly from a vascular risk factor to a dementia label.

The relationship may announce itself through cognitive decline close to a cerebrovascular event. It may instead appear as a pattern dominated by slowed information processing, impaired complex attention and frontal-executive dysfunction. Neither route eliminates the need to consider alternative brain disease or systemic disorder. Conversely, absence of a dramatic stepwise history does not rule out a vascular disorder, because gradual and slowly progressive presentations occur with small-vessel disease affecting white matter, basal ganglia or thalamic structures.

Temporal	Executive	Focal	Imaging
EVENT LINK	COGNITIVE PROFILE	CLINICAL EVIDENCE	PARENCHYMAL INJURY

These are converging lines of evidence, not interchangeable labels. A temporal link is powerful when clearly documented, but a characteristic cognitive profile can be equally important in a gradual subcortical presentation. Focal findings strengthen vascular attribution, while imaging establishes the burden and location of parenchymal injury. The clinician then asks whether the whole pattern is internally consistent. This is a causal formulation, not a checklist detached from the patient.

PITFALL

Do not equate a vascular risk factor or an incidental vascular lesion with vascular dementia. Risk, lesion and cause are different levels of inference. The cognitive syndrome and the cerebrovascular disease must fit each other.

9.2 Classification: several maps of the same territory

The classification varies with the purpose of the source. A clinical manual emphasises course and lesion distribution; an aetiological scheme separates infarction, small-vessel disease, hypoperfusion and haemorrhage; an examination-oriented table may preserve older vascular-dementia labels. These systems overlap substantially and should not be memorised as mutually exclusive diseases.

The contemporary clinical account describes **four** main forms: **poststroke neurocognitive disorder**, which becomes manifest immediately after a stroke; **subcortical ischaemic vascular neurocognitive disorder**; **multi-infarct cortical neurocognitive disorder**; and cortical-subcortical vascular neurocognitive disorder. The point of this division is practical. It asks whether the syndrome follows a recognised stroke, reflects predominantly deep small-vessel injury, accumulates with cortical infarction, or combines cortical and subcortical disease.

CLASSIFICATION LENS	NAMED FORMS	CLINICAL USE
Temporal onset	Acute-onset vascular dementia; poststroke neurocognitive disorder	Highlights a close relationship between a cerebrovascular event and cognitive change
Accumulating cortical injury	Multi-infarct dementia; cortical vascular neurocognitive disorder	Links progressive symptoms to repeated transient ischaemic episodes and accumulating infarcts
Deep small-vessel injury	Subcortical vascular dementia	Emphasises white-matter injury with relative preservation of the cerebral cortex
Combined distribution	Mixed cortical and subcortical vascular dementia	Recognises disease involving both compartments
Critical lesion	**Strategic infarct dementia**	Names the aetiological subtype without replacing lesion-specific assessment
Reduced perfusion	**Hypoperfusion dementia**	Classifies by the vascular mechanism rather than by cortical location alone
Bleeding	**Haemorrhagic dementia**	Separates haemorrhagic from ischaemic vascular injury
Residual categories	Other vascular dementia; vascular dementia unspecified	Allows classification when a more specific subtype is unsupported

Because these labels classify different axes, they need not behave as rival boxes. A label may describe timing, another the anatomical distribution and another the vascular mechanism. In a case formulation, state which axis each descriptor answers and select the term that best communicates the dominant clinical pattern. This avoids false precision when the available history and imaging support a broad vascular attribution but do not justify a narrowly named subtype.

A broader aetiological classification also names Alzheimer disease with cerebrovascular disease and hereditary vascular dementia, including CADASIL as a subtype label. Those labels matter because vascular and degenerative pathology may coexist, and because some vascular disorders are inherited. Their detailed diagnosis and management are not inferred from the label alone. Mixed dementia management is addressed with vascular dementia management elsewhere in this chapter, while the inherited and post-stroke vascular syndromes are covered in the Stroke, TBI, delirium and focal brain syndromes notes.

9.3 Clinical phenotypes: course, distribution and cognitive pattern

Classically, vascular dementia evokes abrupt onset, fluctuations and stepwise deterioration. Those features remain useful clues, especially when deficits change in relation to recognised cerebrovascular events. They are not universal. Acute-onset vascular dementia may follow several strokes or a severe stroke, while multi-infarct dementia produces progressive symptoms as

transient ischaemic episodes and infarcts accumulate. In contrast, small-vessel disease may produce gradual onset and slow progression. A good history therefore reconstructs change over time rather than forcing every patient into the stepwise template.

The cognitive phenotype is often uneven. Information processing, complex attention and frontal-executive functions may be prominent, so relatives may report slowness, difficulty shifting set, reduced initiation, loss of efficiency in multistep tasks and a need for repeated prompting. These complaints can be more revealing than an isolated report of forgetfulness. The examination should relate the pattern of cognitive inefficiency to focal neurological findings and to evidence of cerebrovascular disease, while remaining alert to an alternative or additional disorder.

Useful clinical clues can be organised without pretending that an individual clue is diagnostic:

- a cognitive change that is temporally linked to a cerebrovascular event;
- an uneven profile with prominent processing-speed, attention or executive impairment;
- focal neurological signs or symptoms that support brain vascular injury;
- a course whose fluctuations or increments correspond to vascular events rather than ordinary day-to-day variability.

The final clause is important. Fluctuation is a descriptive feature, not a vascular signature by itself. Similarly, somatic complaints and nocturnal confusion appear among the features sampled by the ischaemic scale, but neither establishes vascular causation. The pattern gains meaning only when it converges with the history, examination and imaging.

GOOD TO REMEMBER

Ask the informant to anchor each loss of function to an event, admission or new neurological deficit. A timeline often distinguishes a true event-linked decline from a vague retrospective impression that the course was “stepwise.”

9.4 The subcortical syndrome

Subcortical vascular dementia deserves separate attention because it is a common source of diagnostic error. It is associated with a history of hypertension and foci of white-matter injury, with the cerebral cortex relatively preserved. The resulting syndrome is not simply “memory loss with vascular risk.” It is a disorder of cognitive control, speed and retrieval, accompanied by characteristic behavioural and neurological features.

The described profile includes executive dysfunction, poor verbal fluency, psychomotor slowness, perseveration and inattention. Memory impairment is characterised by poor retrieval with recognition remaining intact. This distinction is clinically useful: the patient may struggle to generate stored information without help yet recognise it when the correct material is presented. That pattern points toward inefficient access and organisation rather than proving that information was never encoded. It supports a subcortical formulation but does not replace assessment of the entire syndrome.

Apathy and depression may accompany the cognitive changes. Pseudobulbar palsy may provide an additional neurological clue. The behavioural presentation can be misread as lack of effort because the patient initiates slowly, speaks little and needs prompting. Equally, psychomotor slowness can depress performance across many tasks, making the cognitive deficit appear globally worse unless time and executive demand are considered.

MNEMONIC

Slow, Set, Search, Spirit, Speech

The subcortical spine is **slow** processing and movement, impaired executive **set**, inefficient memory **search** with relatively intact recognition, reduced **spirit** through apathy or depression, and impaired **speech** output through poor verbal fluency, with pseudobulbar features as a neurological clue.

The diagnostic value lies in the configuration. Executive dysfunction plus slowed processing, impaired fluency and retrieval difficulty is more coherent than any isolated deficit. Neuroimaging then tests whether the distribution and burden of vascular injury can plausibly explain that configuration. The physics and general interpretation of imaging modalities are covered in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

9.5 Contemporary diagnostic criteria

The **DSM-5-TR criteria for major or mild vascular neurocognitive disorder** begin by requiring the corresponding major or mild neurocognitive syndrome. Vascular aetiology is then supported through either a temporal relationship between cognitive deficits and cerebrovascular events, or a decline prominent in complex attention, including processing speed, and frontal-executive function. There must also be evidence of cerebrovascular disease from the history, physical examination or neuroimaging that is sufficient to account for the deficits. Another brain disease or systemic disorder must not explain the presentation better.

DIAGNOSTIC LAYER	QUESTION TO ASK	MEANING
Neurocognitive syndrome	Are criteria for major or mild neurocognitive disorder met?	Establishes that there is a syndrome to explain
Vascular clinical pattern	Is onset event-linked, or is decline prominent in complex attention, processing speed and frontal-executive function?	Provides a clinically coherent vascular phenotype
Cerebrovascular evidence	Does history, examination or neuroimaging show disease sufficient to account for the deficits?	Moves from association toward attribution
Exclusion	Is another brain disease or systemic disorder a better explanation?	Prevents premature closure
Certainty	Is the evidentiary threshold for probable disorder met?	Separates a supported vascular attribution from a possible one

Probable vascular neurocognitive disorder is diagnosed when there is neuroimaging evidence of significant parenchymal injury attributable to cerebrovascular disease, a documented temporal relationship between the syndrome and cerebrovascular events, or clinical and genetic evidence of cerebrovascular disease. If these supports are absent but the clinical criteria otherwise point to vascular aetiology, the diagnosis is **possible vascular neurocognitive disorder**. "Probable" therefore reflects the strength of causal evidence; it is not a synonym for greater cognitive severity.

MNEMONIC

TIME

Temporal event link or characteristic cognitive pattern; **I**njury from cerebrovascular disease sufficient to explain the deficit; **M**ajor or mild neurocognitive syndrome established; **E**xclude a better brain or systemic explanation.

9.6 Research and older examination criteria

The **NINDS-AIREN criteria** are the most widely used research criteria for vascular dementia. They require evidence of cerebrovascular disease from both clinical and neuroimaging findings, together with a temporal relationship between the vascular changes and the development of dementia. This makes them useful when a study needs a relatively well-defined vascular group. Across several clinical criteria sets, probable and possible vascular dementia diagnoses showed high specificity but low sensitivity. A strict research definition may therefore identify convincing cases while failing to capture every clinically relevant presentation.

Older manuals remain useful for understanding examination language. Under DSM-IV(R), dementia required either focal neurological signs and symptoms or evidence of cerebrovascular disease judged to be aetiologically relevant. The ICD-10 vascular dementia formulation required evidence of focal brain damage, aetiologically relevant cerebrovascular disease and an uneven distribution of cognitive deficits. The contrast is not cosmetic: the latter makes unevenness an explicit requirement, whereas the former allows diagnosis through either focal neurological features or relevant cerebrovascular evidence.

For current classification, the primary manual should be consulted for the exact wording. The supplied evidence supports the contemporary DSM cross-map and the older ICD comparison, but not a faithful reproduction of the current criteria. That limitation is preferable to silently importing remembered wording into a diagnostic standard.

TRAP **Do not present research criteria as though they were a sensitive bedside screen.** Their demand for converging clinical, imaging and temporal evidence improves specificity but can miss clinically plausible vascular presentations.

9.7 The ischaemic scale: what it can and cannot say

The **Hachinski Ischaemic Scale** was among the earliest criteria used in vascular-dementia research. It scores a vascular-looking clinical pattern through features such as abrupt onset,

stepwise deterioration, fluctuation, nocturnal confusion, somatic complaints, and vascular risks or signs. This list is illustrative rather than a complete reproduction of the weighted scale. The instrument has not been well validated, although interrater reliability can be good.

Its central limitation is conceptual. The scale estimates whether clinically significant cerebrovascular disease is present; it cannot demonstrate that the vascular disease caused the dementia. This distinction matters because multiple small infarcts frequently coexist with a primary degenerative dementia. A high vascular signal may therefore identify comorbidity rather than a pure vascular aetiology, which limits the scale's clinical usefulness.

A source reports that a score **greater than 4** was used as an exclusion criterion in a drug trial for Alzheimer disease because it was considered suggestive of vascular dementia. That is an applied trial threshold, not a validated general interpretation scheme for routine practice. It must not be converted into the familiar remembered low, mixed and high bands when the source does not supply those bands. Nor should the illustrative feature list be typeset as though it were the complete weighted item set.

The correct use of the scale is modest. It can prompt a careful vascular history and neurological examination, and it can summarise a cluster of vascular clues in a reproducible way. It cannot replace neuroimaging, establish lesion-cognition concordance, exclude coexisting degeneration or settle aetiology by arithmetic. Modern diagnostic reasoning therefore places the score beneath, not above, the clinical formulation.

PITFALL

A numerical score can create false certainty. Before acting on it, state which findings produced the score, whether cerebrovascular disease is objectively demonstrated, and whether that disease actually explains the cognitive phenotype.

9.8 A compact clinical and examination synthesis

A strong answer begins with the diagnostic principle, then classifies, phenotypes and applies criteria. Start by defining vascular dementia as a major neurocognitive syndrome attributable to sufficient cerebrovascular disease. Name the principal poststroke, subcortical, multi-infarct cortical and cortical-subcortical forms. Add the aetiological labels of strategic infarction, hypoperfusion and haemorrhage only to show the breadth of vascular mechanisms, not to launch into lesion syndromes owned elsewhere.

Next, describe the course without overgeneralising. Abrupt onset, stepwise deterioration and fluctuation are useful clues, but gradual progression occurs in small-vessel disease. Then give the characteristic cognitive profile: slowed information processing, impaired complex attention and frontal-executive function. For the subcortical form, add poor verbal fluency, psychomotor slowness, perseveration, inattention, retrieval-based memory impairment with intact recognition, apathy, depression and pseudobulbar palsy.

Finally, show how criteria convert description into diagnosis. Establish major or mild neurocognitive disorder; demonstrate either an event-linked onset or a characteristic attention-

executive decline; show cerebrovascular disease sufficient to account for the deficits; and exclude a better explanation. Distinguish probable from possible by the strength of imaging, temporal, clinical and genetic support. Research criteria demand clinical and imaging evidence plus temporal relatedness and may trade sensitivity for specificity. The ischaemic scale is an adjunct that detects vascular features, not a causal test.

> Memorise the hierarchy: cognitive syndrome, vascular phenotype, sufficient cerebrovascular evidence, temporal or anatomical concordance, exclusion of a better cause, then certainty level.

10 · Vascular dementia management, secondary prevention and mixed dementia

The marks lie in separating three questions that look deceptively similar. First, how should a person with vascular dementia receive ordinary dementia care? Second, which measures prevent further cerebrovascular injury? Third, when degenerative and vascular processes coexist, which component should drive treatment? A strong answer does not promise that control of vascular risk reverses established cognitive impairment. It explains that prevention of another vascular event is valuable in its own right, may prevent additional cognitive injury, and must be distinguished from a drug having a direct disease-modifying effect on vascular dementia.

Management is therefore broader than prescribing a cognitive enhancer. It begins with the care setting and immediate clinical problem, proceeds through secondary prevention, and ends with an integrated formulation of cognition, function, behaviour, vascular recurrence risk and support needs. The available evidence also demands restraint. **Treatment uncertainty in pure vascular dementia** is not therapeutic nihilism: management options are limited and chiefly address underlying cerebrovascular risk, while no available drug is formally licensed for vascular dementia in the United Kingdom. Mixed pathology changes the reasoning because a coexisting degenerative component may supply a separate indication for cognitive-enhancer treatment.

LOCUS	FOCUS	MODUS	REVIEW
CHOOSE THE CARE SETTING	DEFINE THE PHASE TARGET	COMBINE TREATMENT MODES	REASSESS BENEFIT AND HARM

10.1 The therapeutic frame: LOCUS, FOCUS and MODUS

LOCUS asks where care should occur. Stable cognitive impairment, vascular-risk review and longitudinal support usually belong in outpatient care. A sudden focal neurological change, abrupt loss of function or an acute safety problem requires an urgent medical pathway rather than routine adjustment of dementia medication. Inpatient care is justified by the severity and immediacy of the medical or behavioural problem, not by the diagnostic label alone. This prevents a common category error: treating a new clinical event as if it were merely another step in chronic cognitive decline.

FOCUS asks what is being treated in the present phase. The immediate focus is recognition of a new vascular or medical event and protection from harm. The short-term focus is medication reconciliation, clarification of vascular indications and restoration of a workable routine. The

medium-term focus is prevention of recurrent cerebrovascular injury while tracking cognition, function and behaviour. The long-term focus is sustained risk-factor care, realistic goals, caregiver partnership and review of whether each intervention still offers net benefit.

MODUS asks whether all relevant modes have been considered. Pharmacological care includes treatment of vascular risk and, in selected mixed cases, treatment directed at the degenerative component. Procedural care may be relevant for suitable carotid disease. Psychological care includes explanation, adaptation to deficits and support for adherence. Social care includes supervision, environmental structure and support for those carrying day-to-day responsibility. Detailed cognitive-enhancer pharmacology and general behavioural and psychological symptom management are taught elsewhere in this chapter; here the task is to decide whether vascular or mixed pathology changes their indication.

MANAGEMENT AXIS	QUESTION AT REVIEW	PRACTICAL OUTPUT
LOCUS	Is this stable follow-up or an acute change?	Outpatient review or urgent medical assessment
FOCUS, immediate	Is there new neurological or medical injury?	Identify and manage the acute problem
FOCUS, continuing	What can cause further vascular injury?	Individual secondary-prevention plan
MODUS, drug	Does each medicine have a defined indication?	Prescribe for stroke prevention, cognition or behaviour explicitly
MODUS, procedural	Is a vascular lesion amenable to intervention?	Appropriate specialist assessment
MODUS, psychosocial	What impairs adherence, function or safety?	Education, structure and caregiver support

RULE **Name the indication for every intervention.** A statin may be prescribed for vascular prevention, while a cognitive enhancer may be considered because of a degenerative component; neither should be described vaguely as a treatment that reverses vascular dementia.

10.2 Secondary prevention: prevent additional vascular injury

The core management task is **vascular secondary prevention**. In a person with established stroke, it is reasonable to address risk factors when the individual risk-benefit balance is favourable. The treatment plan should consider hypertension, hyperlipidaemia, smoking and diabetes; antiplatelet treatment when indicated by the history of stroke disease; and anticoagulation in atrial fibrillation. Significant carotid stenosis may warrant surgical assessment, with the cited reference identifying possible benefit when stenosis is **greater than 75%**. These measures are not a generic dementia prescription. Each follows from the person's vascular mechanism, history, contraindications and capacity to participate in monitoring.

The reasoning is causal but modest. A further stroke may add new cognitive, behavioural or functional disability to an already vulnerable brain. Reducing recurrent stroke risk can therefore protect the remaining level of function and may slow deterioration caused by repeated injury.

This does not prove that the same treatment removes established vascular lesions or directly alters the underlying dementia process. The candidate who preserves that distinction can reconcile apparently conflicting textbook statements without pretending that the evidence is cleaner than it is.

The **stroke-prevention versus dementia-modification distinction** is particularly important for statins and aspirin. Stroke literature supports treating appropriate vascular indications, yet the cited dementia evidence does not conclusively show that treatment of hyperlipidaemia with statins or clotting abnormalities with aspirin changes the incidence or progression of vascular dementia. A review cited in the same source found no studies supporting statins as a treatment for vascular dementia itself. Thus, prescribe a statin because hyperlipidaemia or cerebrovascular disease warrants it, not because the medicine has been established as a cognitive enhancer.

- Confirm the vascular indication and the event being prevented.
- Review bleeding risk, interactions, adherence and the burden of monitoring.
- Treat smoking and diabetes as part of the same vascular formulation.
- Use specialist assessment when carotid intervention is potentially relevant.
- At follow-up, reassess both recurrent events and everyday cognitive or functional change.

GOOD TO REMEMBER

A family may hear "there is no clearly effective drug for vascular dementia" as "nothing can be done." Correct that misunderstanding. Prevention of another stroke, rational treatment of comorbidity, functional support and review of mixed pathology remain active treatment, even when restoration of lost cognition is not promised.

10.3 Cognitive enhancers: small signals, uncertain clinical importance

NICE 2006 guidance concluded that acetylcholinesterase inhibitors and memantine produced small cognitive benefits of uncertain clinical significance in mild-to-moderate vascular dementia, with insufficient evidence to support widespread use. This remains a useful examination formulation because it separates a detectable change on a cognitive outcome from a change that patients and caregivers can recognise in daily life. A statistically favourable result does not automatically establish meaningful functional benefit, global improvement or a routine indication.

A later evidence summary gives the same caution greater pharmacological detail. In vascular cognitive impairment, a systematic review found a slight cognitive benefit with donepezil and galantamine at the reviewed regimens. The vascular cognitive impairment review examined the standard Alzheimer regimens of **donepezil 5 mg or 10 mg and galantamine 16-24 mg**, tested here off their licensed indication. The size of change was considered unlikely to be clinically important. The higher reviewed donepezil regimen and the galantamine regimen were probably associated with more adverse events than placebo, while evidence for rivastigmine was less certain. These are trial regimens for vascular cognitive impairment, not a licence to reproduce the full dementia prescribing schedule or to bypass ordinary tolerability assessment.

The best synthesis is that **no drug is clearly effective in pure vascular dementia**, whereas acetylcholinesterase inhibitors may be beneficial in mixed dementia. That conclusion is compatible with selected trial signals if "effective" means a clinically worthwhile and broadly applicable treatment rather than any statistically detectable cognitive change. Before prescribing, ask what diagnosis supplies the indication, what outcome would count as success, how adverse effects will be recognised and when treatment will be reconsidered.

TRAP **Do not convert statistical efficacy into settled clinical effectiveness.** The cited analyses are not neatly concordant: one describes small cognitive benefits of uncertain clinical importance and insufficient support for widespread use, while another reports significant efficacy on cognitive outcomes and a favourable safety account. A further review reports more adverse events with some regimens. State the conflict, distinguish statistical from clinical significance, and do not resolve it by fiat.

PITFALL

Starting a cognitive enhancer simply because imaging shows vascular lesions confuses pathology with indication. First decide whether the clinical formulation is predominantly vascular, predominantly degenerative, or genuinely mixed. Then document the target outcome and review it rather than continuing treatment indefinitely by inertia.

10.4 Aggression and other behavioural presentations

Behavioural disturbance requires the same disciplined formulation. Clarify the behaviour, its setting, precipitating factors, risk, caregiver response and possible medical contributors before selecting medication. Environmental modification, communication strategy, routine and caregiver support remain foundational. The detailed assessment of behavioural and psychological symptoms, antipsychotic risk and general antipsychotic pharmacology belong respectively to the relevant dementia section and to the Schizophrenia: management, antipsychotics and adverse effects notes.

Evidence for vascular-specific pharmacological alternatives is sparse. A small case series reported that **gabapentin for aggression** was associated with reduced aggression in vascular dementia or mixed vascular and Alzheimer pathology at **200-600 mg/day**; some participants were subsequently able to stop antipsychotics. This was not a randomised trial, so it should be presented as a weak signal rather than a standard treatment algorithm. The indication attached to the cited regimen is aggression in vascular or mixed dementia, not uncomplicated cognitive decline.

In practice, weak evidence demands stronger review discipline. Define the target behaviour in observable terms, look for reversible precipitants, involve caregivers in monitoring, and stop or change an intervention when benefit is absent or harm outweighs it. Avoid presenting a small uncontrolled observation as equal to replicated comparative evidence. The appropriate answer is neither "never consider" nor "recommended treatment," but "limited evidence, individualised use, explicit target and close reassessment."

10.5 Mixed dementia: recognising more than one active process

Mixed dementia is a clinical formulation, not a compromise label. **Mixed dementia** commonly refers to the coexistence of vascular dementia and Alzheimer disease. The point is not merely that vascular lesions and degenerative pathology can both be found. The clinician must decide whether both plausibly contribute to the person's neurocognitive, functional or behavioural syndrome. A vascular history without clinical relevance should not be promoted automatically to a causal diagnosis, and a progressive amnestic syndrome should not make vascular contributions invisible.

Mixed pathology becomes especially important in later-onset presentations. **Late-onset mixed pathology** is more likely to be clinically recognised, and community samples often show more than one pathological contribution, sometimes alongside other diagnoses. Autopsy evidence makes the same caution concrete. In a European autopsy series, Alzheimer plus vascular pathology was reported in **5.5% overall, 10.6% above 90 years, and 5.2% at 60-69 years**. These are autopsy-series figures, not the prevalence of a clinical diagnosis in an outpatient service. They support diagnostic openness, not indiscriminate use of the mixed label.

Recognition rests on convergence. The temporal course may contain both progressive decline and changes plausibly linked to cerebrovascular disease. The cognitive profile may combine cortical impairments with slowed processing, attentional difficulty or executive dysfunction. Medical history and neuroimaging may demonstrate cerebrovascular disease, but their contribution must be interpreted in relation to symptoms and function. Detailed vascular-dementia subtypes, diagnostic criteria and the ischaemic score are covered in the preceding vascular-dementia section; imaging techniques themselves belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

MNEMONIC

Two tracks, one patient

Keep both tracks visible: **prevent further vascular injury** and **treat the predominant dementia process**. The tracks interact, but their indications and expected outcomes should remain explicit.

10.6 Diagnostic formulation across the major classifications

The international diagnostic classification recognises a dedicated **ICD-11 mixed Alzheimer and vascular category**, coded **6D80.2**. It requires that the diagnostic requirements for dementia due to Alzheimer disease are met and that part of the neurocognitive, functional or behavioural syndrome is attributable to coexisting cerebrovascular disease demonstrated by clinical history, medical testing or neuroimaging. The expected course remains progressive, with possible combined impairment in cortical functions and in attention, processing speed or executive and frontal functions.

The **DSM-5-TR comorbidity formulation** reaches the same clinical destination by a different route. When major or mild neurocognitive disorder due to Alzheimer disease co-occurs with major or mild vascular neurocognitive disorder, both diagnoses should be made. For examination

purposes, the distinction is straightforward: the international classification supplies a named mixed category, while the American manual records the co-occurring aetiological diagnoses. Neither approach permits the clinician to infer causal contribution merely from an incidental lesion.

QUESTION	EVIDENCE SOUGHT	INTERPRETIVE TASK
Is a degenerative dementia syndrome present?	Progressive cognitive and functional history	Establish the degenerative component rather than assuming it
Is cerebrovascular disease present?	Clinical history, medical tests and neuroimaging	Document vascular disease
Does vascular disease contribute?	Temporal, anatomical and cognitive concordance	Link evidence to symptoms and function
How should it be coded?	Chosen diagnostic system	Use the mixed category or record both aetiological diagnoses
What drives treatment?	Predominant cause and active risks	Match each intervention to its indication

10.7 Integrated management when pathology is mixed

The governing principle is **management according to the predominant cause**. "Predominant" does not mean "only." It identifies which process best explains the current syndrome and therefore which disease-specific treatment framework should lead. A predominantly vascular picture places prevention of further cerebrovascular injury at the centre. A substantial degenerative component may justify cognitive-enhancer treatment under that indication. In either case, active vascular risks still deserve attention, and cognitive, behavioural, functional and caregiver outcomes still require longitudinal review.

This formulation should be written as a short causal map. State the evidence for a progressive degenerative process, the evidence for cerebrovascular disease, and why each is judged clinically contributory. Then attach each intervention to one of those components. Such documentation prevents two opposite errors: withholding potentially useful treatment because vascular disease is present, and prescribing as though a mixed label proves that every dementia medicine will help.

A practical mixed-dementia plan therefore combines prevention, selective symptomatic treatment and supportive care. It also preserves proportionality. The potential benefit of vascular prevention depends on the relevant vascular indication and risk-benefit profile. The potential benefit of a cognitive enhancer depends on the degenerative contribution, modest expected effect and tolerability. Psychological and social interventions should address function, communication, adherence and caregiver strain without waiting for perfect aetiological certainty. Goals should remain observable and revisable.

Follow-up should return to the causal map rather than merely renew prescriptions. Ask whether any new vascular event has occurred, whether cognition or everyday function has changed, whether the target behaviour remains present, and whether the family can still carry out the plan.

Review adherence and adverse effects alongside the burden of appointments and monitoring. If the balance of disability changes, reconsider which process is predominant and whether the present treatment priorities still fit. This longitudinal method is especially important when the course contains both gradual decline and superimposed vascular injury, because a static label can conceal a changing clinical problem.

> In vascular and mixed dementia, prevent further vascular injury, identify the predominant cause, and never mistake a small cognitive signal for proven disease modification.

10.8 How to write the management answer

Begin with setting and phase: state whether the patient is stable or acutely changed, then use LOCUS, FOCUS and MODUS to organise care. Next, describe vascular secondary prevention with individual risk-benefit assessment. Explicitly separate reduction of recurrent stroke from direct treatment of established dementia. Then discuss cognitive enhancers cautiously: small cognitive benefits may occur, clinical importance is uncertain, evidence summaries conflict, and routine widespread use in pure vascular dementia is not established.

Finish by defining mixed dementia, explaining how vascular and degenerative evidence are linked to the clinical syndrome, and stating the diagnostic-system formulation. Management follows the predominant cause while continuing to address both active processes. If behavioural symptoms are mentioned, assess them before prescribing and grade the evidence honestly. This sequence earns marks because it is clinically reasoned rather than a list of drugs, and because it makes uncertainty visible without turning uncertainty into inaction.

11 · Frontotemporal dementia: the behavioural variant and the primary progressive aphasias

The diagnostic centre is the leading network failure, not memory loss by default.

Frontotemporal degeneration can announce itself through altered social conduct and executive control, or through a progressive language-led syndrome. The high-yield task is therefore to identify what changed earliest, describe the dominant phenotype precisely, and then apply the relevant diagnostic frame without forcing every presentation into an amnestic dementia template.

The behavioural variant and the primary progressive aphasias belong in a continuous clinical argument because behaviour, social cognition, executive control and language can overlap as degeneration spreads. They must nevertheless remain distinguishable at presentation. A vague label such as “frontal dementia” loses marks and clinical information. A strong formulation names the syndrome, shows the defining findings, states the relatively preserved functions, and acknowledges when the language phenotype points away from frontotemporal pathology.

2-31 per 100,000	20-25%	ABOUT 5%	APPROXIMATELY 60%
POPULATION PREVALENCE ESTIMATES	PRESENT AFTER AGE 65	UNSELECTED DEMENTIA AUTOPSY SERIES	BEHAVIOURAL-VARIANT PRESENTATION

11.1 The frontotemporal clinical spectrum

Frontotemporal neurocognitive disorder is uncommon in population terms but disproportionately important in psychiatric practice because its earliest manifestations may look like a disorder of motivation, impulse control, personality or communication. The behavioural variant is the commonest presentation, accounting for **approximately 60%** of cases in the cited diagnostic-manual account. A meaningful minority present after 65 years, so older age must not be used to dismiss the diagnosis.

The accompanying figure should be read as a phenotype map. At the behavioural pole, early dysfunction concerns social comportment, empathy, motivation, repetitive behaviour, eating and executive control. At the language pole, the dominant impairment may concern word meaning, grammatical or motor production, or retrieval with phrase and sentence repetition. These are clinical entry points rather than sealed compartments. Behavioural change may appear during a language-led illness, and language difficulty may emerge during a behaviour-led illness.

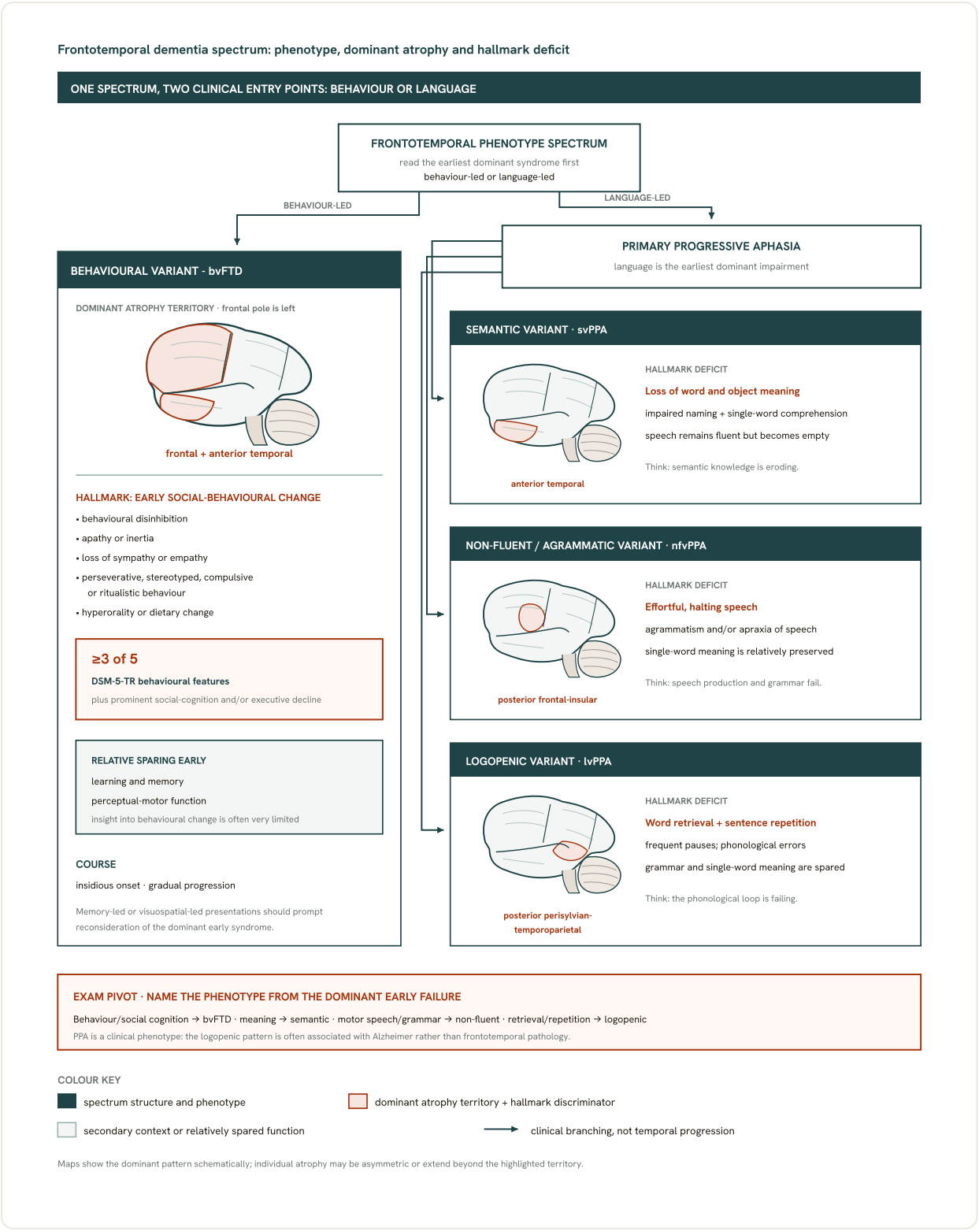

Fig 32.5 **The frontotemporal dementia phenotype map.** Behaviour-led disease maps to frontal and anterior temporal involvement; language-led disease separates into semantic, non-fluent/agrammatic and logopenic primary progressive aphasia by the dominant early language failure and its characteristic network. The logopenic phenotype is often associated with Alzheimer pathology rather than frontotemporal lobar degeneration.

Course reinforces the seriousness of early recognition. Median survival is **6-11 years after symptom onset** in the cited account, with faster decline and shorter survival than in typical Alzheimer disease. That figure describes a group trajectory, not an individual prognosis. Clinically, the useful implication is that apparently “social” or “personality” symptoms can

represent a progressive neurological syndrome with major consequences for judgement, relationships, occupation and care planning.

RULE **Classify the earliest dominant syndrome before interpreting later overlap.** Early social-executive change supports behavioural-variant frontotemporal dementia; progressive language-led change requires analysis of meaning, production, retrieval and repetition before a subtype is assigned.

11.2 Behavioural variant: recognise change from the person's baseline

The **behavioural variant of frontotemporal dementia** is defined clinically by a progressive alteration in how the person initiates action, regulates conduct, understands other minds and adapts behaviour to context. The word "change" matters. Lifelong bluntness, unconventionality or rigid habits are not equivalent to a newly progressive syndrome. The history should reconstruct premorbid personality and compare it with current behaviour across home, work and social settings.

Apathy or inertia may be described as loss of spontaneous activity, reduced initiation, diminished interest in former responsibilities or prolonged passivity unless another person prompts action. The patient may not complain of distress about this loss. Relatives often report that the person "could do it but does not start," which points the interview toward initiation and goal-directed behaviour rather than ability alone. The examination should test whether prompting briefly restores action and whether the person appreciates the consequences of disengagement.

Behavioural disinhibition ranges from loss of manners and tact to plainly socially inappropriate conduct. The key is failure to use social context to inhibit an impulse. Familiarity with strangers, intrusive comments, impulsive purchases or disregard for interpersonal boundaries may be more diagnostically revealing than a conventional memory complaint. The clinician should document the actual behaviour and its novelty rather than substitute a moral description such as "difficult" or "selfish."

Loss of sympathy or empathy is more than irritability. The person may fail to register another person's emotional state, respond coldly to suffering, or lose the reciprocal concern previously evident in close relationships. Family members experience this as a profound personality change. Because the patient may explain the behaviour fluently, the clinician must compare verbal explanation with conduct in real situations. Social knowledge stated in the abstract does not guarantee that it guides behaviour.

Perseverative, stereotyped or compulsive behaviour includes repeated acts, fixed routines and ritualised patterns that continue despite reduced usefulness. The form matters more than whether the act resembles an ordinary habit. Ask what happens if the routine is interrupted, whether the behaviour has become narrower or more frequent, and whether it serves an understandable anxiety-reducing purpose. In bvFTD, repetitive conduct can coexist with striking indifference to its impact.

Hyperorality and dietary change may appear as altered food preference, excessive oral exploration or a new pattern of eating that relatives identify as uncharacteristic. This feature is not merely "good appetite." Its diagnostic weight comes from novelty, repetition and its place within the wider behavioural-executive syndrome. Questions about food seeking, preference shifts, table behaviour and oral habits are often more productive than asking whether appetite has increased.

Limited insight is characteristic. Individuals may minimise change, rationalise serious consequences or regard relatives as unnecessarily restrictive. This does not make the interview futile; it changes the evidentiary balance. Collateral history becomes central, while the patient's account remains valuable for language, thought form, emotional response and awareness of disagreement. Executive testing may show impairment with relative sparing of memory and visuospatial functioning, but a neat test profile is not required for family-observed behavioural decline to deserve investigation.

GOOD TO REMEMBER

Ask the informant for concrete before-and-after examples. "He has changed" is weak evidence; a new loss of tact, initiation, empathy, behavioural flexibility or dietary restraint establishes the domain, context and functional consequence of change.

11.3 Diagnostic criteria and probability language

The **DSM-5-TR behavioural-variant criteria** begin only after criteria for major or mild neurocognitive disorder are met. They then require insidious onset and gradual progression. The behavioural syndrome requires **at least three of five behavioural features**, together with prominent decline in social cognition and/or executive abilities. The feature set is:

- behavioural disinhibition;
- apathy or inertia;
- loss of sympathy or empathy;
- perseverative, stereotyped, compulsive or ritualistic behaviour; and
- hyperorality and dietary change.

DIAGNOSTIC LAYER	REQUIRED CONTENT	WHY IT MATTERS
Entry syndrome	Major or mild neurocognitive disorder criteria are met	Behavioural symptoms alone do not establish the neurocognitive diagnosis
Course	Insidious onset and gradual progression	Frames the presentation as a progressive degenerative syndrome
Positive phenotype	At least three of the five specified behavioural features, plus prominent social-cognitive or executive decline	Combines observable behaviour with the affected cognitive systems
Relative preservation	Learning and memory, and perceptual-motor function, are relatively spared	Prevents reflex classification as a primarily amnestic or perceptual-motor syndrome
Exclusions	The picture is not better explained by cerebrovascular disease, another neurodegenerative disease, substance effects or another disorder	Requires an aetiologic differential rather than checklist diagnosis
Probability	Probable when a causative genetic mutation is demonstrated or neuroimaging shows disproportionate frontal or temporal involvement; otherwise possible	Separates a compatible clinical syndrome from one with specified aetiologic support

"Relative sparing" is frequently misread as "normal." A patient may have some forgetfulness, inefficient learning or visuospatial difficulty and still show a clearly disproportionate behavioural-executive syndrome. The task is comparative: determine which domain drove the illness, which impairment dominates current disability, and whether the overall pattern satisfies the stated framework. Later generalisation does not erase the presenting phenotype.

The International Behaviour-variant FTD Criteria Consortium revisions published in 2011 use a hierarchical classification of possible, probable and definite bvFTD, supported across the hierarchy by radiological, genetic and neuropathological information. That framework should not be silently merged with the manual formulation above. Its category names should be attributed to the consortium framework rather than mapped onto the manual's probable and possible split.

TRAP **Do not diagnose bvFTD by counting colourful behaviours alone.** The manual requires the neurocognitive syndrome, insidious progressive course, the threshold behavioural cluster, prominent social-cognitive or executive decline, relative sparing and appropriate exclusions. A behaviour checklist detached from course and cognition is incomplete.

11.4 Clinical examination, function and associated motor signs

Assessment is strongest when history, examination and everyday function converge. Begin with chronology: what was the earliest convincing change, who noticed it, and how has it progressed? Then sample initiation, inhibition, cognitive flexibility, rule maintenance, social judgement and

awareness of deficit. A calm, superficially cooperative interview can obscure severe dysfunction if the clinician does not ask how the person behaves outside the consulting room.

Collateral interviewing should explore work errors, financial judgement, vulnerability to exploitation, unsafe impulsivity, eating behaviour, interpersonal rupture, neglect of responsibilities and response to feedback. These examples are not separate diagnostic criteria. They are ways of showing that the core behavioural and executive changes have crossed into real function. When accounts conflict, document the discrepancy itself. Limited insight can be part of the syndrome, but informant frustration can also colour interpretation.

The bedside cognitive profile should not be reduced to a total screening score. Observe whether the patient grasps the interpersonal setting, modifies an answer after correction, sustains a rule, generates alternatives and recognises another person's perspective. Memory and perceptual-motor performance may be relatively spared in the formal diagnostic profile. General cognitive-screen administration and scoring belong to the Psychometry, Assessment and Descriptive Psychopathology notes; here their role is to describe the pattern and severity, not to replace clinical formulation.

Motor examination remains relevant even in an apparently behavioural presentation. About **20%** of individuals with bvFTD show signs of parkinsonism in the cited account. Motor neuron disease can also coexist and should be named when weakness, wasting or fasciculations accompany the cognitive-behavioural syndrome, but its frequency, molecular basis and detailed overlap belong with the dedicated frontotemporal molecular and motor-neuron-disease discussion. The practical point here is to examine movement, tone, gait, bulk and power rather than treating bvFTD as purely psychiatric.

> **PITFALL**
>
> Do not allow fluent conversation or adequate bedside recall to overrule a compelling history of progressive social-executive failure. Conversely, do not convert any late-life disinhibition into bvFTD without demonstrating progression, cognitive-system involvement and exclusion of a better explanation.

11.5 Primary progressive aphasia: classify the failed language operation

In progressive aphasia, "speech difficulty" is only the opening observation. The clinician must determine whether the central failure concerns semantic knowledge, grammatical or motor production, or retrieval with repetition. The **primary progressive aphasia** presentation has gradual onset and a progressive language-led course. Connected speech, confrontation naming, single-word comprehension, sentence comprehension, repetition, reading, writing, object knowledge, grammar, articulation and prosody should be sampled in a coordinated examination.

Taxonomy requires explicit attribution. The DSM-5-TR account describes **two commonly described language subtypes** within frontotemporal neurocognitive disorder: semantic and agrammatic or nonfluent. It separately names logopenic progressive aphasia, links it to left temporoparietal dysfunction and states that Alzheimer pathology often causes it. Other major

textbook conventions discuss semantic, nonfluent or agrammatic, and logopenic presentations together as the recognised PPA variants. The framing differs, while the clinical phenotypes remain useful.

The ICD-11 clinical description offers a compact discriminator: primary deficits concern word meaning in the semantic subtype, word production in the agrammatic subtype, and word finding in the logopenic subtype. This is an entry map, not a complete bedside diagnosis. Each label must be tested against associated deficits and relative preservations, because several patients can all pause for words while failing for different reasons.

AXIS	SEMANTIC VARIANT	NONFLUENT OR AGRAMMATIC VARIANT	LOGOPENIC VARIANT
Core failure	Confrontation naming and single-word comprehension	Agrammatism or effortful, halting speech	Single-word retrieval plus sentence and phrase repetition
Connected speech	Fluent and grammatically correct despite loss of semantic precision	Nonfluent, effortful; agrammatism is usual but not invariable	Slow because of word-finding pauses, without defining agrammatism
Relative preservation	Repetition and speech production are usually spared	Single-word comprehension and object knowledge are spared	Single-word comprehension, object knowledge and motor speech are spared; articulation and prosody are preserved
Associated clue	Impaired object knowledge, surface dyslexia or dysgraphia may occur	Apraxia of speech is common, and complex syntax may be difficult	Phonological errors may occur in speech and naming
Typical atrophy or dysfunction	Bilateral anterior temporal, usually greater on the left	Predominantly left inferior frontal and insular	Left temporoparietal dysfunction
Usual pathology framing	Associated with the FTD spectrum	Associated with the FTD spectrum	Associated with Alzheimer disease

MNEMONIC

Meaning - Making - Repeating

Meaning fails in semantic PPA, speech **making** fails in nonfluent or agrammatic PPA, and **repeating** phrases or sentences fails alongside word retrieval in logopenic PPA. The mnemonic directs examination; the full subtype still depends on the wider pattern.

11.6 Semantic variant PPA: words remain fluent but lose meaning

The **semantic variant of primary progressive aphasia**, also called semantic dementia, has impaired confrontation naming and impaired single-word comprehension as its core. Speech can remain fluent, well articulated and grammatically correct, yet become progressively empty or

imprecise because semantic knowledge is degraded. This contrast is crucial: fluency describes the mechanics and flow of speech, not the richness or accuracy of meaning.

At the bedside, naming failure should be tested alongside comprehension. A person may not merely fail to retrieve "apple"; they may substitute a broad category such as "food," and later may refer to nouns as "things." Ask the patient to identify, define and match words and objects rather than relying on picture naming alone. Impaired object knowledge supports loss of the underlying concept, whereas preserved repetition and speech production help separate semantic breakdown from a production disorder.

Surface dyslexia and dysgraphia may accompany the syndrome. They show that semantic knowledge contributes to reading and spelling patterns that cannot be managed reliably by a simple sound-based route. The finding should be interpreted within the language profile rather than treated as an isolated literacy deficit. Educational history, language proficiency and premorbid reading ability remain essential context in multilingual Indian practice, especially when testing is performed in a language that is not the patient's most familiar one.

The typical structural association is atrophy in the ventral and lateral portions of the bilateral anterior temporal lobes, usually greater on the left. Predominantly right-sided semantic degeneration can look different: emotional detachment, loss of empathy, compulsions, impaired emotional processing and difficulty recognising familiar faces may appear early. This is the bridge back to the behavioural spectrum. It also explains why a language-only interview can miss the syndrome when the right temporal presentation is socially dominant.

11.7 Nonfluent or agrammatic PPA: production becomes effortful

The **nonfluent or agrammatic variant of primary progressive aphasia**, also called progressive nonfluent aphasia, requires one of two core findings: agrammatism in language production, or effortful and halting speech. The patient may speak slowly and labour over utterances. Agrammatism appears as omission or misuse of grammatical structure, while impaired motor planning for speech can distort the route from intended utterance to articulated output.

Apraxia of speech is common in the detailed textbook description, but language and motor speech should still be examined separately. Ask whether grammatical organisation fails independently of motor speech and whether halting output reflects language formulation, speech production, or a mixture. Laboured output should not automatically be labelled agrammatism, and grammatical simplification should not automatically be explained by articulatory difficulty.

Comprehension of syntactically complex sentences may be impaired, even while single-word comprehension and object knowledge remain relatively spared. This dissociation is clinically elegant and frequently examined. A patient may understand the words individually yet fail to compute who did what to whom when grammatical structure carries the meaning. Word-finding difficulty is generally milder than in semantic PPA, although mild anomia may occur and may be more noticeable for verbs.

The associated atrophy is predominantly left inferior frontal and insular. Behavioural change is usually limited early, and individuals may retain more insight and adherence to social norms than those with bvFTD. Behavioural symptoms may follow if degeneration extends into right frontal regions. Thus, preserved social conduct does not argue against a frontotemporal-spectrum language syndrome; it helps identify the current phenotype and stage of network involvement.

11.8 Logopenic PPA: retrieval and repetition expose the distinction

The **logopenic variant of primary progressive aphasia** has impaired single-word retrieval in spontaneous speech and naming, together with impaired repetition of sentences and phrases. Speech becomes slow because the patient searches for words, not because articulation is effortful or grammar is collapsing. Phonological errors may occur, but articulation, prosody and motor speech are relatively preserved.

Repetition is the decisive stress test. A patient with semantic PPA may repeat material despite not understanding key words; a patient with nonfluent or agrammatic PPA may struggle because production is effortful; a patient with logopenic PPA shows the characteristic conjunction of retrieval pauses and poor repetition of phrases and sentences while single-word comprehension and object knowledge remain relatively intact. The examiner should therefore describe the reason repetition fails, not merely record "impaired."

The major nosological caution is pathological. Logopenic PPA is associated with left temporoparietal dysfunction and is commonly linked to Alzheimer pathology, whereas semantic and nonfluent or agrammatic PPA are associated with the FTD spectrum. Calling every progressive aphasia "frontotemporal dementia" therefore confuses a clinical language phenotype with its usual underlying disease. Conversely, acknowledging the Alzheimer association should not erase the value of the logopenic clinical label.

TRAP **Do not present logopenic PPA as unambiguously the same kind of FTD-spectrum subtype as semantic and nonfluent PPA.** It belongs in the clinical PPA comparison, but the diagnostic manual and textbook pathology framing link it more often to Alzheimer disease.

A compact synthesis is to listen for fluency, then test meaning, grammar, motor speech, retrieval and repetition. Fluent but semantically empty speech points toward semantic PPA. Effortful, halting or grammatically impoverished production points toward nonfluent or agrammatic PPA. Word-finding pauses with disproportionately impaired phrase and sentence repetition point toward logopenic PPA. In every case, the subtype is a pattern of deficits and preservations, not a synonym for any isolated naming failure.

Memorise the organising contrast: bvFTD leads with progressive social-executive and behavioural change; semantic PPA loses word meaning, nonfluent or agrammatic PPA loses fluent grammatical production, and logopenic PPA combines word-retrieval difficulty with impaired phrase and sentence repetition and is associated with Alzheimer disease.

12 · Frontotemporal dementia: molecular pathology, genetics and the motor-neurone-disease overlap

The examination hinge is a three-way mapping. A frontotemporal clinical syndrome must be related to its dominant molecular pathology, its possible genetic cause, and the possibility of motor-neurone disease. These are related layers, but they are not interchangeable. A behavioural or language phenotype describes the patient; a proteinopathy describes the tissue; a pathogenic variant or repeat expansion describes a cause. The marks lie in moving accurately between those layers without claiming that phenotype alone proves genotype or pathology.

This framework also explains why frontotemporal dementia and amyotrophic lateral sclerosis cannot be kept in separate conceptual boxes. Some families and patients express predominantly cognitive-behavioural disease, some predominantly motor disease, and some both. Shared molecular pathology, particularly **transactive response DNA-binding protein pathology**, provides the bridge. The practical consequence is reciprocal vigilance: assess motor function in frontotemporal syndromes and assess behaviour, executive function and language in motor-neurone disease.

12.1 From clinical syndrome to molecular disease

Frontotemporal lobar degeneration is the pathological umbrella underlying several frontotemporal clinical phenotypes. Molecular classification asks which abnormal protein predominates in neuronal or glial inclusions. The broadest useful division is between **FTLD-tau**, a group with tau-positive inclusions, and the tau-negative group with ubiquitin and p62-positive inclusions, most often represented by **FTLD-TDP**. A smaller **FTLD-FUS** category is particularly relevant to behavioural presentations. These labels are pathological, not alternative names for the behavioural variant or a primary progressive aphasia.

RULE **Keep phenotype, protein and gene on separate lines of the answer.** State the clinical syndrome first, then the likely proteinopathy, then the associated genetic causes. A strong association supports a hypothesis; it does not make bedside phenotype a molecular assay.

The distribution is broad enough to make all of these categories important. Tau-positive disease accounts for **36-50%** of frontotemporal lobar degeneration, TDP-positive disease represents about **50%** of frontotemporal dementia, and FUS pathology accounts for about **10%** of behavioural-variant frontotemporal dementia. The denominators differ, so these figures should not be forced into a single pie chart. Their value is to show that tau and TDP pathology dominate, while FUS is a smaller but examinable group.

36-50%	ABOUT 50%	ABOUT 10%	30-60%
FTLD WITH TAU PATHOLOGY	FTD WITH TDP PATHOLOGY	BVFTD WITH FUS PATHOLOGY	FTD WITH SUBCLINICAL MOTOR EVIDENCE

Within the tau-positive group sit classic tauopathies including Pick disease, corticobasal degeneration, progressive supranuclear palsy and dementia caused by a tau-gene mutation. Within the tau-negative ubiquitin/p62-positive group, intracellular TDP-positive inclusions are

the common pattern. This first-pass taxonomy is more useful than memorising disconnected lists because it predicts where the major genes fit.

12.2 Gene-to-protein mapping

The common familial causes cluster around three major genes: **MAPT**, **GRN**, also called PGRN in some texts, and the **C9ORF72** repeat expansion. The first maps to tau pathology. The progranulin gene maps to TDP pathology despite not encoding TDP itself. The repeat expansion is likewise associated with TDP pathology but may also generate ubiquitin/p62-positive, TDP-negative inclusions, especially in the cerebellum. Thus, a gene may predict the inclusion class without being the protein deposited in the inclusion.

GENETIC CAUSE	DOMINANT PATHOLOGICAL ASSOCIATION	CLINICAL OR ANATOMICAL CLUE
Tau-gene mutation	Tau-positive inclusions	Behavioural presentation is common; onset tends to be younger, with symmetric anteromedial temporal atrophy
Progranulin-gene mutation	TDP-positive inclusions	Behavioural and neuropsychiatric features are common; language and extrapyramidal involvement may appear, with asymmetric frontotemporal-parietal atrophy
Major repeat expansion	TDP-positive plus ubiquitin/p62-positive, TDP-negative inclusions	Behavioural disease, motor-neurone disease, or both; more generalised atrophy with thalamic and sometimes cerebellar involvement
VCP mutation	TDP-positive inclusions	Behavioural change, executive dysfunction and aphasia; may occur with motor disease, **inclusion-body myopathy** or Paget disease of bone
TARDBP mutation	TDP-related disease	Behavioural or semantic presentation, with or without motor-neurone disease
CHMP2B mutation	Ubiquitin/p62-positive but TDP-negative inclusions	Behavioural frontotemporal dementia or combined frontotemporal and motor disease
TBK1 loss-of-function mutation	FTD-MND spectrum association	Motor disease may accompany semantic or non-fluent aphasic presentations
FUS-related disease	FUS proteinopathy	Combined frontotemporal and motor-neurone phenotype or amyotrophic lateral sclerosis

The table is a map of associations, not a diagnostic algorithm. A behavioural phenotype can arise from more than one genetic or protein category, and the same gene can produce different phenotypes. Conversely, apparently sporadic disease does not establish absence of a genetic cause. Family history, neurological examination, neuroimaging and appropriate genetic assessment must be interpreted together.

The map matters because each layer answers a different question. Phenotype guides what is examined and followed; the atrophy pattern tests anatomical coherence; pathology explains the protein class; genetics may identify an aetiological route and inform relatives. Collapsing these questions produces false certainty. Keeping them separate allows convergence: a result becomes persuasive when the history, examination, imaging, pedigree and molecular finding point in the same direction, while discordance becomes a reason to recheck assumptions rather than discard inconvenient evidence.

MNEMONIC

Three layers: Face, Filing, Fault

Face is the clinical phenotype seen at the bedside; **Filing** is the protein inclusion category used by pathology; **Fault** is the causal genetic lesion. The mnemonic prevents the common error of treating one layer as proof of another.

12.3 The major familial patterns

The tau-gene form tends to present with a behavioural syndrome and at a younger age. The progranulin form also commonly produces a behavioural syndrome, but neuropsychiatric symptoms, early language involvement and extrapyramidal features are notable. Around half of affected patients in the cited series have extrapyramidal symptoms. The repeat-expansion form commonly produces behavioural frontotemporal dementia, amyotrophic lateral sclerosis, or their combination; apathy, disinhibition, impaired empathy and executive dysfunction are characteristic behavioural features. These are tendencies, not mutually exclusive templates.

The numerical contribution of a gene depends on the denominator. Progranulin loss-of-function mutations may account for **up to 5-10% of all FTD**, while a separate familial-FTD table assigns this gene a larger share of familial cases. Those statements are compatible because “all FTD” and “familial FTD” are different populations. This is exactly why an answer should write the denominator beside the proportion rather than listing a naked percentage.

Use the phenotype to prioritise, not to close, the differential. A predominantly behavioural presentation can arise from the major tau, progranulin or repeat-expansion causes. Early language involvement with asymmetric frontotemporal-parietal atrophy supports the progranulin pathway, while a combined behavioural and motor-neurone phenotype makes the major expansion especially relevant. Behavioural change, executive dysfunction and aphasia accompanied by myopathy or bone disease form a more distinctive clue to the valosin-containing-protein pathway.

Less common associations broaden the phenotype. A transactive DNA-binding-protein gene mutation may produce behavioural or semantic disease with or without motor-neurone involvement. The charged multivesicular-body-protein gene is unusual because its inclusions are ubiquitin/p62-positive but TDP-negative. A loss-of-function kinase mutation can produce combined frontotemporal and motor disease, including semantic and non-fluent aphasic presentations associated with amyotrophic lateral sclerosis. These rarer patterns are best retained as discriminating clues after the major trio is secure.

12.4 The repeat expansion as the FTD-ALS bridge

One lesion unifies the continuum especially clearly. The major hexanucleotide repeat expansion is the most common genetic cause of both familial frontotemporal dementia and familial amyotrophic lateral sclerosis. Its usual clinical expressions are behavioural frontotemporal dementia, motor-neurone disease, or a combination. Its underlying pathology is characteristically TDP-related, although the additional cerebellar ubiquitin/p62-positive, TDP-negative inclusions remind the reader that its tissue signature is not completely uniform.

Psychosis is a useful clinical flag in this genetic context. Hallucinations and delusions occur in 30-50% of expansion carriers with frontotemporal disease in the cited account. This does not mean that psychosis identifies the mutation, nor that every late-onset psychotic presentation is neurodegenerative. It means that new psychotic symptoms should not be allowed to obscure a progressive behavioural-executive syndrome, especially when motor disease or a relevant family history is present. The formal differentiation of behavioural-variant frontotemporal dementia from primary psychiatric disorders belongs in the dedicated differential-diagnosis section.

Neuroimaging offers another clue. Compared with other genetic forms, expansion-associated disease has a more generalised atrophy pattern, with thalamic and sometimes cerebellar atrophy as distinguishing features. This should be read probabilistically. It raises coherence between the clinical and genetic hypotheses; it does not by itself establish a molecular diagnosis. The principles and physics of the modalities belong in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

TRAP **Do not quote one universal prevalence for the repeat expansion in familial FTD.** The New Oxford Textbook of Psychiatry gives about 25% of familial FTD, while separate passages in another major textbook give materially discordant estimates, including an internally lower estimate and another close to the New Oxford figure. State the source and denominator, and acknowledge the discrepancy rather than averaging it or resolving it by fiat.

12.5 When and how to think genetically

Genetic thinking begins with a pedigree, not with indiscriminate testing. Ask about progressive behavioural change, language decline, motor-neurone disease and related neurological syndromes across generations. Clarify the phenotype and age at onset in affected relatives where possible, while recognising that relatives may have been labelled with a psychiatric disorder, “dementia”, weakness, or speech difficulty without a molecular diagnosis. A negative or vague family history lowers confidence but does not convert the case into proven non-genetic disease.

Testing should be considered when **one first-degree relative** is affected in a family compatible with the major progranulin, tau or repeat-expansion causes. Testing for the expansion deserves particular consideration in behavioural-variant frontotemporal dementia, and in late-onset psychiatric presentations when one first-degree relative has frontotemporal dementia or amyotrophic lateral sclerosis. The indication rests on the combined phenotype and pedigree, not on a single symptom.

GOOD TO REMEMBER

Before requesting testing, write down the question the result is meant to answer: confirmation in an affected person, clarification of a familial syndrome, or assessment of an at-risk relative. Then arrange appropriate genetic counselling. A result can affect relatives as well as the person tested, so consent must include familial implications, uncertainty and the possibility that phenotype cannot be predicted precisely.

In practice, construct a multigenerational pedigree with behavioural, language and motor phenotypes recorded separately. When feasible, testing an affected relative first gives the result a clinically anchored context. Use counselling before and after testing, and do not present a pathogenic finding as a precise forecast of symptoms or course. Imaging and pathology associations remain supportive mappings rather than substitutes for a validated molecular result.

Presymptomatic testing raises additional autonomy, confidentiality and family-communication issues. Those issues should be handled through a clinical genetics pathway rather than as a routine laboratory add-on. For the psychiatrist, the core task is to recognise the indication, document capacity and consent carefully, avoid coercive family dynamics, and continue clinical care regardless of whether testing is accepted.

12.6 Motor-neurone disease within frontotemporal degeneration

The overlap is both clinical and pathological. One source reports co-occurring motor-neurone disease in 5-10% of people with FTD; another reports that 10-15% develop it. These adjacent but non-identical ranges should be presented separately because the wording and sampled populations may differ. More importantly, motor disease may precede, accompany, or follow the diagnosis of frontotemporal dementia. Timing therefore cannot be used to exclude the relationship.

Subclinical involvement is even more frequent: electromyographic evidence or mild motor signs such as fasciculations are reported in 30-60% of patients with frontotemporal dementia. Clinically evident motor disease occurs most often with the behavioural variant and less often with semantic or non-fluent aphasic syndromes. Conversely, frontotemporal dementia has been reported in as many as 48% of patients with bulbar-onset amyotrophic lateral sclerosis. This reciprocal enrichment is why screening in only one direction misses disease.

STARTING PRESENTATION	WHAT TO SEEK	INTERPRETIVE POINT
Frontotemporal behavioural syndrome	Weakness, wasting, fasciculations, speech or swallowing change, and evolving functional motor difficulty	Motor disease may emerge before, during or after the cognitive-behavioural diagnosis
Progressive language syndrome	Motor symptoms and signs, particularly when semantic or non-fluent language change coexists with amyotrophic lateral sclerosis	Consider the FTD-MND spectrum, including the kinase loss-of-function association
Motor-neurone disease	Apathy, disinhibition, impaired empathy, executive dysfunction and progressive language change	Cognitive-behavioural symptoms may be part of the same neurodegenerative process
Late-onset psychiatric presentation	Progression, neurological signs, functional decline and a first-degree family history of frontotemporal dementia or amyotrophic lateral sclerosis	A psychiatric label should not terminate neurological and genetic assessment

Pathologically, affected people have ubiquitin-positive and TDP-positive inclusions in lower motor neurons of the spinal cord and in hippocampal granule cells. The shared TDP pathology supports the view that frontotemporal dementia and motor-neurone disease form a spectrum rather than merely co-occurring by chance. This is a disease-model statement, not a claim that every case at either end has clinically obvious involvement of the other.

At review, the motor component should be treated as longitudinal information rather than a single checkbox. Record weakness, wasting, fasciculations, speech and swallowing change, and compare them over time. In the opposite direction, speak with an informant about altered initiative, social conduct, empathy, judgement and language because disability can make cognitive-behavioural change easy to overlook. When examination or history raises concern, neurological collaboration and targeted motor assessment are more defensible than reassurance based on the absence of a dramatic motor presentation.

PITFALL

Do not wait for dramatic weakness before considering the overlap. Mild fasciculations, subtle wasting, changing speech or swallowing, or an unexpectedly abnormal motor examination may be the clue. Equally, do not attribute apathy or reduced speech automatically to respiratory burden or disability in motor-neurone disease without examining executive, behavioural and language change.

12.7 Integrating phenotype, imaging, pathology and pedigree

A disciplined synthesis begins at the bedside and moves outward. First define whether the dominant syndrome is behavioural, semantic-language, non-fluent-language, motor, or combined. Next ask whether the imaging distribution supports a known genetic pattern: symmetric anteromedial temporal involvement for the tau-gene form, asymmetric frontotemporal-parietal

involvement for the progranulin form, or more generalised disease with thalamic and cerebellar involvement for the major expansion. Then add the pedigree and motor examination. Only after these steps should the gene-to-protein map be used to prioritise molecular explanations.

This approach prevents two opposite errors. Overcalling occurs when a suggestive phenotype is treated as proof of a mutation. Undercalling occurs when a psychiatric presentation or apparently isolated motor syndrome is allowed to conceal progressive frontotemporal disease. In both directions, longitudinal change matters: progression and recruitment of another domain make a shared neurodegenerative process more coherent, whereas a static or internally inconsistent picture should prompt reconsideration without reflexively forcing a genetic label.

- **Phenotype:** identify the dominant cognitive-behavioural, language or motor syndrome.
- **Pattern:** describe the atrophy distribution without turning it into a genetic test.
- **Pedigree:** search for differently expressed but potentially related syndromes in relatives.
- **Protein:** map the prioritised gene to tau, TDP, ubiquitin/p62 or FUS pathology.
- **Plan:** arrange counselling and targeted testing when the phenotype-family combination supports it.

Several associations deserve special recall. Progranulin and valosin-containing-protein mutations map to TDP-positive disease. The charged multivesicular-body-protein mutation maps to ubiquitin/p62-positive but TDP-negative disease. The major expansion may show both patterns. The kinase loss-of-function pathway should be considered when amyotrophic lateral sclerosis accompanies semantic or non-fluent aphasia. Together, these exceptions show why “tau-negative” is only an entry point, not a complete molecular diagnosis.

12.8 Writing the high-scoring synthesis

A complete answer can be organised as a compact causal chain. Begin with the pathological division into tau-positive and predominantly TDP-related tau-negative disease, while naming the smaller FUS group. Map the major familial genes to those proteins. Give the characteristic behavioural, language, motor and imaging clues without implying deterministic prediction. Then explain the frontotemporal dementia and motor-neurone disease continuum through shared TDP pathology, reciprocal clinical screening and the major repeat expansion. End with pedigree-based testing and counselling.

Use denominators precisely. “All FTD”, “familial FTD”, “familial FTD-MND”, “amyotrophic lateral sclerosis” and “behavioural-variant FTD” are not interchangeable study populations. The same discipline applies to clinical versus subclinical motor disease. Where authoritative textbook estimates disagree, name the disagreement rather than manufacturing consensus. Where the pathogenic repeat-count threshold is not supplied by the available source, omit the number rather than importing one from memory.

> FTD is a phenotype-to-protein-to-gene problem, and its motor-neurone overlap is best understood as a shared TDP-pathology spectrum.

The safest final sentence is clinical: frontotemporal syndromes require active enquiry for motor disease, motor-neurone disease requires active enquiry for behavioural and language change, and a suggestive family history should trigger genetics-informed assessment rather than an automatic test order. This closes the loop from molecular pathology back to patient care without confusing association with proof.

13 · Differentiating bvFTD from primary psychiatric disorders and from Alzheimer's disease

The difficult bvFTD diagnosis is rarely the florid textbook presentation. It is the patient whose altered conduct, affect, beliefs or social judgement first looks psychiatric, or whose dysexecutive and behavioural syndrome is attributed to Alzheimer disease (AD). The marks lie in showing how the clinician moves beyond resemblance: establish progression, obtain collateral evidence of change from baseline, examine cognition and neurological signs, look for a coherent neurodegenerative pattern, and use disease-directed biomarkers when the competing explanation is AD.

The differential is consequential because psychiatric presentation is common, while neither a behavioural phenotype nor a single abnormal investigation settles aetiology. The task is not to decide whether behaviour is "neurological" or "psychiatric" by appearance. It is to ask which formulation best explains the whole trajectory, including function, cognition, examination, imaging and follow-up. Full diagnostic features of bvFTD and the primary progressive aphasias are covered with the frontotemporal dementia syndromes; this section owns the distinction from primary psychiatric disorders and AD.

13.1 Why bvFTD enters psychiatry first

Behavioural change can precede an obvious complaint of cognitive failure. Patients may therefore be brought for apparent depression, psychosis, bipolar illness, compulsive behaviour or personality change rather than for "dementia." **Behavioural-variant frontotemporal neurocognitive disorder** is often mistaken for a primary mental disorder and commonly first reaches psychiatric services. The psychiatrist is not merely receiving a referral error; psychiatry may be the natural first clinical setting in which the syndrome becomes visible.

The scale of the problem is substantial. **Up to 50%** of people with bvFTD are initially diagnosed as having a primary psychiatric disorder, most commonly depression. A separate source reports that **6%** initially receive a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, depression or an unspecified psychotic state. These figures describe differently framed observations and should not be combined into a new estimate. Their shared lesson is that an initial psychiatric label cannot close the case when the subsequent course suggests neurodegeneration.

UP TO 50%	6%	10-40%
FIRST LABELLED PSYCHIATRIC	SPECIFIED INITIAL PSYCHIATRIC LABELS	CLINICAL BVFTD WITH AD PATHOLOGY

Diagnostic revision must nevertheless be disciplined. A psychiatric diagnosis is not disproved merely because the patient later behaves unusually, and a late behavioural presentation is not automatically bvFTD. The correct question is whether progressive neurocognitive decline emerges over time and whether the behavioural presentation sits within convergent evidence of a frontotemporal neurodegenerative syndrome. This approach avoids two forms of stigma: dismissing neurological illness as "just psychiatric," and treating psychiatric illness as neurologically unreal.

RULE **Trajectory outranks first impression.** When bvFTD and a primary psychiatric disorder look similar at presentation, progressive neurocognitive decline and convergent evidence of neurodegeneration carry more diagnostic weight than the original symptom label.

13.2 The longitudinal discriminator

The central discriminator is progressive change from the person's previous level. According to **DSM-5-TR**, the development of progressive neurocognitive difficulties over time helps separate behavioural-variant frontotemporal neurocognitive disorder from primary mental disorders. "Progressive" should not be used as a decorative adjective. It requires evidence that cognition, behaviour or everyday competence is worsening rather than merely remaining unusual, fluctuating with context, or being described differently by different observers.

Collateral history is therefore structural evidence, not an optional supplement. The informant should reconstruct what the person was like before the change, what appeared first, what has accumulated since, and which ordinary roles have become unreliable. Concrete examples are superior to labels. "He has lost empathy" is less informative than a description of repeated socially inappropriate decisions that are new for him and persist despite their consequences. The interviewer then tests whether examples across home, work and relationships form a single evolving pattern.

Serial review also protects against premature certainty. At an early encounter, the clinician may reasonably retain competing formulations. Follow-up asks whether new executive or social-cognitive difficulty appears, whether functional decline becomes demonstrable, and whether neurological or imaging evidence develops. The diagnosis should become more confident because independent lines of evidence converge, not simply because the same behavioural complaint has been repeated at several visits.

The physiological attribution of psychiatric symptoms must also be explicit. If delusions or other symptoms characteristic of a primary mental disorder are judged to arise from the physiological effects of frontotemporal degeneration, the appropriate mental disorder due to frontotemporal degeneration is coded rather than the corresponding primary disorder. The point is causal formulation: the symptom is acknowledged fully, but its diagnostic home changes when the evidence supports a neurodegenerative cause.

TRAP **"Behavioural symptoms mean psychiatric disease; memory symptoms mean dementia."** bvFTD commonly presents to psychiatry, and the useful distinction comes from progression, functional change, focused examination and evidence of neurodegeneration, not from sorting symptoms into crude professional territories.

13.3 Focused assessment when the presentation looks psychiatric

The **Neuropsychiatric International Consortium for Frontotemporal Dementia (NIC-FTD)** developed guidance specifically to assist this differential. Its value is methodological: take a detailed symptom history, add tools designed for frontotemporal presentations, perform a purposeful bedside examination, and integrate the findings with imaging and biological evidence. A generic psychiatric interview alone may describe the presenting symptom accurately while failing to test the neurodegenerative alternative.

FTD-directed instruments supported in that guidance include the Frontal Behavioral Inventory, Stereotypy Rating scale, DAPHNE, and Frontotemporal Dementia versus Primary Psychiatric Disorder Checklist. These instruments organise observations relevant to the differential; they are not substitutes for diagnosis. Their outputs must be interpreted beside informant history, baseline personality and function, because a scale records a pattern within the information supplied to it.

Bedside assessment should deliberately look for **executive dysfunction and impaired social cognition**. Social cognition is typically more impaired in bvFTD than in primary psychiatric disorders. The examiner should also look for parkinsonism and upper motor-neurone signs. These findings matter because they widen the syndrome beyond a purely descriptive account of mood, belief or conduct. Their absence does not settle the differential, but their presence can create clinically coherent convergence.

DIAGNOSTIC AXIS	FINDING THAT FAVOURS BVFTD	INTERPRETIVE CAUTION
Course	Progressive neurocognitive difficulty over time	Do not infer progression from a single dramatic encounter
Function	Continuing decline from the person's baseline	Apparent preservation requires corroboration in real roles
Cognition	Executive and social-cognitive impairment	A general screen may not capture the relevant pattern
Neurological examination	Parkinsonism or upper motor-neurone signs	Absence does not exclude bvFTD
Structural pattern	Frontal or anterior temporal atrophy	Interpret within the clinical syndrome
Neuronal injury marker	Raised serum or CSF neurofilament light may support neurodegeneration	No universal numeric cut-off is supplied here
Follow-up	Accumulating concordant evidence of decline	Non-progression raises the phenocopy question

General administration and scoring of cognitive screens belongs in the Psychometry, Assessment and Descriptive Psychopathology notes. In this differential, the purpose of testing is narrower: identify whether the profile and everyday history support progressive executive and social-cognitive dysfunction, and decide whether specialist neuropsychological assessment would resolve a meaningful uncertainty.

GOOD TO REMEMBER

Write down one concrete baseline-to-current example for behaviour, cognition and function. If the formulation rests only on adjectives such as "odd," "apathetic" or "disinhibited," the evidence is too impressionistic to distinguish degeneration from a primary psychiatric presentation.

13.4 Imaging and biomarkers: seek convergence, not a magic test

Structural evidence becomes useful when it matches the syndrome. **Frontal or anterior temporal atrophy** makes bvFTD more likely in the psychiatric differential. Imaging should therefore be read as part of a pattern: the site of atrophy, the clinical phenotype and the longitudinal course should tell a compatible story. Imaging modality principles and physics are covered in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

Serum or CSF neurofilament light chain, as an indicator of neurodegeneration, may help distinguish bvFTD from primary psychiatric disorders. It does not identify an FTD subtype, and the permitted evidence gives no numeric decision threshold. A result should therefore be interpreted through the reporting laboratory and the clinical question rather than compared with a remembered value. The absence of a cut-off in this fragment is deliberate, not an invitation to improvise one.

A broader limitation must remain visible: **no serum or CSF biomarker** has been identified that distinguishes FTD from normal controls, and no biomarker differentiates FTD subtypes from one another. By contrast, accepted CSF biomarker combinations can help distinguish AD from FTD. Thus, biomarkers answer different questions. Neurofilament light may contribute evidence of neurodegeneration in the psychiatric differential; the amyloid and tau profile is used when AD is the competing pathology.

The CSF examination procedure and generic constituents are covered in the Neurology foundations for psychiatrists notes. Here, the psychiatrist's task is to choose the diagnostic question, interpret the disease-directed pattern, and avoid turning a supportive result into a stand-alone verdict.

PITFALL

Do not use a normal-looking scan or an isolated laboratory result as a shortcut to "primary psychiatric disorder." Revisit image pattern, timing, functional trajectory and the exact biological question the assay can answer. Conversely, do not diagnose bvFTD from a supportive marker without a compatible syndrome.

13.5 The phenocopy problem

bvFTD phenocopy syndrome describes a subset diagnosed clinically with bvFTD after caregiver-reported personality and behavioural change, but who do not show subsequent disease progression. The key discriminators are the absence of functional decline and the absence of imaging change over time. Its long-term prognosis is good, making an underlying neurodegenerative disorder less likely, although some phenocopy subjects may carry a genetic form of bvFTD.

Phenocopy is not a synonym for fabrication, trivial symptoms or an incompetent initial assessment. It is a longitudinal conclusion arising when a presentation resembles bvFTD but fails to acquire the expected evidence of progression. The clinician must therefore preserve the original observations while revising the causal interpretation. Caregiver reports can be accurate descriptions of changed behaviour even when the subsequent course does not support active neurodegeneration.

The concept prevents diagnostic inertia. Once "bvFTD" appears in a record, later clinicians may reinterpret every behaviour through that label and stop asking whether function or imaging has actually changed. A phenocopy-aware review returns to measurable trajectory. The same discipline works in the opposite direction: absence of decline over an insufficiently informative observation period should not be inflated into certainty. The permitted evidence establishes the defining lack of functional and imaging progression, but does not supply a minimum surveillance interval.

Genetics adds a final caution. The presence of a genetic form in some phenocopy subjects means that non-progression cannot be translated into a universal claim of "non-genetic" or "non-FTD." It is better to document the observed course precisely and keep the aetiological formulation proportionate to the evidence. Detailed FTD molecular genetics belongs with the molecular pathology and motor-neurone-disease overlap discussion.

13.6 Distinguishing bvFTD from AD

Behavioural presentation does not guarantee frontotemporal pathology. Some **10-40%** of patients clinically diagnosed with bvFTD have subsequently shown AD pathology on amyloid PET or post-mortem evaluation. Yet diagnoses made in an expert centre are reported to be almost never due to AD pathology. The contrast is instructive: careful phenotyping and appropriate biomarkers can sharply reduce pathological misclassification, while a label based on behaviour alone remains vulnerable to overlap.

The most relevant clinical competitor is **behavioural-variant Alzheimer disease**. Compared with bvFTD, this AD presentation has worse memory impairment; its memory deficit does not differ from typical AD. Its executive impairment is greater than that seen in both bvFTD and typical AD. Therefore, "executive dysfunction equals bvFTD" is unsafe. The profile must be read across domains, with particular attention to the relative memory burden and the possibility that marked behavioural and executive change can arise from AD pathology.

AXIS	BVFTD	BEHAVIOURAL-VARIANT AD	HOW TO USE THE DISTINCTION
Presenting frame	Behavioural frontotemporal syndrome	Behavioural syndrome caused by AD pathology	Presentation alone does not establish pathology
Memory	Less impaired in the direct comparison	Worse than bvFTD and similar to typical AD	Weight the relative memory burden
Executive function	Less impaired in the reported comparison	More impaired than bvFTD and typical AD	Do not treat executive severity as FTD-specific
Amyloid pathology	Should prompt reconsideration of the clinical label	Supports the AD explanation	Use disease-directed evidence when phenotype overlaps
CSF amyloid signal	Higher relative to AD	Amyloid-beta-42 reduced relative to FTD	Interpret as part of the combined CSF pattern
CSF tau signal	Lower relative to AD	Total tau and phosphorylated tau increased relative to FTD	Combine with amyloid measures and ratios
Final formulation	Integrate phenotype, longitudinal course, imaging and pathology-directed biomarkers		A syndromic label and pathological cause are related but distinct

The accepted **combined CSF amyloid and tau profile** uses amyloid-beta-42, total tau and phosphorylated tau. In AD relative to FTD, CSF amyloid-beta-42 is reduced, while total tau and phosphorylated tau are increased. Diagnostic accuracy can be improved by combined analysis of amyloid-beta-42/amyloid-beta-40, total tau/amyloid-beta-42, or phosphorylated tau/amyloid-beta-42 ratios. No numeric concentration or ratio cut-off is supplied, so the examination-safe answer is the direction and combination, not an invented threshold.

Amyloid PET and CSF biomarkers should be used to answer the pathology question raised by clinical overlap. They do not replace the neurobehavioural history. Conversely, a convincing behavioural history should not prevent pathology-directed testing when the memory and executive profile or other evidence makes AD plausible. Structural and functional neuroimaging in dementia, and fluid biomarkers across dementias, are treated in their dedicated sections; the point here is how they resolve this particular differential.

13.7 Genetic and treatment clues without overreach

Some genetic presentations intensify the psychiatric resemblance. Carriers of **C9ORF72 mutations** may have psychosis as the dominant presenting problem and may initially be diagnosed with obsessive-compulsive disorder, schizophrenia or bipolar disorder. Carriers of GRN mutations may present with bulimia, personality change, sexual disinhibition, ritualistic behaviour or paranoia. These associations should raise diagnostic awareness; they do not justify genetic attribution from phenomenology alone.

Correct differentiation also changes therapeutic expectations. Cholinesterase inhibitors, including galantamine, and memantine are effective for cognitive or behavioural symptoms in AD but have shown no efficacy in FTD. By contrast, **SSRIs and trazodone for bvFTD behavioural symptoms** may improve disinhibition, depression, compulsive behaviour and carbohydrate craving. Olanzapine may help aggression, agitation and psychosis, but dopamine antagonism carries a risk of parkinsonism.

This is a diagnostic consequence, not a full prescribing algorithm. At the LOCUS of care, the clinician still targets the presenting risk and distress while the aetiological formulation is refined. The FOCUS is the symptom causing current impairment, and the MODUS may include environmental, caregiver, psychological and pharmacological measures appropriate to the person. Dementia cognitive-enhancer prescribing and behavioural-symptom management are covered elsewhere in the chapter. General antipsychotic pharmacology and adverse-effect teaching belongs in the Schizophrenia: management, antipsychotics and adverse effects notes.

Response to treatment should not be used backwards as a diagnostic test. Improvement in depression, agitation or compulsive behaviour does not prove a primary psychiatric disorder, because symptom-directed drugs may improve behavioural symptoms of bvFTD. Equally, non-response to an AD-effective cognitive drug does not by itself prove FTD. Treatment history contributes context, while diagnosis continues to rest on syndrome, trajectory and disease-directed evidence.

13.8 An integrated bedside and examination answer

Use a staged formulation rather than a checklist verdict. Begin with the behavioural syndrome and the patient's previous baseline. Establish whether progressive neurocognitive and functional decline is present. Obtain concrete collateral examples. Examine executive function, social cognition and neurological signs. Then seek convergent structural and biological evidence. If there is no functional or imaging progression, reconsider phenocopy. If AD remains plausible, use the memory-executive profile and pathology-directed biomarkers.

MNEMONIC

TRACE the behaviour

Trajectory of progressive decline; **R**elative or caregiver examples from baseline; **A**ssessment of executive function, social cognition and neurological signs; **C**oncordant frontal or anterior temporal imaging; **E**vidence from neurodegeneration markers or AD-directed biomarkers when the differential requires it.

The sequence can be operationalised in a short clinical answer:

- State why bvFTD is frequently labelled psychiatric and identify progressive neurocognitive decline as the key longitudinal discriminator.
- Add focused examination, FTD-directed scales, frontal or anterior temporal atrophy and neurofilament light as convergent evidence, while refusing an unsupported cut-off.

- Close the AD comparison with the memory-executive pattern, amyloid and tau directions, and the possibility of phenocopy when progression fails to appear.

When evidence conflicts, explain the conflict rather than averaging it away. A strongly psychiatric-looking presentation with progressive functional loss, impaired social cognition and concordant atrophy supports bvFTD despite the referral label. A behavioural syndrome with disproportionate memory impairment and an AD biomarker pattern supports behavioural-variant AD. A bvFTD-like presentation without functional or imaging progression raises phenocopy. Each conclusion is a synthesis of independent axes.

> In a behavioural presentation, diagnose bvFTD by progressive neurocognitive decline plus convergent clinical, imaging and biological evidence; then actively exclude phenocopy and Alzheimer pathology.

The mature formulation should state what is established, what remains provisional and what observation would change the diagnosis. That makes uncertainty clinically useful. It also prevents the two classic failures in this topic: retaining a primary psychiatric label after evidence of neurodegeneration has accumulated, and assigning bvFTD from behaviour alone without proving progression or addressing AD overlap.

The treatable, the rapid and the borderline

14 · Reversible dementias: the systematic workup and the treatable causes

Why it matters clinically. The phrase “reversible dementia” is useful only if it changes the diagnostic method. It should prompt a deliberate search for conditions that imitate, cause or compound a neurocognitive syndrome and for which directed treatment may improve cognition, behaviour or function. It should not imply that every positive finding explains the whole presentation, or that treatment restores every patient to the previous baseline.

The marks lie in showing a reproducible sequence: define the syndrome and tempo, identify red flags, perform a focused neurological and general examination, obtain a core laboratory screen, use structural imaging to exclude important intracranial causes, and order targeted tests when the history or examination supplies a reason. The answer becomes clinically mature when it closes the loop from abnormal result to treatment and reassessment rather than ending with a list of investigations.

TEMPO	SCREEN	IMAGE	REASSESS
FRAME THE SYNDROME	CORRECTABLE CAUSES	STRUCTURAL LESIONS	ATTRIBUTE RESPONSE

14.1 What “reversible” should mean

The **reversible-cause paradigm** is an instruction to look for therapeutic opportunity, not a promise of cure. Identifying vitamin deficiency, hypothyroidism or normal-pressure hydrocephalus can produce some symptomatic improvement. That wording matters:

improvement may be partial, a coexisting degenerative disorder may remain, and delay may limit recovery even when the cause is treatable. A candidate who writes “fully reversible” converts a clinical possibility into an unsupported guarantee.

Potentially reversible causes are uncommon but important. In old-age psychiatric and geriatric practice, estimates place them **between 1% and 8%** of patients with dementia. Low frequency does not justify omission because the consequence of missing a treatable intracranial, nutritional, endocrine, infective or metabolic disorder is disproportionate. Conversely, the search must remain disciplined: indiscriminate testing creates incidental findings that can be mistaken for causal explanations.

RULE **Screen systematically, investigate selectively, and verify attribution longitudinally.** A reversible abnormality becomes the cause of cognitive impairment only when the clinical context fits and treatment produces a coherent response, while alternative or coexisting neurocognitive disorders remain under review.

The useful distinction is between reversibility of a cause and reversibility of the entire cognitive syndrome. A deficiency can be corrected without every deficit resolving. A structural lesion can be treated while residual disability persists. A metabolic encephalopathy can clear while an underlying dementia becomes visible. Therefore document the pre-treatment phenotype and function, correct the identified disorder, and reassess the same domains. Without that comparison, “response” becomes impression rather than evidence.

TRAP **Equating a treatable test result with complete reversal of dementia.** The verified outcome is some improvement in symptoms, not a universal return to baseline. The finding may be contributory, coincidental or superimposed on a progressive disorder.

14.2 Build the workup around tempo and examination

A systematic workup begins before the laboratory form. Establish whether the complaint reflects impaired acquisition, retrieval, language, executive control, behaviour, arousal or general slowing, and whether everyday function has changed. Reconstruct onset, progression, fluctuation and the order in which cognitive, gait, urinary, focal neurological and systemic features appeared. An informant can clarify chronology, but discrepancies between accounts should be examined rather than averaged away.

Tempo changes the question. A slowly progressive amnestic syndrome and a fluctuating or rapidly evolving global disturbance should not receive identical differentials. Examine consciousness, attention, speech, eye movements, visual fields, motor tone, power, reflexes, coordination, gait and involuntary movement, then add general examination for nutritional, endocrine, hepatic, renal, infective or malignant clues. The purpose is not to perform an unstructured “complete examination.” It is to generate hypotheses that determine which reversible pathways deserve priority.

Several categories should remain visible from the outset. **Depressive pseudodementia** may resemble a neurocognitive disorder and is differentiated in its dedicated section. **Normal-**

pressure hydrocephalus, subdural haematoma and intracranial tumour are structural possibilities. Deficiency, endocrine, infective, alcohol-related, metabolic and immune-mediated disorders broaden the search beyond the brain scan. The detailed phenotype and management of normal-pressure hydrocephalus and depressive pseudodementia belong to their respective sections of this chapter.

Red flags against a straightforward Alzheimer disease diagnosis include onset at an unusually young age, fluctuation in consciousness, behavioural or personality disturbance overshadowing cognitive loss, rapid progression, gait impairment, lateralised findings, movement disorder, myoclonus, rigidity or bradykinesia. A patient **younger than 65 years** deserves particular diagnostic caution, while development over **6 to 12 months** should redirect attention toward rapidly progressive, infective, immune-mediated and other alternative causes. This section names those routes; rapidly progressive and prion dementias are taught elsewhere in this chapter, and the autoimmune and limbic encephalitis workup belongs in the Neuropsychiatry of systemic and neurological disease notes.

- Describe the cognitive-behavioural syndrome and establish functional decline rather than accepting “memory loss” as the phenotype.
- Use onset, tempo, fluctuation and symptom order to rank structural, systemic and progressive explanations.
- Let examination findings determine targeted tests while retaining a standard core screen for correctable contributors.

14.3 The core laboratory screen

The **baseline laboratory screen** is designed to rule out correctable or contributory causes, not to diagnose a particular degenerative dementia. It includes complete blood count, serum electrolytes, renal and hepatic function, glucose, albumin and protein, vitamin B12 and folate, thyroid-stimulating hormone, urinalysis and a syphilis screen. History-guided additions include a further syphilis test, erythrocyte sedimentation rate and HIV testing. The exact request should reflect local laboratory pathways and the patient’s exposure and examination findings.

WORKUP DOMAIN	CORE OR TARGETED COMPONENTS	QUESTION ANSWERED
Haematological and biochemical	Complete blood count, electrolytes, glucose, albumin and protein	Is a general medical or nutritional disturbance contributing to cognitive dysfunction?
Organ function	Renal and hepatic function	Is impaired clearance or organ failure producing a metabolic cognitive syndrome?
Endocrine	Thyroid-stimulating hormone; calcium is captured through the chemistry assessment	Is an endocrine abnormality present that warrants disease-specific evaluation?
Nutritional	Blood concentrations of vitamin B12 and folate	Is a highly treatable deficiency present?
Infective	Syphilis screening; HIV testing when indicated by history	Does the clinical context justify a directed infective pathway?
Urinary and inflammatory	Urinalysis; erythrocyte sedimentation rate when history guides it	Is there evidence of a contributory systemic process requiring clarification?

Interpretation is the difficult part. An abnormal value must be judged for severity, temporal fit and capacity to explain the observed phenotype. A mild unrelated abnormality should not stop evaluation of a progressive syndrome. Equally, a convincing correctable abnormality should not be filed as "medical" and ignored by psychiatry. The result should trigger confirmation where appropriate, referral or treatment, and repeat cognitive-functional assessment after correction.

Vitamin B12 and folate deficiency are relatively rare but highly treatable causes, so their blood concentrations should be checked in cognitive decline. Numeric reference cut-offs and detailed replacement regimens are intentionally not reproduced here because the disease-level teaching belongs in the Endocrine and metabolic psychiatry notes. The same boundary applies to thyroid, calcium, glucose, hepatic and renal disorders: this chapter teaches their place in the dementia workup, not their full systemic management.

> **GOOD TO REMEMBER**
>
> A laboratory panel is not complete when the results return. Record which abnormality plausibly explains which cognitive or neurological domain, arrange correction or specialist evaluation, and specify what clinical change will be reassessed.

14.4 Structural imaging: routine purpose and selective priority

Structural neuroimaging in the dementia workup looks for normal-pressure hydrocephalus, subdural haematoma, brain tumour or metastases, and cerebrovascular events. Computed tomography is generally sufficient for this exclusionary task. Magnetic resonance imaging is preferred when small or deep infarcts and vascular changes are the concern, and contrast-enhanced magnetic resonance imaging is appropriate when suspicion of tumour is high. The scan answers an anatomical question; it does not replace clinical phenotyping.

Where resources require prioritisation, **selective-imaging criteria** include recent onset, age under the stated threshold, fluctuations, focal symptoms or signs, headache, papilloedema or field defects, malignancy or head injury, seizures, previous stroke or transient ischaemic attacks, incontinence, and gait ataxia or apraxia. Strict application of these criteria detects **about 80%** of potentially reversible causes. That residual miss rate explains why many clinicians prefer structural imaging for every patient with dementia when feasible.

IN INDIA

Computed tomography may be the realistic initial structural study when access, cost or urgency limits magnetic resonance imaging. Use it deliberately to exclude hydrocephalus, subdural collection, mass lesion and major vascular pathology, then escalate to magnetic resonance imaging when the clinical question requires better definition of small, deep or vascular lesions. Resource limitation changes sequencing, not the obligation to recognise red flags.

Imaging should be read against the bedside hypothesis. Ventricular enlargement gains meaning when gait and urinary chronology support hydrocephalus. A collection matters when the history and examination make it plausible. A mass lesion becomes more concerning with focal findings, headache, papilloedema, field loss or malignancy. Conversely, a scan described as “atrophy” does not settle the aetiology of cognitive decline and should not terminate the reversible-cause search.

PITFALL

Do not let a normal scan close the workup or an abnormal scan monopolise it. Structural imaging cannot exclude nutritional, endocrine, infective or metabolic causes, while incidental anatomical abnormalities may not account for the cognitive syndrome.

Imaging modality physics belongs in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. Here, the examination answer should remain clinical: state what structural imaging is meant to exclude, why one modality may be preferred for a particular anatomical question, and how imaging findings will be integrated with tempo and examination.

14.5 A cause-based map of treatable pathways

The list of causes is easiest to retain as mechanisms linked to the test that opens each pathway. The categories overlap: a deficiency may coexist with alcohol-related illness, renal or hepatic dysfunction may alter attention as well as memory, and a structural lesion may produce psychiatric or focal neurological features. The map is therefore a set of prompts, not mutually exclusive boxes.

CATEGORY	EXAMPLES TO NAME	HOW THE PATHWAY OPENS	BOUNDARY OF THIS SECTION
Structural and psychiatric	Depressive pseudodementia, benign subfrontal tumour, normal-pressure hydrocephalus, subdural haematoma	Phenotype, neurological examination and structural imaging	Detailed diagnosis and treatment of pseudodementia and hydrocephalus are taught separately
Endocrine and nutritional	Hypothyroidism, hypercalcaemia, hypoglycaemia, Cushing disease and Addison disease; vitamin B12, thiamine, niacin and pyridoxine deficiency	Chemistry, thyroid and vitamin testing guided by clinical context	Disease mechanisms, cut-offs and replacement regimens belong in the Endocrine and metabolic psychiatry notes
Infective	HIV, neurosyphilis and cryptococcal infection; Whipple disease also appears in the broader reversible-cause list	Exposure and systemic clues followed by directed serology or cerebrospinal-fluid evaluation	Use a targeted pathway rather than indiscriminate infective panels
Metabolic and substance-related	Hepatic and renal insufficiency, alcohol-related dementia and **Wilson disease**	Organ-function tests, exposure history and disease-specific evaluation	Systemic diseases themselves belong in the Endocrine and metabolic psychiatry notes
Immune-mediated and endocrine-associated	Hashimoto encephalopathy and paraneoplastic or autoimmune limbic encephalitis	Atypical tempo, behavioural change, seizures or neurological signs prompt specialist assessment	The autoimmune and limbic encephalitis workup belongs in the Neuropsychiatry of systemic and neurological disease notes

Thiamine deficiency requires a specific conceptual pointer. Untreated deficiency may present acutely as Wernicke encephalopathy and may progress to Korsakoff psychosis. The acute entity is the therapeutic emergency; the chronic amnestic sequel is not a reason to delay treatment while awaiting a tidy dementia assessment. Full nutritional-disease teaching belongs in the Endocrine and metabolic psychiatry notes, while Korsakoff amnestic syndrome is covered in the Stroke, TBI, delirium and focal brain syndromes notes.

Alcohol-related cognitive impairment should not be reduced automatically to thiamine deficiency, nor should a vitamin result be treated as an adequate account of every cognitive symptom. The history must link exposure, nutrition, systemic illness and course. This is a general attribution principle across the table: name the treatable route, investigate it appropriately, and continue evaluating any residual pattern after correction.

MNEMONIC

MAP: Metabolic, Anatomical, Psychiatric

Metabolic gathers endocrine, nutritional, infective, organ-failure and substance-related pathways; **Anatomical** prompts hydrocephalus, collection, tumour and vascular disease; **Psychiatric** keeps depressive pseudodementia visible. MAP is a retrieval spine, not a substitute for tempo, examination or targeted testing.

14.6 Targeted infective, metabolic and fluid studies

Neurosyphilis illustrates why "order syphilis serology" is an incomplete answer. Begin with a treponemal test. A negative result makes syphilis very unlikely, although repeat testing may be needed after possible recent exposure. If the treponemal test is positive, add a nontreponemal test. A positive nontreponemal result leads to lumbar puncture and cerebrospinal-fluid analysis; a positive cerebrospinal-fluid VDRL confirms neurosyphilis, while false-negative results can occur. Supportive cerebrospinal-fluid abnormalities may justify presumptive diagnosis and treatment in the appropriate setting, with a low treatment threshold in HIV infection.

The sequence matters because each step changes the probability and the indication for the next. It also prevents two opposite errors: calling any positive syphilis test "neurosyphilis," and excluding neurosyphilis solely because a confirmatory cerebrospinal-fluid test is negative. This is a pointer to the infective reversible pathway, not a full account of general paresis or syphilis treatment.

Hepatic encephalopathy is linked to elevated serum ammonia. The classical examination clue is asterixis, and the electroencephalogram may show triphasic waves. Lactulose acidifies the gastrointestinal tract and converts ammonia to ammonium, which does not cross the blood-brain barrier, thereby reversing the encephalopathy. In a patient labelled as having dementia, fluctuation, motor signs and hepatic dysfunction should therefore trigger a metabolic formulation rather than premature attribution to degeneration.

Cerebrospinal fluid has a selective role in the broader differential. It can demonstrate altered amyloid-beta and tau patterns in Alzheimer disease and elevated **14-3-3 protein** and neuron-specific enolase in prion disease. These studies are not part of a universal "reversible dementia panel," and their interpretation belongs with the suspected syndrome. Dementia-specific biomarkers are covered elsewhere in this chapter; lumbar-puncture technique and generic cerebrospinal-fluid examination belong in the Neurology foundations for psychiatrists notes.

14.7 Acting on a positive screen

A workup earns its value through action. LOCUS depends on clinical stability. A stable patient may complete the core screen and imaging through outpatient care, whereas acute fluctuation, impaired consciousness, rapidly evolving neurological signs or a suspected metabolic or infective encephalopathy requires urgent hospital assessment. The decision is driven by syndrome and physiological risk, not by whether the referral label says "dementia."

FOCUS is phased. The immediate target is a dangerous active cause such as encephalopathy, infection or intracranial pathology. The short-term target is correction of deficiency or endocrine and organ-function disturbance, together with treatment of the identified structural or psychiatric condition. The longer-term target is to determine what cognition and function remain after treatment, whether improvement is stable, and whether a coexisting progressive neurocognitive disorder is becoming clearer.

MODUS includes cause-specific medical treatment, procedural or surgical care for appropriate structural lesions, psychiatric treatment when depressive pseudodementia is established, rehabilitation, risk reduction, family education and serial clinical review. This section can verify lactulose as a route for hepatic encephalopathy and correction of identified vitamin, thyroid or hydrocephalus-related causes as routes to some symptomatic improvement. Detailed regimens, procedures and systemic-disease guidelines belong to their owning chapters or specialist services.

- Confirm that the abnormality is real and clinically relevant before declaring it causal.
- Treat or refer according to urgency, while documenting the cognitive, neurological and functional baseline.
- Reassess the same domains after correction and continue the dementia evaluation if deficits persist or progress.

Improvement should be described by domain rather than as a global impression. A patient may become more alert while memory remains impaired, walk better while executive dysfunction persists, or regain initiative while instrumental function remains limited. Domain-based reassessment prevents both therapeutic nihilism and exaggerated claims of cure. It also provides a cleaner baseline for later follow-up.

14.8 Examination synthesis

A strong long answer opens by qualifying the term: potentially reversible causes are uncommon, clinically important, and may yield some improvement rather than guaranteed full recovery. It then presents the sequence of history, tempo, cognitive and neurological examination, core laboratory tests and structural imaging. Red flags justify accelerated or targeted investigation, while the positive result must be linked to a plausible mechanism and followed through to treatment and reassessment.

The cause list should be organised, not dumped. Name structural and psychiatric mimics, endocrine and nutritional causes, infections, organ-failure and substance-related states, and immune-mediated disorders. Add one or two pathways to show method: the staged serological and cerebrospinal-fluid approach to neurosyphilis, or the clinical and treatment logic of hepatic encephalopathy. Then state the ownership boundaries rather than drifting into full endocrine, nutritional, autoimmune or hydrocephalus teaching.

The final sentence should restore diagnostic humility. Correction of a reversible contributor neither proves that it caused every deficit nor excludes a coexisting progressive dementia. Failure to improve does not retrospectively make the workup unnecessary, because the investigation may

still have treated a harmful contributor. The defensible endpoint is a revised formulation based on treatment response, residual phenotype and longitudinal course.

> "Reversible dementia" means a systematic search for treatable contributors followed by cause-specific treatment and domain-based reassessment; it does not mean that complete cognitive recovery is guaranteed.

15 · Depressive pseudodementia: features and differentiation from true dementia

Why it matters clinically. A patient with low mood, slowed thinking and poor recall may look as though a progressive dementia has begun. The reverse error is equally consequential: a progressive cognitive disorder may first become visible through depression. The marks in this topic therefore lie not in reciting a stereotype, but in showing how history, observed behaviour, repeated bedside testing, mood assessment and longitudinal review are integrated without prematurely declaring either reversibility or degeneration.

Depressive pseudodementia is the more common and clinically important form of pseudodementia in which depressive illness presents with prominent memory, concentration and intellectual complaints. The traditional label remains useful as a clinical shorthand, but it can falsely imply that the impairment is unreal, voluntarily produced or guaranteed to disappear. When the cognitive disturbance meets the clinical threshold for dementia, many neuropsychiatrists prefer **reversible dementia syndrome**. This wording recognises genuine disability while leaving the trajectory open. The central task is to identify the depressive contribution, treat it, and continue surveillance for an underlying progressive disorder.

15.1 Terminology, validity and the continuum model

"Pseudo" should never be read as "pretended." The patient may be unable to work, manage domestic tasks or sustain ordinary conversation because attention, motivation, speed and retrieval have collapsed under a severe depressive state. The cognitive syndrome is real even when it later improves. A more accurate conceptual model is a **clinical continuum**. At one end, the depressive syndrome accounts for most of the cognitive disturbance. At the other, a progressive subclinical neurodegenerative disorder generates the impairment and depression adds to its severity. Many patients cannot be placed confidently at either end during the initial assessment.

This continuum changes the diagnostic question. The clinician should not ask only, "Is this depression or dementia?" The more useful questions are: How much of the current disability is state-dependent? Is there evidence of a progressive cognitive process independent of mood? What happens when time, encouragement and repeated learning opportunities are provided? Does cognition improve with remission, remain impaired, or deteriorate despite mood recovery? These questions allow a provisional formulation that can be revised as longitudinal evidence accumulates.

RULE **Reversibility is a longitudinal observation, not an assumption made from the first interview.** Diagnose and treat the depressive syndrome, document the cognitive phenotype, investigate competing causes, and deliberately reassess cognition after mood improvement.

The older description of pseudodementia as a readily correctable cause is therefore incomplete. It remains treatable, but it may also be a **harbinger of dementia**. The label should open a treatment window without closing the diagnostic work-up.

15.2 Clinical phenotype of depressive pseudodementia

The usual presentation is an older adult who complains of poor memory and concentration, sometimes while denying overt depression. The onset is relatively acute or subacute rather than an unmistakably gradual story of accumulating decline. Patients may emphasise inability, mental blankness and loss of competence. Their account can sound globally catastrophic, yet performance across the encounter may fluctuate. A past or family history of affective illness supports the formulation, but it cannot prove that the cognitive syndrome is purely depressive.

When sadness is minimised or denied, look for the **biological and cognitive features of depression**: disturbed sleep, low energy, psychomotor retardation, loss of interest in usual activities or hobbies, pessimistic thinking and rumination. The distinction is not made by vegetative symptoms alone. Sad mood and psychic depressive features are particularly useful when deciding whether depression is superimposed on a dementia syndrome rather than dementia occurring alone. The interview should therefore examine affective experience, self-appraisal and loss of pleasure as carefully as appetite or sleep.

MNEMONIC

PACE

A bedside spine for depressive pseudodementia: **P**resentation relatively acute or subacute; **A**ffective and biological clues; **C**ognitive performance patchy; **E**ncouragement and repeated trials may improve performance.

Psychomotor slowing deserves active observation. Long response latency, sparse speech and reduced spontaneous elaboration may look like aphasia or loss of knowledge. In depressive pseudodementia, however, language output is often slow and limited without the paraphasic errors that would make an acquired language disorder more persuasive. The examiner should separate reduced production from disordered language content. The same principle applies to everyday function: failure to initiate an activity is not equivalent to loss of the cognitive capacity needed to perform it, although both can coexist.

15.3 Bedside cognitive pattern

Attention is commonly impaired, so later failures may reflect weak engagement with the material at the point of encoding. Registration of a name and address and performance on digit span may initially be poor. The crucial manoeuvre is not merely to record failure, but to repeat the task with

calm pacing, sufficient time and explicit encouragement. Improvement across repeated trials supports a depressive contribution. A single hurried score conceals this dynamic information.

Memory and executive performance are often **patchy and inconsistent**. A patient may fail a formal item, then later reveal relevant information in conversation; solve a demanding component, then stop at an easier component; or show wide variation when effort and confidence change. Inconsistency is useful only when observed carefully. It should not be translated into malingering, and it does not exclude coexisting brain disease.

The characteristic verbal response is the **"don't know" answer**. This differs clinically from an incorrect but confident response, circumlocution or a paraphasic error. The depressed patient may abandon retrieval early, express certainty that recall is impossible, or refuse to guess because failure fits a pessimistic self-model. Encouragement may recover information that was accessible but not produced. By contrast, persistent loss of newly learned material despite adequate acquisition raises greater concern for a progressive amnestic process. The relevant contrast is with rapid forgetting, which is not the expected depressive pattern.

Acute	Patchy	"Don't know"	Recheck
ONSET CLUE	PERFORMANCE	RESPONSE STYLE	TRAJECTORY

Testing conditions themselves become diagnostic evidence. Depression need not substantially impair performance when the examiner provides adequate time and encouragement. This **effort and encouragement effect** is not a licence to coach the patient toward a desired diagnosis. Standard instructions should be preserved, while latency, persistence, response to reassurance and learning over repeated attempts are documented separately. The examiner is studying the process of performance, not only the final total.

15.4 Differentiation from a progressive dementia syndrome

The accompanying figure and the table below organise the discriminating features. No feature is decisive in isolation. Their value comes from convergence: tempo, depressive phenomenology, response style, consistency, learning across trials, error type and subsequent course should point in the same direction before confidence rises.

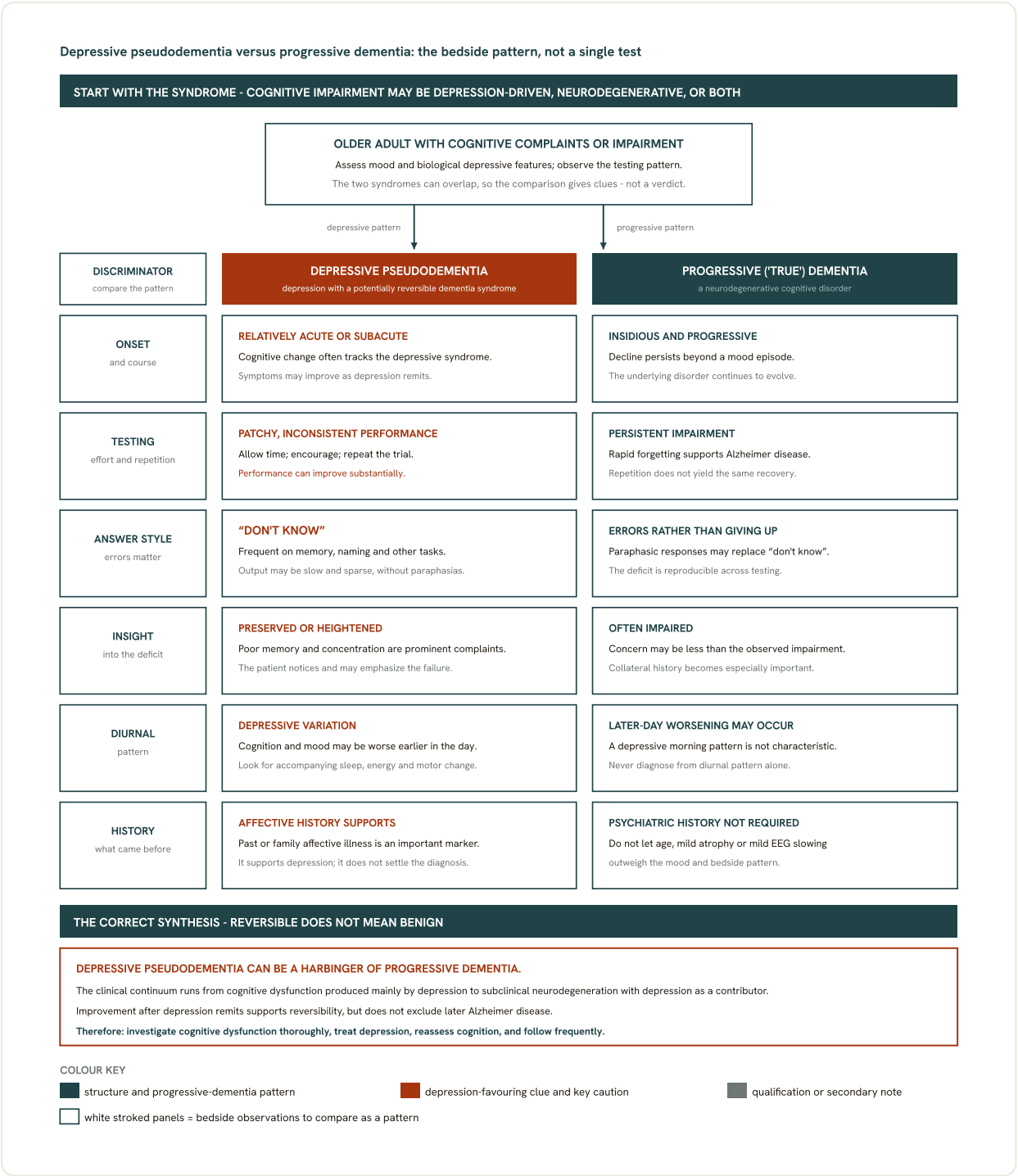

Fig 32.6 Depressive pseudodementia versus progressive dementia. Relatively acute onset, patchy effort-dependent performance, frequent "don't know" responses, preserved concern about deficits, depressive diurnal variation and an affective history favour depression with a reversible dementia syndrome; insidious progression, rapid forgetting, reproducible errors and reduced insight favour progressive dementia. The syndromes overlap: apparent cognitive recovery after depression does not exclude later Alzheimer disease, so diagnostic workup and frequent follow-up remain essential. (Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 2024; Kaufman's Clinical Neurology for Psychiatrists; Hodges, Cognitive Assessment for Clinicians.)

CLINICAL AXIS	DEPRESSIVE PSEUDODEMENTIA FAVOURED	PROGRESSIVE DEMENTIA FAVOURED	HOW TO USE THE DISTINCTION
Tempo	Relatively acute or subacute onset	Progressive course that becomes clearer with serial history	Anchor the history to change from the patient's prior level rather than to the consultation date
Subjective account	Prominent complaints of poor memory and concentration; overt depression may be denied	Complaint and observed impairment may not align	Obtain an informant account without treating either account as automatically superior
Depressive clues	Sleep disturbance, low energy, psychomotor slowing, anhedonia, pessimism and rumination	Depressive features may be absent, secondary or superimposed	Assess psychic depressive experience as well as vegetative change
Task engagement	Early abandonment, low confidence and "don't know" responses	May attempt answers despite errors	Record the response process rather than reducing it to correct versus incorrect
Consistency	Patchy performance across tasks or across the interview	A more coherent cognitive pattern may emerge	Seek convergence across history, examination and formal assessment
Repeated trials	Registration and span may improve with repetition, time and encouragement	New learning may remain impaired despite adequate opportunity	Document acquisition and retention separately
Error quality	Slow, sparse language without paraphasic errors; naming may elicit "don't know"	Specific error patterns may suggest an acquired cognitive syndrome	Distinguish reduced output from disordered content
Course after treatment	Cognition may improve or largely subside with remission, although deficits may remain	Persistent or progressive impairment becomes more evident	Reassess formally after mood improvement and continue follow-up

The table is asymmetric by design: the permitted bedside evidence describes the depressive pattern in detail, but "true dementia" is not a single neuropsychological phenotype. Its presentation varies with aetiology and disease stage. Accordingly, the right-hand column states directional concerns rather than pretending that every progressive dementia produces the same errors. Detailed dementia phenotyping belongs with the disorder-specific sections and formal cognitive assessment.

15.5 Diagnostic method and common clinical errors

A safe assessment begins with chronology and functional change. Establish what changed, how quickly it became apparent, whether the course tracks mood, and which activities fail because the patient cannot initiate them versus cannot understand, remember or sequence them. Interview an informant where possible, but examine discrepancies rather than resolving them by authority. Observe affect, psychomotor activity, spontaneity, latency and error style throughout the encounter. Bedside tasks then test hypotheses raised by the history.

The working formulation should remain layered. State whether a depressive syndrome is present, describe the cognitive domains affected, record features supporting state-dependent impairment, and state whether a progressive disorder remains possible. In an older depressed adult, cognitive dysfunction warrants a thorough diagnostic work-up and frequent follow-up aimed at identifying treatable neurocognitive disorders. The systematic reversible-dementia work-up is covered elsewhere in this chapter. General administration and scoring of cognitive screens belong to the Psychometry, Assessment and Descriptive Psychopathology notes.

- Repeat selected learning and attention tasks rather than treating the initial failure as final.
- Record “don’t know,” paraphasic errors, intrusions, abandonment and response latency separately.
- Link functional loss to its mechanism: poor initiation, poor persistence, failed acquisition or failed retention.
- Arrange reassessment after meaningful mood improvement, even when cognition appears to recover.
- Escalate to psychiatric opinion and formal neuropsychological evaluation when simple cognitive testing cannot resolve the distinction.

PITFALL

Age-related mild slowing on electroencephalography or cerebral atrophy on structural imaging can be overvalued when mood is under-assessed. Such findings do not substitute for a clinical account of tempo, depressive phenomenology, testing behaviour and trajectory. Imaging interpretation for dementia belongs with the dementia-specific assessment; modality principles are reviewed in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

At times, simple cognitive tests cannot distinguish depressive pseudodementia from a progressive dementia. That is not a failed examination. It is the correct recognition that bedside certainty has reached its limit. Psychiatric assessment clarifies the depressive syndrome, while formal neuropsychological evaluation examines the architecture and validity of performance in greater depth. Longitudinal review then supplies evidence that no cross-sectional test can provide.

15.6 The remission paradox

The classic teaching is that cognition improves or largely subsides after remission of depression, hence the terms **dementia syndrome of depression** and depression with reversible dementia.

This is clinically useful because it directs active treatment and reassessment. Yet "reversible" must describe an observed course, not a diagnostic promise. Even after mood symptoms settle, abnormal executive function, processing speed, memory consolidation and working memory may persist in many older patients with depression. Older adults with both depression and diabetes are particularly vulnerable to cognitive deficits.

TRAP **Do not write that late-life depression-associated cognitive impairment either always reverses or generally never reverses.** Separate chapters in the same major textbook place different emphasis on the evidence: the geriatric account defines a syndrome that improves or largely subsides with remission, while the main dementia discussion stresses persistence, especially in memory and executive function. The defensible answer surfaces the tension: substantial improvement may occur, residual deficits are common, and subsequent decline remains possible.

This apparent contradiction dissolves clinically when state and trait are separated. Depressive slowing, reduced effort and inefficient encoding may improve, while pre-existing vulnerability or an emerging progressive process remains. The patient can therefore be better without being cognitively normal. A binary endpoint such as "pseudodementia cured" misses domain-specific residual deficits, and a stable total score may conceal a changed pattern of strengths and weaknesses.

Remission also provides a cleaner diagnostic window. Reassessment should ask whether attention and engagement improved, whether acquisition now benefits from repetition, whether functional independence returned, and whether any impairment continues to progress outside depressive episodes. The goal is not to retrospectively prove that the original diagnosis was wrong. It is to update the formulation using better conditions for observing cognition.

15.7 Prognosis and surveillance

The prognostic message is deliberately uncomfortable. Pseudodementia predicts later **Alzheimer disease** in some, but not all, patients. Depression may have been a prodromal manifestation of the primary cognitive disorder, or the depressive cognitive syndrome may identify a subgroup with an underlying progressive process. Apparent recovery therefore lowers immediate impairment but does not erase future risk.

Even among people with nearly complete cognitive recovery, irreversible dementia has been reported at about **20% per year** during follow-up. Many may remain nondemented for **1 to 2 years** before irreversible dementia appears. In older adults with depression and mild cognitive impairment, about **40%** progressed to that disease within **27 months**. Recency adds prognostic weight: active depression in the recent past is a marker of greater risk than a remote history. This is another reason to interpret the cognitive presentation in temporal relation to the depressive episode rather than treating "past depression" as a single undifferentiated variable. Another account reports that patients initially appearing to have depression-induced cognitive impairment develop the same dementia **almost six times** as frequently as age-adjusted counterparts.

GOOD TO REMEMBER

A good response to depression treatment changes care but does not end it. Record a post-remission cognitive baseline, explain the need for surveillance without deterministic language, and ask the patient and family to return if function declines. Follow-up is part of the diagnosis because conversion risk remains elevated even after apparent cognitive recovery.

These figures should not be converted into a prediction for an individual patient. Their proper use is to justify structured follow-up, not to announce inevitable degeneration. The clinician should avoid both false reassurance and fatalism. A patient may remain cognitively stable; another may reveal a progressive disorder only after depressive symptoms remit. Clear documentation of baseline function, mood state and cognitive pattern makes later change interpretable.

15.8 The dissociative look-alike

The umbrella term pseudodementia has also been used for **hysterical pseudodementia**, a distinct syndrome from depressive pseudodementia. Its onset may be fairly abrupt, and the patient often appears unconcerned. Memory loss can be paradoxically greater for highly salient personal or remote autobiographical events than expected in an organic amnesic disorder; personal identity may be lost. Performance may become strikingly worse under formal testing than during informal conversation about recent events.

An identifiable precipitant such as bereavement, marital difficulty or offending, together with a past psychiatric history, may support this formulation. Some patients show **Ganser syndrome** features, particularly approximate answers: the response comes close to the correct answer but remains incorrect. This pattern differs from the pessimistic “don’t know,” slowed sparse output and repetition-sensitive acquisition that characterise depressive pseudodementia.

The distinction matters because “pseudodementia” is not a unitary explanation. Abrupt onset and inconsistent testing can occur in both forms, but the affective context, autobiographical pattern, concern about deficits and quality of wrong answers differ. Neither pattern should be diagnosed from theatricality or intuition. The clinician must describe positive features, assess mood and context, and still exclude an underlying neurocognitive disorder.

15.9 Examination synthesis

A high-quality answer begins by defining depressive pseudodementia as genuine cognitive impairment associated with depression, preferably framed as a potentially reversible dementia syndrome rather than feigned illness. It then states the continuum from predominantly depressive cognitive dysfunction to depression superimposed on subclinical progressive disease. The discriminating core follows: relatively acute or subacute onset, depressive biological and psychic features, prominent complaints, impaired attention, patchy performance, “don’t know” responses, slow sparse language without paraphasia, and improvement with time, encouragement and repeated trials.

The answer must then qualify the distinction. Bedside testing can remain indeterminate, requiring psychiatric and formal neuropsychological assessment. Improvement with remission may be large, yet executive, processing-speed, consolidation and working-memory deficits can persist. Finally, apparent recovery does not abolish later dementia risk, so thorough work-up and repeated follow-up are integral rather than optional. This final qualification separates an old mnemonic answer from clinically current reasoning.

> Depressive pseudodementia may improve with remission, but its bedside pattern is probabilistic and its future course is not guaranteed: treat the depression, document the cognitive process, and follow the patient longitudinally.

16 · Normal pressure hydrocephalus: triad, diagnosis and shunt response

Why it matters clinically. Normal-pressure hydrocephalus is a high-value diagnosis because an apparently dementing illness may reflect a disorder of cerebrospinal-fluid dynamics for which drainage can produce meaningful clinical relief. The marks lie less in reciting a slogan than in recognising the internal order of the syndrome: gait disturbance leads the clinical picture, cognition has a subcortical character, urinary symptoms evolve, imaging supports but does not independently establish the diagnosis, and response to temporary cerebrospinal-fluid removal helps select patients for permanent drainage.

The central reasoning problem is uncertainty. Ventricular enlargement is not unique to this disorder, the complete syndrome need not present as a perfectly synchronised package, a favourable drainage test is more persuasive than an unfavourable one, and shunt benefit is not completely predictable. A strong answer therefore moves from phenotype to concordant investigations and then to a balanced therapeutic decision. It neither dismisses a treatable possibility because cognition is impaired nor labels every enlarged ventricular system as the cause of that impairment.

GAIT	COGNITION	BLADDER	DRAINAGE
LEADING CLUE	SUBCORTICAL	PROGRESSIVE	PREDICTIVE TEST

16.1 The syndrome and the pressure paradox

Normal-pressure hydrocephalus describes ventricular enlargement occurring despite apparently normal cerebrospinal-fluid pressure. The apparent paradox matters. “Normal pressure” should not be interpreted as proof that pressure has never been abnormal or that cerebrospinal-fluid dynamics are physiologically normal. Intermittent pressure surges may contribute even when pressure appears normal at examination. The diagnostic target is therefore a dynamic clinical syndrome, not merely a single pressure reading.

Hydrocephalus is classified according to the site of obstruction to cerebrospinal-fluid flow. In **communicating hydrocephalus**, the block lies outside the ventricular system; in **non-communicating hydrocephalus**, it lies within the ventricular system. Compensated hydrocephalus differs conceptually because clinical signs and cerebrospinal-fluid dynamics have

stabilised while pressure remains elevated. These distinctions prevent the loose use of "hydrocephalus" as though every form shared the same pressure state, mechanism, presentation and management logic.

RULE **Diagnose a clinicoradiological syndrome, not a scan or a pressure value in isolation.** The diagnostic argument becomes coherent only when the characteristic clinical pattern, ventricular enlargement and the response to temporary drainage are interpreted together.

For the psychiatrist, the syndrome sits at the interface between cognitive medicine and neurological examination. A referral framed as "dementia" may conceal the decisive motor clue, while a referral framed as "walking difficulty" may understate executive slowing or loss of initiative. History and examination must therefore be deliberately integrated. The family's account of sequence is especially valuable because the order in which gait and cognitive symptoms appeared changes the weight placed on this diagnosis.

16.2 The triad as an ordered clinical pattern

The **clinical triad** comprises gait apraxia, cognitive impairment and urinary incontinence. Its components are not equally informative at every stage. Gait apraxia is generally the initial, most consistent and most prominent feature. The cognitive disorder follows a subcortical pattern, while urinary urgency and frequency may precede established incontinence. Thus, the triad is best used as a structured search pattern rather than as a demand that every component be fully developed before the diagnosis is considered.

DOMAIN	CHARACTERISTIC EXPRESSION	DIAGNOSTIC USE	EXPECTED TREATMENT SIGNAL
Gait	Apraxic, magnetic pattern with impaired alternation, weight transfer and turning	Usually the leading and most dependable clinical clue	Often the earliest domain in which improvement becomes evident
Cognition	Slowed thought, reduced initiative and relative preservation of language skills	Supports a subcortical cognitive syndrome rather than an isolated cortical-language presentation	May not improve during a temporary drainage test even when gait improves
Urinary function	Urgency and frequency progressing to incontinence	Evolution matters more than waiting for complete loss of continence	Can improve after treatment

The ordering has a practical consequence. If cognitive decline clearly precedes gait dysfunction, normal-pressure hydrocephalus becomes less likely. This is not equivalent to saying that cognitive symptoms exclude it. Rather, the chronology is discordant with the usual pattern and should prompt a more critical search for another explanation of cognitive decline, ventricular enlargement, or both. Conversely, a prominent gait disorder accompanied by compatible subcortical cognitive and urinary changes creates a more persuasive syndrome.

MNEMONIC

Gait leads, thought slows, bladder warns

This spine preserves the clinically useful order without importing an unverified eponym or ward mnemonic: gait is the leading clue, cognition is slowed and subcortical, and urinary urgency or frequency warns before established incontinence.

16.3 Gait apraxia: the bedside discriminator

Gait apraxia is the key bedside feature. The problem is not captured adequately by saying only that the patient "walks slowly." The patient may fail to alternate leg movements correctly, fail to transfer weight onto the forward foot, or pick up the same leg again instead of progressing in sequence. The weight-bearing foot may appear stuck to the floor, producing the magnetic quality. Turning is fragmented and requires multiple small steps rather than a smooth change of direction.

The examination should make these failures visible. Observe initiation, straight walking, foot clearance, alternation, weight shift and turning as separate tasks. A global label such as "unsteady" loses the information needed for diagnostic reasoning. Ask what exactly interrupts forward progression: failure to release the planted foot, failure to move weight forward, disordered sequencing, or instability during the turn. Description precedes interpretation. This is particularly important when the history has already been framed as falls, weakness, ageing or "poor effort."

A useful bedside contrast is that stepping over a stick may remain preserved. This indicates that the stepping reflex is relatively intact even though ordinary gait sequencing is impaired. The contrast helps clarify why the disorder is described as apraxic: the legs can produce a stepping response under a particular cue, but the self-generated sequence of normal walking is disrupted. It also guards against treating the abnormality as a simple loss of strength.

- Watch the first steps after the command to walk, because initiation may expose the magnetic quality.
- Describe forward weight transfer and foot alternation, and observe a turn rather than judging only straight walking.
- Use the preserved ability to step over an obstacle as a clinical contrast, not as a reason to call the gait normal.

GOOD TO REMEMBER

Record gait before and after temporary cerebrospinal-fluid removal in concrete, observable language. "Better" is weaker evidence than a documented change in initiation, alternation, weight transfer, foot release or turning.

Gait is also the most useful early treatment signal. It is generally the first feature to improve, and improvement after temporary cerebrospinal-fluid removal supports the diagnosis and predicts benefit from permanent drainage. Cognitive change need not accompany that immediate gait

response. An examiner therefore expects the candidate to prioritise gait assessment both for recognition and for testing reversibility.

16.4 Cognitive and urinary components

The dementia has a **subcortical cognitive pattern**. Thought is slowed, and the motor slowing may be evident alongside it, while language skills are relatively spared. This profile matters because "dementia" is otherwise too broad a label to connect the cognitive presentation to the gait syndrome. The psychiatrist should seek reduced speed of thinking, delayed generation of responses and diminished spontaneous engagement rather than assuming that every cognitive complaint will present primarily as forgetting or loss of language.

Abulia is common. Clinically, diminished initiative may be misread as indifference, depression, oppositional behaviour or poor cooperation. Within the syndrome, it should be interpreted beside slowed thought and gait rather than in isolation. The interview may appear sparse because the patient generates little spontaneously, yet this does not by itself establish a primary mood explanation. Depressive pseudodementia and broader comparative differentiation from depression and delirium are addressed elsewhere in this chapter; the present task is to recognise the characteristic cognitive tone of normal-pressure hydrocephalus.

The urinary component begins with **urgency and frequency** and progresses to incontinence. Asking only whether the patient is incontinent can therefore miss the evolving syndrome. History should establish the direction of change and its relationship to gait and cognition. Urinary symptoms also have therapeutic relevance because they can improve with treatment. Their presence strengthens the clinical pattern, but the leading diagnostic weight remains with gait.

TRAP **Waiting for fully developed incontinence before considering the diagnosis.** Urgency and frequency may be the urinary expression before incontinence appears, while gait usually supplies the earlier and more reliable clue.

16.5 Imaging, cerebrospinal fluid and diagnostic synthesis

Structural imaging shows **ventricular dilatation**, particularly involving the temporal horns. There may also be signs suggesting cerebrospinal-fluid reabsorption across ventricular surfaces. These findings are supportive, but they are nonspecific. Imaging alone cannot reliably establish that ventricular enlargement is responsible for the patient's gait and cognitive syndrome.

The central imaging differential is **hydrocephalus ex vacuo**, in which ventricular enlargement resembles that seen with cerebral atrophy. The practical question is causal: does the enlarged ventricular system belong to a pressure-dynamics syndrome capable of responding to drainage, or does it accompany loss of brain volume? A report of "dilated ventricles" does not answer that question. Clinical sequence and phenotype remain indispensable, and temporary drainage may add functional evidence.

Cerebrospinal-fluid pressure is normal in normal-pressure hydrocephalus, as are protein and glucose concentrations. Normal routine cerebrospinal-fluid findings therefore do not invalidate

the syndrome. Equally, the word “normal” must not become a shortcut to diagnosis: normal pressure and constituents do not distinguish this condition without the compatible clinical and imaging context. The procedure and generic study of cerebrospinal-fluid constituents belong in the Neurology foundations for psychiatrists notes.

Imaging modality principles and physics belong in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. Here, the clinically relevant use of imaging is narrower: establish ventricular enlargement, note supportive features, examine whether atrophy offers a competing explanation, and integrate the result with gait-led clinical findings. This preserves the distinction between knowing how an imaging modality works and knowing what a finding contributes to a particular diagnosis.

PITFALL

Do not let the radiology label close the case. Ventricular enlargement may resemble hydrocephalus ex vacuo, so attributing cognition and gait to normal-pressure hydrocephalus from imaging alone risks both inappropriate surgery and failure to identify another cause.

A disciplined synthesis can be stated as a chain. First, establish whether the gait phenotype is genuinely apraxic and whether it led the illness. Next, seek the compatible subcortical cognitive and evolving urinary features. Then ask whether imaging demonstrates ventricular enlargement without treating that finding as diagnostic by itself. Finally, use the response to temporary cerebrospinal-fluid removal to refine the probability of shunt-responsive disease. Each link answers a different question; none is a substitute for the others.

16.6 Temporary cerebrospinal-fluid removal

The **large-volume tap test** involves withdrawing **30-60 mL** of cerebrospinal fluid by lumbar puncture. An alternative is a series of **three** lumbar punctures. The test is worthwhile because it asks a functional question that static imaging cannot answer: does temporary drainage improve the characteristic clinical deficit?

Gait is the principal outcome. Improvement in gait after cerebrospinal-fluid removal indicates normal-pressure hydrocephalus and predicts benefit from permanent drainage. Dementia need not improve during the test for the result to be meaningful. This asymmetry is clinically sensible within the verified syndrome: gait is usually the leading feature and the first to respond to treatment. Insisting on an immediate cognitive response would therefore discard useful positive evidence.

- Define gait abnormalities before drainage, then re-examine the same domains after drainage.
- Interpret gait improvement as positive evidence for both the diagnosis and likely benefit from permanent drainage.
- Do not require cognitive improvement for a positive gait response, and do not use a negative test as an absolute exclusion.

A negative test does not preclude the diagnosis. That statement is more than a caveat: it defines the direction in which the evidence should be used. A positive gait response is affirming and predictive; a negative response is not sufficiently decisive to close the diagnosis. When the phenotype and imaging remain persuasive, the result must be placed back into the total clinical argument rather than converted into a binary rule.

General lumbar-puncture technique, contraindications and the generic cerebrospinal-fluid examination procedure belong in the Neurology foundations for psychiatrists notes. Within this topic, the examiner is testing the indication, volume of removal, outcome domain and interpretation. The best answer therefore centres on large-volume removal, documented gait response, its predictive value for shunting, and the limited exclusionary value of a negative result.

16.7 Shunt treatment and response

Management is a selection problem. LOCUS begins with coordinated specialist assessment and proceeds to neurosurgical care when permanent drainage is being considered. FOCUS is functional: relieve the gait-led syndrome, improve urinary dysfunction where possible, assess cognitive change without demanding it as the earliest response, and avoid exposing an unsuitable patient to a procedure whose benefit cannot be predicted with certainty. MODUS is procedural drainage supported by careful clinical observation and follow-up; the verified treatment is insertion of a ventricular shunt.

A **ventricular shunt** is inserted into a lateral ventricle and drains cerebrospinal fluid into the chest or abdominal cavity. This can relieve normal-pressure hydrocephalus. The decision is not trivial, because a clinically beneficial response is difficult to predict. A compatible gait-led syndrome and improvement after temporary drainage provide a more persuasive basis for treatment than ventricular enlargement alone.

Response should be understood by domain. Gait is generally the first feature to improve. Urinary symptoms can also improve. Cognitive improvement may be less immediately evident during temporary drainage and should not be made the sole test of success. This domain-based view prevents the vague statement that “the patient improved” and keeps assessment aligned with the syndrome’s natural hierarchy.

Shunt insertion is prone to complications, including subdural haematoma and infection. Surgical complications can be serious and occur in up to **30%** of cases. The procedure can be beneficial in hydrocephalus, but it should not be undertaken lightly. The therapeutic argument must therefore contain both halves: a potentially reversible disorder deserves active assessment, and the possibility of reversibility does not justify indiscriminate shunting.

The treatment discussion should link the evidence explicitly. A gait-led clinical syndrome supplies pre-test coherence. Imaging confirms ventricular enlargement but remains nonspecific. A positive gait response to cerebrospinal-fluid removal supports normal-pressure hydrocephalus and predicts benefit from permanent drainage. A negative response weakens neither the diagnosis nor the treatment case absolutely. The final decision requires judgement because neither imaging nor temporary drainage makes shunt response perfectly predictable.

No single numerical improvement rate should be quoted when it is not supported by the source base. The defensible examination statement is that benefit is difficult to predict, gait is the earliest expected responder, urinary symptoms may improve, and serious complications must be weighed. This is both more accurate and more clinically useful than false precision.

16.8 A compact diagnostic answer

A complete short-note answer begins by defining normal-pressure hydrocephalus as ventricular enlargement despite apparently normal cerebrospinal-fluid pressure, possibly reflecting intermittent pressure surges. It then states the gait-cognition-urinary triad and immediately qualifies its order: gait apraxia is generally initial, consistent and prominent, whereas cognitive decline clearly preceding gait dysfunction makes the diagnosis less likely.

The gait description earns clinical depth. Mention impaired alternation, failure of forward weight transfer, repetition of movement with the same leg, a stuck weight-bearing foot and a multi-step turn, while stepping over a stick remains possible. Characterise cognition as slowed and subcortical with relative language preservation and common abulia. Describe urinary urgency and frequency progressing to incontinence.

Complete the answer with investigation and management logic. Imaging demonstrates ventricular enlargement, especially at the temporal horns, but cannot diagnose the disorder alone because the appearance is nonspecific and may resemble hydrocephalus ex vacuo. Cerebrospinal-fluid pressure, protein and glucose are normal. Large-volume removal or serial lumbar punctures are used as a predictive test: gait improvement supports the diagnosis and predicts shunt benefit, lack of cognitive improvement does not negate a positive gait response, and a negative test does not exclude the disorder. Permanent ventricular drainage may relieve the syndrome, but benefit is not fully predictable and complications can be serious.

> In normal-pressure hydrocephalus, gait leads the diagnosis and usually the response; imaging supports, temporary drainage predicts, and a negative tap test does not exclude.

17 · Rapidly progressive and prion dementias, and the genetic subcortical dementias

Why the pace changes the whole problem. A dementing illness that accelerates over a short interval is not simply a common dementia running faster. It changes the prior probabilities, raises the cost of delay and demands an intensive search for inflammatory, neoplastic, autoimmune, nutritional, infectious, vascular and prion causes. **Creutzfeldt-Jakob disease** (CJD) must remain one possibility among several throughout that urgent search.

The diagnostic task has two simultaneous aims. The first is rescue: identify processes in which prompt causal treatment may alter outcome. The second is recognition: when rapidly progressive cognitive failure is accompanied by multifocal neurological signs and a characteristic biomarker pattern, investigate prion disease directly. A strong answer therefore moves from tempo and syndrome to targeted exclusion, then to prion phenotype, imaging, cerebrospinal-fluid seeding assay and the level of diagnostic certainty.

PACE	PATTERN	REVERSIBLE	PRION
DEFINE THE PROBLEM	LOCALISE THE SYNDROME	EXCLUDE EARLY	TEST DIRECTLY

17.1 Rapidly progressive dementia is a diagnostic emergency

Rapidly progressive dementia (RPD) is a clinical problem defined primarily by its relatively abrupt onset and progression, not by a single aetiology. Its differential is distinct from that of a typically insidious dementia, and the patient requires intensive investigation. A **6-12 months** development is a red flag against a straightforward diagnosis of a conventional slowly progressive dementia. At the still faster end, multifocal neurological deficits emerging over days to weeks strongly raise suspicion of sporadic CJD.

Tempo must be reconstructed rather than guessed from the referral label. Establish the previous cognitive and functional baseline, the first unequivocal change, the order in which cognitive, behavioural, gait, visual, cerebellar and motor abnormalities appeared, and whether decline has been smooth, stepwise or punctuated. Apparent rapidity may reflect late recognition of a longer illness, but true acceleration must be taken seriously. A short downhill course is a useful warning sign for CJD. Tempo alone cannot establish the diagnosis.

RULE **In RPD, search for a treatable cause and investigate prion disease in parallel.** Prion disease should be considered whenever dementia or ataxia progresses rapidly and no better explanation has emerged; serial exclusion alone must not postpone the tests that can support an accurate antemortem diagnosis.

Prion disease can overlap clinically with other neurodegenerative syndromes, including Alzheimer disease, dementia with Lewy bodies and frontotemporal dementia. This overlap is precisely why pace alone is insufficient. The clinician must ask whether the illness has acquired the multifocal neurological texture expected of prion disease and whether the biomarker pattern converges. Conversely, a familiar dementia phenotype should not reassure when the trajectory is implausibly fast.

17.2 The RPD differential: preserve breadth before narrowing

The differential should be organised by mechanism because an unstructured list is easy to truncate. The categories below are not equally likely in every patient, but each represents a route by which a rapidly dementing presentation can arise. Clinical context then determines the order and intensity of testing.

CATEGORY	CAUSES TO NAME	REASONING EMPHASIS
Inflammatory	Cerebral vasculitis, multiple sclerosis, sarcoidosis	Seek evidence that cognition belongs to a broader inflammatory neurological syndrome.
Neoplastic	Primary central nervous system tumour, cerebral metastases, paraneoplastic limbic encephalitis	Consider direct structural disease and remote tumour-associated neurological illness.
Autoimmune	Voltage-gated potassium-channel antibody syndrome	Psychiatric or cognitive prominence can accompany an immune-mediated illness.
Nutritional	Thiamine deficiency and Wernicke-Korsakoff syndrome	Name the deficiency while keeping its disease teaching with the relevant owner chapters.
Infectious	Cerebral abscess, herpes encephalitis, progressive multifocal leucoencephalopathy, HIV, subacute sclerosing panencephalitis, Whipple disease	Use exposure, host context and accompanying neurological features to direct exclusion.
Prion	Creutzfeldt-Jakob disease	Look for rapid multifocal decline and convergent MRI, seeding-assay and other biomarker evidence.
Vascular	Multiple infarcts, including embolic disease related to endocarditis, and CADASIL	Interrogate the temporal pattern and the possibility of recurrent vascular injury.

This is a triage framework, not permission to teach neighbouring disorders inside an RPD answer. The autoimmune and limbic encephalitis workup belongs in the Neuropsychiatry of systemic and neurological disease notes. The endocrine, metabolic and nutritional diseases themselves belong in the Endocrine and metabolic psychiatry notes; the Korsakoff amnestic syndrome and the vascular neurological syndromes belong in the Stroke, TBI, delirium and focal brain syndromes notes. Here their role is to remain visible as competing, potentially actionable explanations.

- First decide whether the pace is genuinely rapid relative to the patient's prior baseline.
- Next identify the dominant accompanying syndrome: encephalitic, cerebellar, multifocal motor, visual, vascular or systemic.
- Then investigate treatable categories while obtaining prion-directed studies when the clinical pattern warrants them.

PITFALL

Do not wait for every reversible investigation to return before requesting diffusion-weighted MRI and a prion seeding assay in a convincing RPD. Sequential testing wastes the information contained in tempo; parallel testing preserves rescue and recognition.

17.3 Human prion disease: proportions and clinical frame

Human prion diseases are rare across populations, occurring at a frequency of 1 to 1.5 cases per million; the United States records approximately 300 diagnosed cases annually. Most are sporadic. The triangulated transmission breakdown is **about 85-90% sporadic, 14-15% genetic and 1% acquired**. These proportions matter because absence of family history or recognised exposure does not meaningfully reduce suspicion for the dominant sporadic form.

CJD may be classified as **sporadic CJD** of unknown aetiology, autosomal-dominant familial CJD, iatrogenic CJD related to contaminated biological material or instruments, and variant CJD associated with consumption of cattle contaminated by bovine spongiform encephalopathy. The transmission label predicts more than provenance. It influences age profile, presenting syndrome, disease duration and the yield of familiar investigations.

Anatomically, CJD affects the basal ganglia and thalamus, the neocortical mantle with frontal and posterior cortical involvement, and the cerebellum. This distributed involvement explains why a single patient may show cognitive deficits, neuropsychiatric change, altered sleep, visual disturbance and gait instability. The syndrome therefore combines cortical and subcortical dysfunction, often with cerebellar participation; reducing it to “dementia plus jerks” loses its diagnostic breadth.

MNEMONIC

PACE: Progression, Associated signs, Convergent tests, Exposure and inheritance

Progression identifies RPD; **A**ssociated signs reveal the multifocal syndrome; **C**onvergent tests support prion disease; **E**xposure and inheritance distinguish acquired and genetic routes. This is an examination spine, not a diagnostic instrument.

17.4 Sporadic CJD: the evolving multifocal syndrome

Sporadic CJD usually begins insidiously with nonspecific behavioural or constitutional change, including anxiety, depression, altered sleep, reduced appetite, fatigue, dizziness, weight loss and social regression. Forgetfulness and failure of higher cortical functions then become clearer. Approximately a third have prodromal headache, fatigue or weight loss, while almost a third initially show purely neurological deficits, especially cerebellar gait ataxia. Thus an early psychiatric or cerebellar presentation does not contradict the later diagnosis.

Onset is usually within **45-90 years, peaking around 65 years**. The classic established picture is rapidly progressive multifocal dementia with myoclonus and gait ataxia. Additional visual, cerebellar, pyramidal and extrapyramidal signs accumulate as anatomical involvement widens.

Startle myoclonus, precipitated by loud noise or touch, is prominent but is often absent early and emerges with progression. Epileptic seizures are uncommon, occurring in only 10%.

Uncommon clinical forms are worth recognising without mistaking them for separate aetiologies. The Heidenhain variant has prominent occipital disease with cortical blindness, visual hallucinations and agnosia. The Brownell-Oppenheimer variant presents as a pure cerebellar syndrome associated with widespread cerebellar pathology. Their examination value is simple: focal prominence early in the course does not exclude a disease that later becomes multifocal.

The downhill trajectory is severe. Progression over weeks may culminate in akinetic mutism and death, often within 2-3 months. Around **70% die in under 6 months and 90% by 1 year**, although duration is variable and a minority have a much longer course. The pace helps distinguish the syndrome clinically, but variability prevents duration from functioning as an absolute exclusion criterion.

17.5 Diagnostic criteria and levels of certainty

The clinical-sign category begins with rapidly progressive dementia and asks for myoclonus, cerebellar or visual signs, pyramidal or extrapyramidal signs, and akinetic mutism. The test category includes periodic sharp-wave complexes on EEG, cerebrospinal-fluid **14-3-3 protein**, characteristic diffusion-weighted or FLAIR MRI abnormalities, and a positive real-time quaking-induced conversion assay.

DSM-5-TR requires motor features of prion disease, namely myoclonus or ataxia, or biomarker evidence when diagnosing major or mild neurocognitive disorder due to prion disease. This diagnostic-manual formulation identifies the necessary neurological or biological support. The more operational sporadic-CJD case definitions below show how clinical signs, tests, duration and seeding evidence are combined into levels of certainty.

DIAGNOSTIC LEVEL	REQUIRED CONSTRUCTION	INTERPRETIVE POINT
Probable sporadic CJD, clinical plus tests	Rapidly progressive dementia, at least 2 clinical signs and at least 1 qualifying test	The diagnosis rests on convergence, not on one nonspecific marker.
Probable sporadic CJD, seeding route	A progressive neurological syndrome with positive cerebrospinal-fluid RT-QuIC	A positive seeding assay can establish the probable category through the alternative route.
Possible sporadic CJD	Rapidly progressive dementia, at least 2 clinical signs and duration shorter than 2 years	This level lacks the qualifying test evidence required by the clinical-plus-tests route.
Definite prion disease	Characteristic neuropathology with prion-protein immunohistochemistry, or a confirmed PRNP mutation in inherited disease	Definitive classification remains tissue- or mutation-based.

Neuropathological confirmation requires classical spongiform change, neuronal loss, astrocytosis and positive prion-protein immunohistochemistry on biopsy or autopsy. Yet modern imaging,

seeding assays and PRNP genotyping permit accurate antemortem diagnosis in the large majority, so brain biopsy is now rarely required. Probable CJD is confirmed as definite at autopsy in more than 95% of cases. The distinction is not between a useless antemortem label and certainty after death; it is between high clinical confidence and the formal requirements for definite disease.

17.6 MRI, cerebrospinal fluid and EEG: use convergence, not hierarchy alone

Brain MRI with diffusion-weighted sequences is the **most sensitive non-invasive diagnostic tool** for sporadic CJD. Typical findings are restricted diffusion in the basal ganglia and thalami with cortical ribboning; regional combinations differ between patients. Signal hyperintensity may also occur in the same regions on T2-weighted or FLAIR images, but is less striking. Imaging modality physics belongs in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the dementia-specific point is the distribution and diagnostic contribution of the abnormal signal.

Routine cerebrospinal-fluid cell count and biochemistry remain normal in sporadic CJD. This does not make lumbar puncture unhelpful: routine examination is essential for excluding other causes of rapid cognitive decline, while disease-associated proteins and seeding assays address a different question. The procedure and generic study of cerebrospinal fluid belong in the Neurology foundations for psychiatrists notes. Routine blood tests are usually normal and, when abnormal, have no particular diagnostic value for sporadic CJD.

Real-time quaking-induced conversion (RT-QuIC) is an amyloid-seeding assay. Repeated shaking and incubation amplify prion seeds from patient cerebrospinal fluid using recombinant prion protein as substrate and a fluorescent thioflavin-T readout. Its sensitivity is comparable to a positive cerebrospinal-fluid 14-3-3 result, but its specificity for sporadic CJD approaches **100%**. Nasal-brushing and skin-seeded assays also show performance approaching that level, but are not yet routine clinical tests.

Protein 14-3-3 and tau are commonly used cerebrospinal-fluid biomarkers with high sensitivity but variable specificity. EEG may show periodic, often triphasic synchronous discharges at 0.5-2 Hz at some point in the illness. These findings must be interpreted as components of a syndrome. A nonspecific injury marker cannot carry the diagnosis alone, and the expected marker pattern differs across sporadic, genetic and variant disease.

TRAP **Do not memorise a single textbook percentage for periodic EEG activity as settled fact.** One standard source reports pseudoperiodic sharp waves in a minority of sporadic cases, whereas another reports the finding substantially more often late in illness. The verified diagnostic-manual statement is qualitative: periodic triphasic synchronous discharges may appear during the course. Quote the pattern and frequency band, not a falsely reconciled prevalence.

GOOD TO REMEMBER

A positive RT-QuIC has far greater rule-in value than a nonspecific rise in an injury-associated cerebrospinal-fluid protein. Still, the best answer is convergent: phenotype, diffusion-weighted MRI and seeding evidence interpreted together.

17.7 Acquired disease: route changes the phenotype

Iatrogenic CJD should be considered in a progressive, predominantly cerebellar syndrome with behavioural disturbance after exposure to human pituitary hormones, human dura mater, an implicated corneal graft or neurosurgical instruments used on a definite or probable prion case. Limb dysaesthesiae are frequent. Incubation may exceed 40 years, so a remote exposure remains relevant.

Route explains the clinical contrast. Intracerebral or optic inoculation produces a classical rapidly progressive dementing picture and may have incubation shorter than 2 years. Peripheral inoculation, especially through pituitary-derived growth hormone, more often produces a progressive cerebellar syndrome reminiscent of kuru, with incubation typically 15 years or longer. MRI may resemble sporadic CJD, but periodic sharp waves are rarely seen. Cerebrospinal-fluid 14-3-3 is detected in only approximately half, and RT-QuIC sensitivity is substantially reduced compared with sporadic disease.

Variant CJD is clinically different. Depression, anxiety, withdrawal or delusions typically precede dementia, and painful sensory symptoms, cerebellar ataxia and abnormal movements may also lead the cognitive syndrome. It predominantly affects young adults and follows a course longer than 6 months. Average onset is 29 years, compared with 65 years in sporadic CJD; neurological features usually follow the initial psychiatric presentation within 6 months, and median survival is 13 months.

The EEG shows nonspecific slowing rather than the periodic sharp-wave pattern of sporadic disease, and cerebrospinal-fluid 14-3-3 may be raised or normal. FLAIR MRI may show the **pulvinar sign**, with thalamic signal more prominent than basal-ganglia signal, in approximately 90%; it may appear late and is not pathognomonic. Tonsillar tissue may demonstrate characteristic prion-protein findings. Unlike sporadic CJD, variant disease can be transmitted by blood transfusion.

17.8 Genetic disease, the Huntington boundary and care priorities

Genetic prion disease accounts for roughly the inherited share already described and may be established by a confirmed **PRNP mutation**. Up to 15% of prion disease cases carry autosomal-dominant mutations in this gene. Family history therefore matters, but its absence should not displace the much larger sporadic category. Genetic counselling detail and mutation-specific syndromes cannot be supplied from the present evidence base and should not be reconstructed from memory.

Huntington disease belongs among the common causes of dementia and within the basal-ganglia-predominant neurodegenerative dementias. In this section it is a pointer, not an

invitation to repeat its genetics, motor-psychiatric-cognitive triad or staging. Full teaching belongs in the Neuropsychiatry of systemic and neurological disease notes. The dementia-lens point is that a genetic subcortical neurodegenerative disorder sits beside prion disease in the broader differential, but its usual disease teaching must remain separate.

Care follows diagnostic clarity. LOCUS depends on clinical instability and diagnostic needs: urgent hospital assessment is appropriate when rapidly progressive cognitive failure and neurological deficits require intensive investigation, while later care may move across specialist, community and palliative settings. FOCUS is to identify a treatable mimic early, establish the level of prion-disease certainty, address distressing cognitive, behavioural and neurological disability, communicate prognosis honestly and support those providing care. MODUS is diagnostic, supportive, psychological and social; no disease-modifying treatment currently exists for CJD.

- Explain that a probable antemortem diagnosis can be highly accurate even though definite classification remains neuropathological or mutation-based.
- Use phenotype, MRI and RT-QuIC together, and interpret negative or low-yield markers in light of the suspected prion subtype.
- Keep reversible RPD causes active until reasonably excluded, while avoiding futile delay once convergent prion evidence is present.

> Rapid dementia demands parallel reasoning: exclude treatable causes urgently, but investigate prion disease directly when rapid multifocal decline, diffusion restriction and prion-seeding evidence converge.

The compact examination answer is therefore coherent rather than encyclopaedic. Define RPD by its abnormal pace, organise the broad differential, describe the evolving multifocal syndrome of sporadic CJD, state the probable and definite diagnostic routes, compare the information supplied by MRI, routine cerebrospinal fluid, 14-3-3, RT-QuIC and EEG, and then distinguish iatrogenic and variant patterns. End by recognising inherited prion disease and naming Huntington disease only at the dementia boundary. That sequence demonstrates the urgency and restraint this topic tests.

18 · Mild cognitive impairment, subjective cognitive decline and the cognitive continuum

Why it matters clinically. The borderline between expected cognitive experience and dementia is not a single test score. Patients may notice decline before testing confirms it; measurable impairment may later appear while everyday independence remains intact; some then progress, some remain stable, and some no longer meet the earlier label. The marks lie in defining each state precisely, separating subjective report from objective performance, and showing why function and trajectory matter more than an isolated complaint.

The useful model is a cognitive continuum, but not an inevitable conveyor belt. **Subjective cognitive decline** describes a perceived worsening without an objective deficit on

neurocognitive testing in the descriptive evidence available here. **Mild cognitive impairment** adds objective or longitudinally demonstrated cognitive decline while basic everyday activities remain preserved and the disturbance does not warrant dementia. **DSM-5-TR mild neurocognitive disorder** occupies the corresponding diagnostic territory, with modest decline but preserved independence. Dementia lies beyond the functional boundary and is discussed elsewhere in this chapter. These labels organise uncertainty; they do not by themselves disclose aetiology or destiny.

Concern	Testing	Function	Course
SUBJECTIVE CHANGE	OBJECTIVE CHANGE	INDEPENDENCE	TRAJECTORY

18.1 The continuum is multidimensional, not merely ordinal

A linear diagram is useful for orientation, but clinical reasoning requires several dimensions. Subjective experience asks whether the person perceives decline from a previous level. Objective assessment asks whether performance is impaired or has demonstrably worsened over time. Functional assessment asks whether the person remains independent, perhaps through greater effort or compensatory strategies. Longitudinal assessment asks whether the state progresses, persists, fluctuates or resolves. A patient can move differently along each axis.

The distinction between impairment and disability is central. Poor performance on a cognitive task establishes neither dementia nor loss of independence. Conversely, a person may report meaningful decline while remaining within expected limits on the tests administered. The clinician must then decide whether the complaint reflects a very early cognitive change, a limitation of the assessment, ordinary variation, or another explanatory condition. The correct response is a formulation with explicit uncertainty, not a forced categorical answer.

RULE **Place the patient on the continuum using complaint, objective cognition, everyday independence and longitudinal course together.** No single component can substitute for the others, and the label should change when later evidence changes the formulation.

This also explains why “pre-dementia” can mislead. It is acceptable as a risk-oriented shorthand only if it does not imply that every patient will progress. Mild impairment is clinically important because the probability of future dementia is higher in several studied cohorts, yet community observations include stability and reversion. The continuum is therefore a map of current cognitive-functional state and future risk, not a declaration of a predetermined biological sequence.

18.2 Subjective cognitive decline: symptom before measurable deficit

In the cited textbook account, subjective cognitive impairment, also termed subjective cognitive decline, is described as the earliest symptomatic manifestation before mild cognitive impairment in a proposed Alzheimer disease sequence. Its defining contrast is straightforward: the person reports worsening memory, but neurocognitive testing does not demonstrate a deficit. This staging statement arose in a biomarker-research discussion and should not be inflated into proof that every such complaint represents that disease.

Subjective memory complaints are common among community-dwelling older adults. Typical concerns involve remembering names, finding the intended word, locating objects and sustaining concentration compared with earlier functioning. The phenomenology is familiar, but familiarity does not make it trivial. The clinician should establish what has changed, when the change was first noticed, whether others observe it, which situations expose it, and whether the person has altered routines to compensate.

Terminology is inconsistent. Some experts use mild cognitive impairment broadly for subjective complaints occurring without overt dementia or obvious affective, anxiety, sleep, pain or attention-related explanations. Others reserve the term for an objectively impaired state or for an early neurodegenerative syndrome. This is not pedantry. Different entry definitions assemble different populations, and those populations will produce different apparent progression rates. A candidate should therefore define the term before quoting prognosis.

PITFALL

Do not tell a patient that a subjective complaint with normal testing is "early Alzheimer disease." The permitted evidence supports a descriptive pre-MCI research stage, not an individual aetiological diagnosis. First describe the complaint, test objectively, assess alternative explanations and observe the trajectory.

The available evidence does not provide a formal operational feature set for subjective cognitive decline. Accordingly, a list of remembered "plus" features should not be manufactured. The defensible definition remains descriptive: perceived decline from prior ability without objective impairment on the assessment used. The limitations of that assessment and the need for follow-up should be stated openly.

18.3 Defining mild cognitive impairment and mild neurocognitive disorder

The **Report of the International Working Group on MCI** requires cognitive decline that does not warrant a dementia diagnosis, or evidence of decline over time on objective cognitive tasks, while basic activities of daily living remain preserved. This formulation is deliberately broader than a memory-only syndrome. It makes two points that survive changes in terminology: decline must be demonstrated clinically or objectively, and basic function remains sufficiently preserved to keep the syndrome on the mild side of the dementia boundary.

The diagnostic-manual formulation requires modest decline from prior performance in at least one cognitive domain. Evidence must come from concern expressed by the patient, an informant or the clinician and from modest impairment on standardised testing or another quantified clinical assessment. The domains considered are complex attention, executive function, learning and memory, language, perceptual-motor function and social cognition. Deficits do not interfere with independence in everyday activities, although greater effort, accommodation or compensation may be necessary. The syndrome must not occur exclusively during delirium and must not be better explained by another mental disorder. Aetiology is then specified rather than assumed.

The older **Mayo Clinic Alzheimer's Disease Research Center criteria** were narrower and memory-centred. They required a memory complaint, preferably corroborated; objective memory impairment adjusted for age and education; preserved general cognitive function; intact everyday activities; and absence of dementia. Their historical importance is conceptual: they identify the classic amnestic presentation from which the broader domain-based framework developed.

AXIS	INTERNATIONAL WORKING-GROUP FORMULATION	DIAGNOSTIC-MANUAL MILD DISORDER	ORIGINAL MEMORY-CENTRED CRITERIA
Core change	Cognitive decline insufficient for dementia, or objective decline over time	Modest decline from prior performance	Memory complaint with objective memory impairment
Evidence	Clinical decline or serial objective decline	Concern plus standardised testing or quantified clinical assessment	Complaint preferably corroborated, with age- and education-adjusted impairment
Cognitive scope	Not restricted to memory	Attention, executive, learning-memory, language, perceptual-motor or social-cognitive domains	Memory-centred, with general cognition preserved
Functional boundary	Basic everyday activities preserved	Independence preserved despite possible extra effort or compensation	Everyday activities intact
Exclusions	Does not warrant dementia	Not exclusively delirium and not better explained by another mental disorder	Not demented

The apparent differences are best understood as evolution, not contradiction. The early criteria selected an amnestic group; later formulations recognise impairment outside memory and place more explicit weight on quantified assessment and maintained independence. In an answer, state which framework is being used rather than mixing elements into an unnamed hybrid.

18.4 Function is the practical boundary

Why function outranks the raw score. The mild diagnosis is not defined by a universal cognitive cutoff in the evidence supplied here. Its practical boundary is independence. A person may take longer, rely on written prompts, reorganise tasks, avoid cognitively demanding situations or need greater effort while still completing essential activities independently. Such compensation is diagnostically informative: it can reveal decline without automatically converting mild impairment into dementia.

Functional questioning should be concrete and anchored to the previous level. Ask how the patient manages complex routines, new information, appointments, travel, communication, household organisation and occupational demands. The issue is not whether another person

sometimes helps, but why help is needed and whether cognitive deficits now interfere with independent performance. Physical limitation, sensory impairment, low mood, reduced opportunity and family overprotection can all change activity without proving cognitive dependence.

Objective cognition must likewise be interpreted as change from prior ability. Education, language, cultural familiarity, sensory status and test conditions influence performance. General administration and scoring of cognitive screens belongs in the Psychometry, Assessment and Descriptive Psychopathology notes. Here, the relevant point is narrower: testing corroborates and characterises decline; it does not replace history, functional analysis or serial observation.

GOOD TO REMEMBER

Document compensation, not merely success or failure. "Independent with a diary and repeated checking" carries more information than "activities intact." It captures the diagnostic-manual distinction between preserved independence and the greater effort used to maintain it.

Exclusion is equally important. A mild cognitive syndrome should not be diagnosed when the disturbance occurs only in delirium or is better explained by another mental disorder. The full comparison with delirium and depression is taught elsewhere in this chapter, while delirium itself belongs to the Stroke, TBI, delirium and focal brain syndromes notes. The aim here is not to teach those disorders, but to prevent their presence from being erased by a convenient cognitive label.

18.5 Phenotyping: amnestic, nonamnestic and domain burden

Once mild impairment is established, phenotype it rather than stopping at the umbrella label. **Amnestic MCI** is dominated by memory impairment, whereas **nonamnestic MCI** is dominated by nonmemory impairment such as executive or language dysfunction. Each may show a **single-domain or multiple-domain pattern**. This classification describes the pattern of impairment and can guide the aetiological hypothesis, but it is not itself an aetiological diagnosis.

The classic mapping links single-domain amnestic impairment more closely with underlying Alzheimer disease pathology. Amnestic impairment affecting multiple domains may be associated with that pathology or with vascular dementia. Nonamnestic impairment is related more closely to dementia with Lewy bodies or frontotemporal neurodegeneration. These are associations, not conversion rules. Detailed criteria for each dementia remain with their disorder-specific sections.

The domain distinction matters because "memory clinic" language can obscure nonmemory presentations. Executive inefficiency may first appear as difficulty planning or shifting strategy. Language decline may appear as impaired retrieval or expression. A person can therefore satisfy a mild cognitive framework without the classic memory-centred picture. Conversely, a memory complaint alone does not establish amnestic impairment until objective assessment confirms the relevant deficit.

MNEMONIC

COFI: Complaint, Objective change, Function, Interval course

Complaint identifies the perceived decline; **O**bjective change establishes the cognitive phenotype; **F**unction locates the mild-versus-dementia boundary; **I**nterval course shows whether the label progresses, persists or recedes.

A robust formulation therefore has two layers. The syndromic layer states that mild cognitive impairment or mild neurocognitive disorder is present and specifies the domains affected. The aetiological layer states what process is suspected and how certain that suspicion is. Keeping the layers separate prevents a common shortcut in which an amnestic phenotype is silently rewritten as confirmed neurodegenerative disease.

18.6 Prognosis: progression, persistence and reversion

Prognosis is probabilistic and population-dependent. In the Mayo Clinic referral sample, conversion to dementia was **12% per year compared with 1% to 2% per year in controls**. A separate account in Kaufman's gives **10% per year compared with 1% to 2% per year in unaffected peers**. These figures are similar in direction, but they are not interchangeable estimates from the same population.

Community findings make the uncertainty more visible. In the Monongahela Valley Independent Elderly Survey, **10% to 17% progressed to dementia, while 33% to 56% became non-MCI**. Thus reversion is not a theoretical footnote. It may reflect genuine improvement, variable classification, fluctuating contributors or regression around a threshold. Whatever the explanation, it invalidates language of inevitability.

Stahl's estimates that **15% to 20% of people aged 65 years or older have MCI**. On clinical grounds without biomarkers, the same source gives **6% to 15% conversion to dementia each year**, with additional cumulative estimates that differ according to follow-up and outcome definition. The wide spread is understandable when some authors include subjective complaints while others require objective impairment or select specialty referrals.

TRAP **Do not quote one MCI conversion rate as universally correct.** Kaplan and Sadock report a referral-sample estimate, Kaufman's gives a separate point estimate, and Stahl's gives a broader clinically defined range without biomarkers. Name the source, setting, case definition, follow-up frame and outcome before using the figure.

EVIDENCE CONTEXT	WHAT THE ESTIMATE SHOWS	WHY IT MUST NOT BE UNIVERSALISED
Specialty referral sample	Higher annual conversion than controls	Clinical selection enriches risk and differs from community ascertainment
Textbook point estimate	Higher annual progression than unaffected peers	A summary estimate does not erase study and definition differences
Community survey	Progression coexists with loss of the MCI label and return to normal	Community cases are broader and the state may not remain stable
Clinical definition without biomarkers	A range of annual conversion and substantial cumulative risk	Subjective and objective case definitions may be mixed across accounts

For the individual patient, predictors and biomarkers may refine risk, but the permitted evidence does not justify a personalised numerical forecast. The defensible communication is that risk is elevated, outcomes vary, and reassessment matters. A change in label over time is new clinical information, not proof that the earlier clinician necessarily made an error.

18.7 Mild behavioural impairment broadens the prodromal lens

Cognitive change is not the only possible early signal. **Mild behavioural impairment** describes the emergence of neuropsychiatric symptoms that can precede cognitive decline and eventually dementia. It can accompany the cognitive deficits of mild cognitive impairment or draw attention before those deficits are obvious. The construct encourages clinicians to regard new behavioural change as potentially informative rather than automatically dismissing it as personality.

The operational framework groups symptoms into motivation, affect, impulse control, social appropriateness, and perception or thought content. A dedicated checklist is available for rating this construct. These categories are not a substitute for psychiatric diagnosis, and the presence of a symptom does not prove neurodegeneration. Their value lies in describing a change from longstanding behaviour, establishing its context, and integrating the behavioural trajectory with cognitive and functional findings.

Mild behavioural impairment also guards against a memory-only model of the continuum. A patient may first present because of apathy, emotional change, disinhibition, socially inappropriate conduct or unusual perceptual and thought experiences. The cognitive examination may then reveal an amnestic or nonamnestic phenotype, remain objectively normal, or change later. The behavioural construct and cognitive labels answer different questions and may coexist.

- Establish that the behaviour is new rather than lifelong.
- Describe the behavioural domain and its consequences without inferring a dementia subtype from it alone.

- Assess cognition and everyday independence in parallel, then review the behavioural and cognitive trajectories together.

The broader lesson is that early neurocognitive illness can be cognitively or behaviourally signalled, but neither signal is self-interpreting. Syndromic description should precede aetiological attribution. This protects against both under-recognition and premature diagnostic certainty.

18.8 Constructing and communicating the final formulation

A good formulation begins with the current state, not the feared destination. State whether there is a subjective complaint, objective decline, preserved independence and a demonstrable longitudinal change. If objective impairment is present, name the affected domains and whether the pattern is amnestic or nonamnestic, single-domain or multiple-domain. Then state exclusions and the degree of confidence in any suspected aetiology.

The history and assessment should answer a compact sequence:

- What has changed from the previous baseline, and is that change subjective, objectively demonstrated or documented serially?
- Does cognitive difficulty interfere with independence, or is independence maintained through effort and compensation?
- Which course is emerging: progression, persistence, fluctuation or reversion?

Communication should separate present diagnosis from future risk. “Your testing shows mild impairment, but you remain independent” is a current-state statement. “Some people progress while others remain stable or improve” is a prognosis statement. “The pattern may suggest a particular cause, but does not prove it” is an aetiological statement. Keeping these sentences separate reduces fatalism and false reassurance.

The same discipline strengthens an examination answer. Define the subjective and objective states, identify preserved independence as the boundary, describe the amnestic and nonamnestic phenotypes, and then discuss prognosis with source and population attached. Add behavioural change as a parallel early signal. Do not drift into detailed dementia biomarkers, imaging, drug treatment or disorder-specific diagnostic criteria, which belong to their dedicated sections.

> MCI means objective or longitudinal cognitive decline without loss of everyday independence; it raises dementia risk but does not make progression inevitable.

The cognitive continuum is therefore best understood as a revisable clinical model. Subjective concern can precede measurable impairment; measurable impairment can coexist with independence; behavioural change can accompany either; and later observation may show progression, stability or reversion. Precision at the borderline does not require false certainty. It requires explicit definitions, careful functional analysis and respect for longitudinal evidence.

19 · Delirium versus dementia versus depression: comparative differentiation

The marks lie in choosing the right discriminator, not in reciting three definitions. Delirium, dementia and depression can all present with poor recall, reduced participation, behavioural change and apparent functional decline. The useful comparison therefore begins with the architecture of the syndrome: consciousness, attention, speed of onset, fluctuation, progression, testing context and what happens over time. A candidate who starts and ends with "memory impairment" has selected the least discriminating common feature.

This section owns the distinction among the three syndromic presentations. It does not reproduce the full diagnosis, investigation or management of delirium, which belongs in the Stroke, TBI, delirium and focal brain syndromes notes. It also does not reteach depressive disorders or general cognitive-screen administration. Its purpose is narrower and clinically more useful: identify which observations change the probability of each explanation, recognise coexistence, and avoid converting a bedside clue into an absolute rule.

19.1 Begin with consciousness and attention

The first division is between cognitive impairment occurring with altered consciousness and cognitive impairment occurring in clear consciousness. In **delirium**, cognitive change accompanies an altered level of consciousness, alertness fluctuates, onset is generally sudden and acute, and **attention** is the hallmark impaired cognitive domain. In **dementia**, cognition is impaired in clear consciousness. This is the highest-yield conceptual distinction because a patient who cannot maintain or direct attention cannot be assessed as though a stable cognitive baseline were being sampled.

"Clear consciousness" does not mean that every person with dementia is calm, fully oriented or free of behavioural symptoms. It means that altered consciousness is not part of dementia by definition. Conversely, altered consciousness is not merely severe forgetfulness. It is a change in the patient's level or stability of awareness and alertness accompanying cognitive impairment. The bedside sequence therefore runs from arousal to attention and only then to the pattern of memory, language and other cognitive findings.

RULE **Test the state before interpreting the score.** Altered consciousness, fluctuating alertness and impaired attention direct the formulation toward delirium; clear consciousness permits a dementia or depression comparison, but does not by itself settle it.

ATTENTION	CLEAR	ENCOURAGE	FOLLOW
DELIRIUM HALLMARK	DEMENTIA CONSCIOUSNESS	TESTING CONTEXT	COGNITIVE TRAJECTORY

19.2 Delirium and dementia: feature-by-feature comparison

The comparison below should be read as a pattern, not as a checklist in which every cell must be present. Its strongest use is relational: acute or subacute change plus fluctuation, altered alertness and impaired attention forms a different syndrome from insidious, slowly progressive decline in

otherwise clear consciousness. Memory impairment alone cannot make that distinction because episodic memory may be impaired in both.

CLINICAL AXIS	DELIRIUM PATTERN	DEMENTIA PATTERN
Onset	Acute or subacute	Insidious
Course	Fluctuating	Slowly progressive
Duration	Hours to weeks	Months to years
Alertness	Abnormally low or high	Typically normal
Sleep-wake cycle	Disrupted	Typically normal
Attention	Impaired	Relatively normal
Orientation	Impaired	Intact in early dementia
Working memory	Impaired	Intact in early dementia
Episodic memory	Impaired	Impaired
Thinking	Disorganised or delusional	Impoverished
Speech	Slow or rapid, and may be incoherent	Word-finding difficulty
Perception	Illusions or hallucinations are common	Typically unimpaired early; **Lewy body dementia** is an exception
Behaviour	Withdrawn or agitated	Varies with dementia type and is often intact early

Several rows deserve interpretation. Orientation and working memory can remain intact early in dementia, so preserved performance in these areas does not exclude a progressive disorder. Episodic memory can be impaired in both conditions, so asking only about delayed recall is diagnostically weak. Perceptual disturbance supports delirium in the broad comparison, but the exception of Lewy body dementia prevents a simplistic “hallucinations equal delirium” answer. Behaviour also overlaps: withdrawal and agitation may arise in delirium, while dementia-related behaviour depends on the underlying type and stage.

The table also explains why serial observation is often more revealing than a single polished interview. Fluctuation is not the same as ordinary variation in effort or mood. It belongs to a larger delirium pattern that includes altered alertness and impaired attention. Slow progression is likewise not established by one poor test; it is a longitudinal conclusion constructed from history, collateral information and change from baseline.

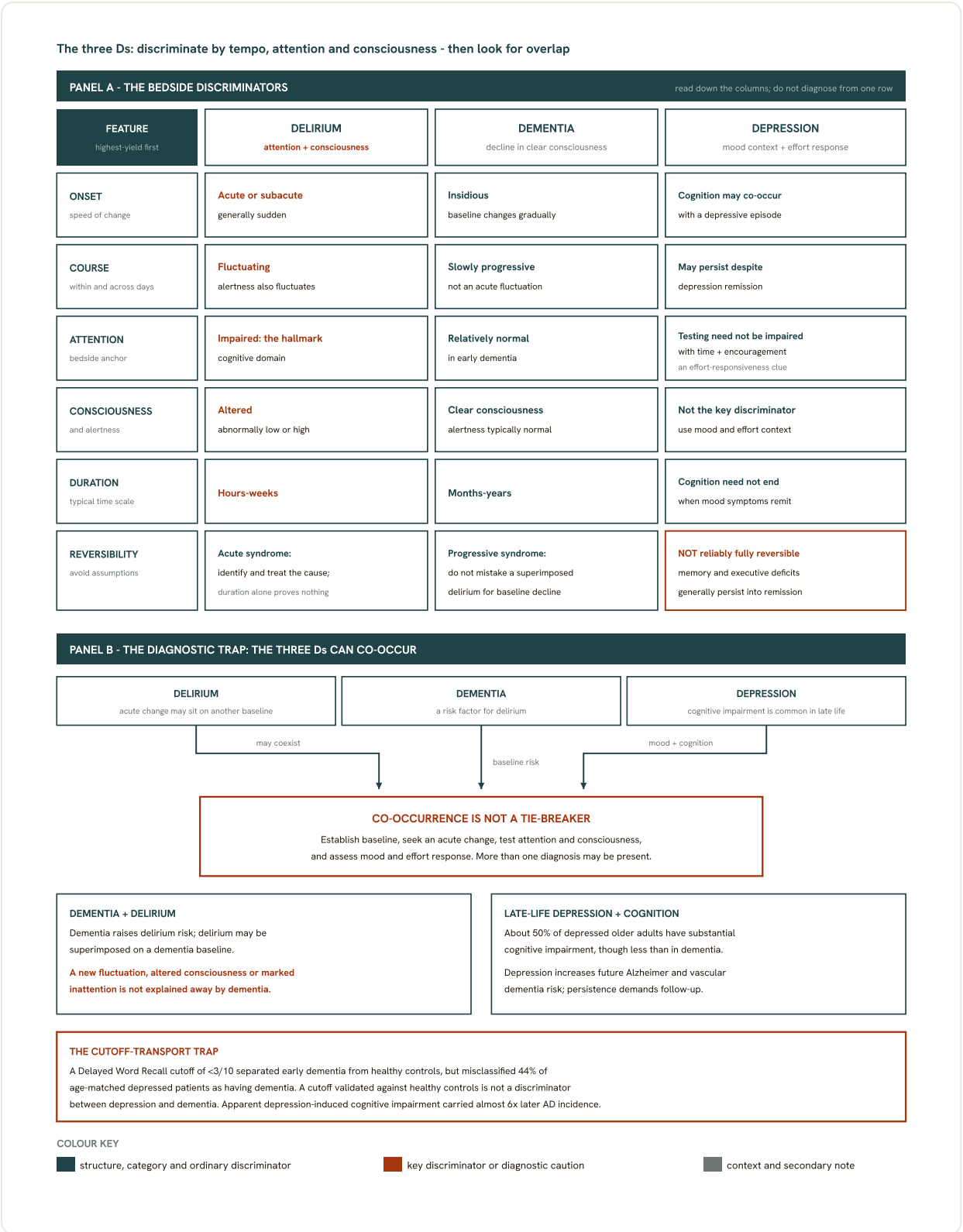

Fig 32.7 The three Ds: delirium, dementia and depression. Acute fluctuation, impaired attention and altered consciousness point to delirium; insidious progression in clear consciousness supports dementia. Depression-associated cognitive impairment may respond to time and encouragement during testing but is not reliably fully reversible, and overlap among the three conditions makes baseline and longitudinal follow-up essential. (Companion to Psychiatric Studies; Kaplan & Sadock's Comprehensive Textbook of Psychiatry 2024; Kaufman's Clinical Neurology for Psychiatrists.)

The accompanying figure should be used as a discriminator rather than as three sealed boxes. The decisive clinical move is to follow the branch that best explains the patient's state, while keeping open the possibility that more than one process is present.

19.3 The coexistence problem: delirium on a dementia baseline

Dementia is a risk factor for delirium, and delirium may be **superimposed on dementia**. This destroys a common false choice. A patient with established progressive cognitive decline can still develop a new acute, fluctuating disturbance of alertness and attention. The prior dementia explains vulnerability and baseline impairment; it does not explain away the new state change.

Clinically, the comparison must therefore be made against the patient's own baseline rather than against an imagined normal older adult. The question is not simply, "Is cognition impaired?" It is, "What has changed from the usual pattern, how rapidly, and in which domain?" A longstanding difficulty with memory may belong to the baseline dementia, while a new inability to sustain attention with unstable alertness indicates an additional syndrome. This reasoning is more dependable than treating the current examination as though it represented the patient's usual level.

Collateral history is valuable here because a fluctuating state may look deceptively coherent during a brief encounter. The informant's task is not to diagnose. It is to describe the baseline, the change and its time course. The examiner then maps that history onto the consciousness-attention-course framework. Full delirium assessment and management remain a separate topic in the Stroke, TBI, delirium and focal brain syndromes notes.

> **PITFALL**
>
> Do not attribute every acute behavioural or cognitive change in a person with dementia to "progression." Progression is characteristically slow, whereas a new fluctuating alteration in alertness and attention raises delirium superimposed on the established baseline.

19.4 Depression-associated cognitive impairment is not a disposable mimic

The older label **pseudodementia** implied that cognitive impairment accompanying depression was merely apparent and would fully reverse when mood improved. That assumption is unsafe. Substantial cognitive impairment is present in about **50%** of depressed older adults, although it is less marked than in dementia and occurs more frequently than in younger depressed patients. The problem is therefore common enough to be part of routine differential diagnosis rather than a rare examination curiosity.

More importantly, cognitive impairment accompanying late-life depression generally persists into remission, especially in memory and executive function. The term "pseudodementia" may still appear in clinical and examination language, but it should not carry the old promise of complete reversibility. Mood recovery and cognitive recovery are related observations, not interchangeable endpoints. A patient may improve affectively yet retain measurable cognitive difficulty.

This changes the interpretation of follow-up. Persistence after mood improvement does not automatically prove that dementia was present from the beginning, just as improvement with encouragement does not prove that the difficulty was wholly caused by depression. The source literature leaves unresolved whether depressed mood in this setting can represent prodromal

dementia or an etiologically related but distinct process. The appropriate stance is longitudinal and probabilistic: document both mood and cognition, observe their trajectories, and resist forcing either into the role of a perfect explanatory variable.

Depression also increases the future risk of both **Alzheimer disease dementia** and **vascular dementia**. This association is clinically important, but it does not permit retrospective certainty about cause in an individual patient. Depression may be a coexisting disorder, a risk marker, a related process or part of an evolving presentation. The distinction must therefore remain open to revision as the longitudinal pattern becomes clearer.

19.5 Bedside testing: effort-responsiveness is a clue, not a verdict

A useful bedside distinction is **effort-responsiveness**. Cognitive performance in depression may improve when the examiner provides sufficient time and encouragement. This contrasts with the more persistent test difficulty expected when an underlying dementia is driving the deficit. The clinical value lies in observing how performance changes under supportive testing conditions, not in judging the patient as motivated or unmotivated.

The examiner can use this clue without turning the encounter into an unstandardised contest:

- First establish whether alertness and attention are stable enough for the result to be interpretable.
- Then allow adequate time and offer neutral encouragement, noting whether engagement and performance improve.
- Finally interpret the response alongside history, functional change, mood and longitudinal course rather than as a stand-alone diagnostic sign.

The response to encouragement is not a licence to dismiss cognitive complaints. Late-life depression can be accompanied by substantial and persistent impairment, so the bedside clue must be held together with the longitudinal evidence. Nor should a poor performance under ordinary conditions be read as proof of dementia when the patient was slowed, discouraged or insufficiently engaged. The comparison is about the pattern of response, not a moral inference about effort.

> **GOOD TO REMEMBER**
>
> When depression and dementia are both plausible, record the testing conditions as carefully as the score. Adequate time, neutral encouragement and observed response can alter interpretation, while follow-up shows whether the cognitive problem tracks mood recovery or persists beyond it.

Detailed administration and scoring of general cognitive screens belongs in the Psychometry, Assessment and Descriptive Psychopathology notes. Here the test is used only as part of differential reasoning. A score is a sample of performance under particular conditions; the diagnosis comes from the syndrome and trajectory in which that sample sits.

19.6 The cutoff trap: healthy controls are the wrong comparator

Separating depression from dementia is particularly difficult because both can produce genuine cognitive test abnormalities. The **Delayed Word Recall Test** illustrates the danger of importing a cutoff from the wrong comparison. A threshold of **fewer than 3 words out of 10** separated early dementia from healthy controls almost perfectly in the original comparison. When the same threshold was applied to dementia versus age-matched clinically depressed patients, **44%** of the depressed group were misclassified as having dementia.

The lesson is broader than this test. A threshold validated against healthy people answers a relatively easy question: who resembles a healthy control and who does not? Clinical practice asks a harder question: which of two disorders capable of impairing cognition better explains this patient? Performance that is unusual for health may be entirely non-specific when depression is the comparator. Diagnostic accuracy cannot be transported unchanged across populations merely because the test and cutoff remain the same.

TRAP **Do not equate "below a dementia-screening cutoff" with "therefore dementia."** A cutoff that performs impressively against healthy controls may perform poorly when the real alternative diagnosis is depression.

For an examination answer, state the comparator explicitly. For a clinical formulation, ask what the threshold was designed to discriminate and whether the patient resembles the population in which it was tested. The correct response to overlap is not to abandon cognitive testing. It is to stop asking a single score to perform the work of history, state examination, functional assessment and longitudinal review.

19.7 Longitudinal risk changes the meaning of "pseudodementia"

Patients thought to have depression-induced cognitive impairment later develop Alzheimer disease dementia almost **six times** as frequently as age-adjusted counterparts. This is a risk association, not a deterministic conversion rule. It does not mean that every depressed older adult with cognitive symptoms has latent dementia, and it does not justify naming a future diagnosis before the longitudinal evidence exists.

The figure matters because it changes follow-up from optional reassurance to part of diagnosis. If cognition improves with time and encouragement, that observation supports one formulation; if impairment persists into mood remission or a progressive pattern emerges, the formulation must be revised. The source evidence also associates depression with future vascular dementia, reinforcing that the relevant outcome is not restricted to a single dementia type.

Two opposite errors follow from ignoring this evidence. The first is false reassurance: declaring the cognitive syndrome "only depression" and ending cognitive surveillance after affective improvement. The second is premature closure in the other direction: treating a risk association as proof that dementia is already present. Longitudinal reasoning avoids both. It preserves therapeutic attention to depression while maintaining proportionate concern about persistent or progressive cognitive change.

19.8 Integrating the three Ds at the bedside and in an answer

Use a hierarchy, not a bag of signs. First determine whether the patient is in a stable state of consciousness and can sustain attention. Next reconstruct onset and course. Then examine the cognitive profile, testing context and response to encouragement. Finally, compare mood and cognition longitudinally. This order prevents an impressive memory deficit from distracting the examiner from a more urgent state disturbance and prevents a low score from being treated as a diagnosis.

DECISION QUESTION	FINDING THAT REDIRECTS REASONING	INTERPRETIVE CONSEQUENCE
Is consciousness altered?	Altered level with cognitive impairment	Prioritise delirium in the differential
Can attention be sustained?	Attention is prominently impaired with fluctuating alertness	Supports the delirium pattern
What is the temporal arc?	Acute or subacute and fluctuating versus insidious and slowly progressive	Separates state change from progressive decline
Does supportive testing matter?	Performance improves with enough time and encouragement	Supports depression-associated impairment, without proving it
What happens after mood recovery?	Cognitive impairment may persist, especially in memory and executive function	Continue longitudinal cognitive review
Was dementia already present?	New state change on a progressive baseline	Consider delirium superimposed on dementia

When findings point in different directions, weight them by discriminating value rather than counting them. Impaired episodic memory contributes little to the delirium-dementia separation because it may occur in both. By contrast, altered alertness, impaired attention and fluctuation form a coherent state-change pattern. Preserved orientation during an interview should also be weighted cautiously because orientation may remain intact early in dementia and a fluctuating delirium may be sampled during a clearer period. The question is which combination best explains the whole presentation, not which diagnosis collects the largest number of isolated signs.

Coexistence should be stated whenever it resolves an apparent contradiction. A progressive cognitive baseline does not cancel a new acute attentional disturbance; it makes delirium superimposed on dementia a necessary consideration. Similarly, a depressive episode does not make persistent cognitive impairment imaginary, and persistent impairment does not by itself reveal whether depression was prodromal, causally related or distinct. The formulation can legitimately contain more than one syndrome and more than one level of certainty.

A useful closing sentence identifies the next discriminating observation. For suspected delirium, that observation is the evolution of alertness and attention within the acute fluctuating course. For a dementia pattern, it is evidence of continued progressive decline from baseline. For depression-associated impairment, it is whether cognition improves under supportive conditions

and how it behaves as the mood episode remits. This makes follow-up part of diagnostic reasoning rather than an admission that the examiner failed to decide.

MNEMONIC

AAT: Arousal, Attention, Trajectory

Arousal asks whether consciousness is altered; **Attention** identifies the hallmark cognitive disturbance of delirium; **Trajectory** separates an acute fluctuating state, an insidious progressive decline and depression-associated cognitive impairment that requires follow-up rather than a promise of reversibility.

A concise written answer can therefore proceed in a disciplined sequence:

- Lead with consciousness, attention, onset and course, because these provide the strongest delirium-dementia separation.
- Add the shared and contrasting cognitive, perceptual, speech and behavioural features rather than presenting memory loss as unique to dementia.
- Close with coexistence and uncertainty: delirium can occur on dementia, depression-related impairment may persist, and a cutoff cannot replace longitudinal diagnosis.

Altered consciousness plus impaired attention and fluctuation points toward delirium; clear consciousness shifts the comparison toward dementia or depression, where trajectory, testing context and follow-up carry the distinction.

The final formulation should remain syndromic and revisable. Name the dominant pattern, state the evidence that supports it, acknowledge any baseline disorder, and identify what observation over time would change the conclusion. That is stronger than claiming certainty from memory impairment, a hallucination, an apparent response to encouragement or a single cutoff. The three Ds are differentiated most safely by combining state, domain and trajectory.

Assessment, biomarkers and the pharmacology of dementia

20 · Cognitive assessment in dementia: bedside batteries and neuropsychological profiles

Cognitive assessment should convert a vague complaint into a defensible pattern. The clinician must decide whether performance is genuinely abnormal, which domains are affected, whether the pattern fits the history and functional decline, and whether a brief screen is sufficient. A total score can support this reasoning, but cannot replace it. The marks lie in choosing the right level of assessment, interpreting performance in context, and describing a profile rather than announcing dementia from a single number.

Bedside testing and formal neuropsychological assessment answer related but different questions. A bedside battery offers a structured snapshot suitable for case finding, comparison over time

and communication between clinicians. Formal assessment examines the pattern in greater depth when the bedside result is equivocal, the presentation is unusual, or a domain-specific question matters. Item-level administration, standardised scoring and the generic psychometric properties of these instruments belong in the Psychometry, Assessment and Descriptive Psychopathology notes. Here the lens is dementia: selection, interpretation, serial use and syndrome-level profiling.

SCREEN	CONTEXT	PROFILE	COURSE
STRUCTURED SNAPSHOT	FAIR INTERPRETATION	DOMAIN PATTERN	SERIAL MEANING

20.1 What a bedside cognitive screen can and cannot establish

A screen is best treated as a structured sample of cognition. It can disclose a low score, an uneven pattern, a striking qualitative error or a discrepancy between the patient's confidence and performance. It can also provide a baseline for later comparison. It does not by itself establish cause, chronicity or functional consequence. Those conclusions require history from the patient and an informant, examination, assessment of everyday functioning and the wider diagnostic workup.

The **Mini-Mental State Examination** became the standard bedside dementia screen because it is regularly used, reproducible and clinically interpretable; its results correlate with histological change in Alzheimer disease. Among well-educated people whose scores are borderline, **10% to 25% may develop dementia within the next 2 years**. The point is predictive enrichment, not certainty. A borderline result identifies a group requiring clinical attention and follow-up; it does not identify which individual will progress.

RULE **Interpret the score as evidence within a formulation, never as the formulation itself.** State the instrument, testing context, domain pattern, functional history and longitudinal direction before drawing an etiological inference.

Before testing, clarify the question. Is the concern early decline despite apparently preserved conversation? Is the aim to document a baseline, follow an established disorder, explore an executive presentation, or decide whether formal testing is needed? The same brief instrument cannot be equally sensitive to every pattern. The question should determine the battery, rather than familiarity with a battery determining the question.

20.2 Interpreting the standard bedside screen in dementia

The total score has meaning only within the source's stated construct. The cited clinical summary gives a **maximum of 30 and describes scores of 20 or less as occurring with dementia, delirium, schizophrenia or affective disorder, alone or together**. Such low scores were not found in normal older people or in people with neurosis or personality disorder in that account. This is not a dementia-specific diagnostic cut-off. It is a broad correlation with markedly abnormal clinical populations. The commonly recalled alternative screening threshold and any India-specific adjustment are not supplied here and should not be substituted from memory.

Functional correlations help show why a total score must be translated back into life. In the same summary, **a total around 20 correlates with inability to keep appointments or use a**

telephone, while around 15 it marks inability to dress or groom. These associations illustrate increasing dependence; they do not permit the clinician to infer a person's exact abilities from the score. Function must still be asked about directly, because performance in a consultation and performance in a familiar environment are not interchangeable.

Serial trajectory may be more informative than an isolated result. If successive scores remain stable for **2 years**, the diagnosis of a relentlessly progressive Alzheimer process should be reconsidered. If they fall precipitously, rapidly progressive causes become more likely. In both situations, the correct response is diagnostic review, not mechanical restaging. Test conditions, intercurrent illness, sensory difficulty, language, mood and participation should be considered before attributing all change to neurodegeneration. Delirium itself is taught in the Stroke, TBI, delirium and focal brain syndromes notes.

GOOD TO REMEMBER

Record the qualitative behaviour beside the score: whether the patient encoded the material, benefited from cueing, lost set, produced intrusions, misunderstood instructions, became impulsive or showed disproportionate difficulty in one domain. That description often carries more diagnostic value than an unqualified total.

20.3 Ceiling effects, domain bias and false reassurance

A familiar screen may be "too easy" for the clinical question. The **ceiling effect** allows mild cognitive impairment and early dementia to escape detection. Age, education and language influence the score. Heavy dependence on orientation, memory and language means that executive dysfunction may be under-sampled, including presentations in which frontal systems are central. The same language dependence makes the instrument less adequate when subcortical white-matter damage is the principal problem.

Domain dependence is especially important when the suspected profile is frontal-executive rather than amnestic. Vascular cognitive impairment literature illustrates the problem: a patient may struggle with planning, set shifting and cognitive control while retaining enough orientation and language to appear reassuring on a language-heavy total. The remedy is not to reinterpret the same total more aggressively. It is to supplement the examination with an instrument that samples the domain of concern and to examine the behaviour displayed during testing.

In Parkinson disease cognition, the **Montreal Cognitive Assessment** is favoured over the standard screen because it covers more cognitive subdomains, has less ceiling effect and is more sensitive to longitudinal change. This is a context-specific illustration of battery selection, not permission to teach Parkinson neuropsychiatry here. That broader subject belongs in the Neuropsychiatry of systemic and neurological disease notes.

TRAP **A high bedside score does not exclude meaningful cognitive disorder.** The classic error is to quote the total, ignore the presenting domain and stop. Early disease, executive syndromes, high premorbid ability and a ceiling-prone instrument can all make the number falsely reassuring.

20.4 Choosing among bedside batteries

The **broader multidomain screen** is more sensitive than the standard examination for mild impairment. It is particularly useful when memory is the only reported symptom or when concern persists despite a high standard-screen score. It is widely used across neurodegenerative dementias and detects early cognitive impairment in Parkinson disease better than the standard screen. Its stronger sampling of frontal dysfunction also makes it more suitable than a brief mental-status instrument when mild cognitive impairment is suspected and the clinical question is not purely orientation and recall.

Choice should balance sensitivity, domain coverage, testing burden, language and educational fit, sensory or motor limitations, examiner competence, permission to use the instrument, and the purpose of serial follow-up. The batteries are not interchangeable labels for "cognition". Their architecture determines what they are likely to reveal.

BEDSIDE OPTION	DOMAIN EMPHASIS IN THE CITED COMPARISON	BEST DEMENTIA-ASSESSMENT USE	MAIN CAUTION
Standard mental-status screen	Orientation, verbal registration and recall, attention, language, praxis and visuospatial performance	Familiar broad snapshot and serial comparison	Ceiling and executive-domain limitations
Broader multidomain screen	Orientation, attention, memory, naming, fluency, repetition and visuospatial-executive performance	Mild or executive concern despite a reassuring standard score	Education-related false-positive classification
Addenbrooke cognitive battery	Attention and orientation, memory, fluency, language and visuospatial performance	Early Alzheimer pattern, Alzheimer versus frontotemporal pattern, separation of organic brain disease from psychiatric states, and selected parkinsonian cognitive syndromes	Use only validated administration and scoring material
Cambridge cognitive battery	Orientation, language, memory, attention, praxis, calculation, abstraction and perception	A more extended generic screen when broader sampling is needed	Greater time burden than briefer bedside options

The standard and broader screens occupy a briefer bedside slot, while the revised Addenbrooke and Cambridge batteries are more extended. Administration time should therefore be selected deliberately rather than treated as an inconvenience discovered midway through testing. A hurried, poorly heard or linguistically mismatched administration is not made valid merely because it finishes quickly.

The **shorter validated Addenbrooke form** can be completed in **under 5 minutes and is scored out of 30**. Publicly available alternatives include the Mini-Cog, St. Louis Mental Status

Examination, Kokmen Short Test of Mental Status and Rowland Universal Dementia Assessment Scale. Their importance is practical because the Mini-Mental State Examination and Montreal Cognitive Assessment are no longer in the public domain and have been monetised. Availability, licensing and authorised materials therefore belong in test selection. Convenience does not justify copying protected item content, and this section deliberately describes rather than reproduces it.

20.5 Language, education and the Indian consultation

Every score is produced by a patient, an examiner, a language and a setting. Education can influence familiarity with test-taking, abstraction, paper-and-pencil demands and the strategies used to solve unfamiliar tasks. Language affects comprehension, lexical access and the meaning of apparently simple instructions. Sensory impairment, fatigue, anxiety, motor slowing and poor rapport can further lower performance without having the same diagnostic significance as neurodegeneration.

The broader screen samples more domains, but **low-education misclassification** is a recognised risk: cognitively normal people with limited educational attainment may be labelled as having dementia. The solution is not to waive concern whenever schooling is limited. It is to interpret performance alongside premorbid opportunity, occupational and daily competence, informant evidence, observed decline and the suitability of the chosen instrument. A decline from the person's own prior level is clinically different from lifelong unfamiliarity with the task.

IN INDIA

Do not import an education-insensitive threshold into a multilingual, variably schooled consultation and call the result objective. Test in the most appropriate available language, document the language and educational context, check hearing and vision, and prefer a validated culturally suitable instrument where available. When fit is doubtful, describe the observed domain pattern and escalate the assessment rather than manufacturing precision.

Translation at the bedside is not neutral. Changing a word, adding an explanation or allowing a relative to coach the patient may alter task difficulty. If an adaptation is necessary, document it and avoid pretending that the resulting total is strictly equivalent to a standard administration. A qualitative account can remain clinically useful even when a normative inference is unsafe.

MNEMONIC

SNAP

Select the battery for the question; **N**ote language, education, sensory and testing context; **A**ssess the pattern across relevant domains; **P**lace the result beside function and progression. The mnemonic prevents a bedside score from becoming a diagnosis by reflex.

20.6 When formal neuropsychological assessment adds value

Formal assessment is most useful when it answers a defined question. Referral is justified when bedside findings and history disagree, decline is subtle but consequential, the pattern is atypical,

executive or language dysfunction requires deeper characterisation, premorbid ability complicates interpretation, or serial measurement must be more domain-sensitive. It can also help examine whether depression or non-credible performance contributes to apparent impairment without reducing that judgement to a single performance sign. Depressive pseudodementia and the broader depression-dementia differential require their own clinical assessment and are not reproduced here.

A useful referral specifies the suspected domains, onset and course, functional change, language, education, occupation, sensory and motor constraints, psychiatric symptoms, medication context and the decision that the result will inform. “Rule out dementia” is too blunt. The neuropsychologist can better select and interpret measures when asked whether the profile is amnestic, dysexecutive, language-led, visuospatial, patchy, or globally slowed, and whether observed weaknesses are consistent with the history.

- **Define the decision:** diagnosis, differential pattern, baseline, progression or capacity for a particular everyday task.
- **Describe the trajectory:** onset, tempo, fluctuation and the relation between complaint and observed decline.
- **State the context:** education, language, occupation, sensory or motor limitation and relevant psychiatric state.
- **Request a profile:** strengths, weaknesses, error types, cueing response and coherence across domains.
- **Reintegrate the result:** compare it with function, examination, investigations and longitudinal observation.

Formal testing remains an examination under conditions, not a direct image of pathology. A profile may support an etiological hypothesis, reveal internal inconsistency or show that a bedside total concealed an important deficit. It should then be reintegrated with the clinical syndrome. Neuropsychological batteries taught as instruments, including their administration and scoring, remain with the Psychometry, Assessment and Descriptive Psychopathology notes.

20.7 Neuropsychological profiles across common dementia syndromes

The profile is a pattern of relative strengths, weaknesses and sequence. Etiological subtyping describes Alzheimer disease as typically memory-led, while frontotemporal lobar degeneration is typically led by speech, behaviour or executive dysfunction rather than by the same early amnestic emphasis. These are characteristic tendencies. They organise the differential but do not prove pathology in an individual patient.

CLINICAL PATTERN	LEADING COGNITIVE OR BEHAVIOURAL FEATURES	INTERPRETIVE CLUE
Alzheimer pattern	Early short-term memory and language impairment, followed by executive and then visuospatial dysfunction	Progressive amnestic-language beginning with later spread across domains
LATE pattern	An amnestic syndrome resembling the Alzheimer presentation	Neuropsychology may show resemblance rather than settle the underlying pathology
Frontotemporal pattern	Relative memory sparing, with language impairment or executive dysfunction predominating	Look beyond recall totals to behaviour, language and cognitive control
Vascular dementia pattern	Patchy deficits shaped by the location of vascular lesions	Uneven performance is more informative than forcing a single smooth sequence
Lewy body pattern	Visuospatial, attention and executive deficits more prominent than memory impairment, with cognitive fluctuation	Visual hallucinations, spontaneous parkinsonism, earlier psychosis or personality change, and REM-sleep disturbance strengthen the clinical pattern
Mild cognitive impairment pattern	Reduced processing speed and choice-reaction performance, with mild inconsistent forgetfulness	Cognitive symptoms occur without the functional impairment that defines dementia in this comparison

The behavioural variant of frontotemporal dementia sharpens the contrast. Patients may lack awareness of inappropriate behaviour, show relatively preserved memory with benefit from cues, and retain general visuospatial ability despite later cognitive deficits in contrast to the rapid memory loss described in the Alzheimer comparison. Cueing response is therefore not a decorative detail: it helps distinguish failure to retrieve efficiently from a more severe failure to retain information.

The table is a set of complementary clinical patterns, not a canonical map covering every domain for every dementia. Mixed pathology, disease stage, premorbid ability and focal presentations can blur the expected shape. Use the profile to generate and test hypotheses, then reconcile it with the course, neurological findings, function and biomarker or imaging workup described in their respective sections.

20.8 Cortical versus subcortical pattern and final synthesis

The **cortical-subcortical distinction** remains a useful descriptive scaffold. A cortical pattern shows module-specific deficits: amnesia, aphasic features and apraxia, while alertness and executive function may be preserved early. A subcortical pattern is characterised by slowing, impaired attention and executive function, reduced verbal output, and forgetfulness that improves with cueing; language structure and praxis remain relatively preserved. The distinction is about the organisation of deficits, not merely their severity.

This contrast explains why a language-heavy bedside screen can miss clinically important subcortical dysfunction. A patient may be slow, inattentive and dysexecutive yet retain naming, praxis and basic language structure. Conversely, a cortical syndrome may show a striking focal failure even when general alertness appears normal. Huntington disease is a standard subcortical example, but its disease-specific neuropsychiatry belongs in the Neuropsychiatry of systemic and neurological disease notes.

PITFALL

Do not equate poor recall with one mechanism. Ask whether material was encoded, retained, retrieved spontaneously or recovered with cueing. Amnesia, inefficient retrieval, inattention and language failure can all produce "memory difficulty", but they imply different profiles.

The final synthesis should read as a compact argument. Name the battery and why it suited the question. Describe testing conditions and any limitation. Report the total only within its proper construct. State the affected and relatively preserved domains, qualitative errors and cueing response. Link the pattern to everyday function and the longitudinal course. Then say which etiological pattern it supports, what it fails to explain, and whether formal assessment or another investigation is needed.

This is also the safest examination strategy. A candidate who lists instruments demonstrates recall; a candidate who explains selection, context, profiles and limitations demonstrates clinical reasoning. Bedside testing begins the cognitive formulation. Neuropsychological profiling refines it. Neither replaces the history of decline or the evidence of functional consequence.

A cognitive score screens; the domain pattern, functional decline, testing context and serial course make it clinically meaningful.

21 · Structural and functional neuroimaging in dementia (MRI, FDG-PET, amyloid-PET, DAT scan)

Neuroimaging earns marks when it answers a clinical question, not when it becomes a catalogue of scans. In a patient with cognitive decline, imaging is used to identify the anatomical pattern, estimate vascular or degenerative burden, look for a functional network signature, or test for a molecular or dopaminergic signal. The report becomes meaningful only after it is reconciled with the history, examination and cognitive phenotype. A scan can strengthen or weaken a diagnostic formulation; it should not replace one.

The useful framework separates structural MRI, FDG-PET, amyloid-PET and tau-PET, and dopamine-transporter imaging. Structural imaging asks where tissue loss or vascular injury is distributed. Metabolic or perfusion imaging asks which networks are functioning abnormally. Molecular imaging asks whether a targeted pathological signal is present. Dopamine-transporter imaging contributes to a narrower differential involving disorders in which that signal is abnormal. The physics, tracer kinetics and acquisition principles belong in the Neurochemistry,

Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the concern here is dementia-specific interpretation.

MRI	FDG	AMYLOID	DAT
ANATOMICAL PATTERN	NETWORK FUNCTION	PATHOLOGICAL SIGNAL	DOPAMINERGIC SUPPORT

21.1 Start with the question the scan must answer

A useful request begins with the unresolved differential. “Cognitive decline” is not enough. The clinician should state whether the dominant uncertainty concerns a degenerative pattern, vascular contribution, frontotemporal distribution, an occipital functional pattern, or a dopaminergic syndrome. This improves the chance that the radiological description is translated into a clinically usable answer. It also prevents the common habit of ordering progressively more specialised tests merely because the preceding result was non-specific.

Before ordering, write down the expected consequence of each possible result. If an amyloid-negative study would meaningfully weaken a proposed AD aetiology, the test has a clear role. If a characteristic functional pattern would resolve a genuine degenerative differential, the request is similarly focused. If neither a positive nor a negative result would alter formulation, counselling or further assessment, the request is poorly framed. This pre-test discipline matters because imaging abnormalities are easy to notice but harder to interpret responsibly. The more specialised the test, the more precisely the clinician should define the probability shift being sought.

MODALITY	PRIMARY CLINICAL QUESTION	BEST USE IN REASONING	MAIN INTERPRETIVE CAUTION
MRI	Where is atrophy or vascular injury distributed?	Match anatomy to the cognitive and behavioural phenotype	Atrophy can support a formulation without being diagnostic by itself
FDG-PET or perfusion imaging	Which cortical or subcortical networks show reduced function?	Compare the observed pattern with characteristic dementia patterns	A pattern must remain concordant with structural imaging and phenotype
Amyloid-PET or tau-PET	Is the targeted molecular signal present, and does it fit the suspected process?	Use molecular evidence to shift the probability of an aetiological diagnosis	Do not turn one biomarker into a complete clinical diagnosis
DAT scan	Is dopamine-transporter imaging abnormal in a relevant syndrome?	Support a dopaminergic differential when clinical uncertainty remains	An abnormal result is shared by several neurological disorders

RULE **Ask anatomy, function, pathology or dopamine-transporter status as separate questions.** Choosing the modality follows from the question; interpreting it requires convergence with the phenotype.

This sequence is also a safeguard against overtesting. Structural and functional findings often answer different parts of the same problem. A mismatch should prompt re-examination of the clinical formulation, image quality, disease stage and competing pathology. It should not be "resolved" by automatically privileging the more technologically impressive scan. In examination answers, state the diagnostic question first, describe the expected distribution next, and finish with the limitation.

The radiology request and the final formulation should use the same vocabulary. If the request asks about a frontotemporal process, the answer should address frontal and anterior-temporal distribution rather than merely stating that atrophy is present. If vascular contribution is the issue, burden, territory and relationship to the clinical deficits matter more than an undifferentiated label of small-vessel change. A precise question invites a pattern-based report; a vague question invites a list of incidental observations.

21.2 Structural MRI: pattern, burden and concordance

MRI contributes by showing the distribution of atrophy, ventricular enlargement and white-matter abnormality. The central interpretive distinction is between a supportive pattern and a stand-alone diagnosis. In AD, MRI findings are **informative rather than diagnostic**. The same principle applies more broadly: the image should fit the syndrome's dominant cognitive, behavioural or neurological features before it is allowed to carry substantial diagnostic weight.

In the amnestic degenerative pattern, medial-temporal atrophy is the structural emphasis. Even at a mild clinical stage, the cited quantitative description reports **20-30%** loss of entorhinal cortex volume and **15-25%** loss of hippocampal volume, together with ventricular enlargement. These figures illustrate an important clinical point: apparently mild symptoms need not imply mild underlying tissue injury. They should not, however, be converted into a bedside cut-off or used as a substitute for formal image interpretation.

Vascular disease requires attention to burden and distribution rather than a reflex equation of any white-matter change with vascular dementia. The supplied description associates vascular dementia with progressively increasing **white-matter hyperintensity burden**. The clinician must still ask whether the imaging pattern plausibly explains the cognitive profile and course. Patchy injury may produce uneven deficits, while diffuse subcortical network involvement may produce a different clinical emphasis. Imaging-clinical concordance is therefore more valuable than the mere presence of an abnormality.

TRAP **Do not reproduce a summary-table error as though it were settled anatomy.** One cited table gives a **summary-table medial-temporal entry for FTD**, yet the same source's detailed disease account describes **frontal and anterior-temporal atrophy**, particularly involving prefrontal cortex, insula, anterior cingulate, striatum and thalamus, with greater involvement of the non-dominant hemisphere. State the inconsistency, then use the detailed syndrome-specific pattern for clinical reasoning.

The conflict is exam-relevant because it tests whether the candidate understands a pattern or merely recalls a row. A behavioural frontotemporal presentation should be examined for a frontal

and anterior-temporal structural distribution, not forced into an undifferentiated medial-temporal template. Conversely, medial-temporal change in a patient with a different phenotype should not erase the clinical syndrome. Mixed or overlapping pathology remains a clinical possibility, but it cannot be declared from an isolated image description.

Read the structural study in a fixed order. Decide whether volume loss is focal or diffuse, symmetrical or asymmetrical, and predominantly medial-temporal, frontal or anterior-temporal. Then assess whether vascular abnormalities are patchy, confluent or anatomically related to the deficits under discussion. Finally, compare these observations with ventricular size and the overall degree of tissue loss. This order converts descriptive radiology into clinical neuroanatomy. It also exposes discordance early: a striking behavioural syndrome with an unrelated structural distribution should trigger reconsideration rather than a forced match.

PITFALL

Do not diagnose vascular dementia from incidental white-matter change alone. First ask whether the amount, location and network effect of the vascular injury are sufficient to account for the observed decline, and whether the clinical course is concordant.

21.3 Functional imaging: recognise distributions, not bright colours

Functional imaging is most useful when it converts a vague impression of “reduced uptake” into a distributed network pattern. FDG-PET is interpreted as a regional metabolic pattern, while perfusion imaging offers a related pattern-based differential. The acquisition physics is not the task here. The task is to identify the dominant regions, decide whether the distribution is coherent, and compare it with the structural and clinical picture.

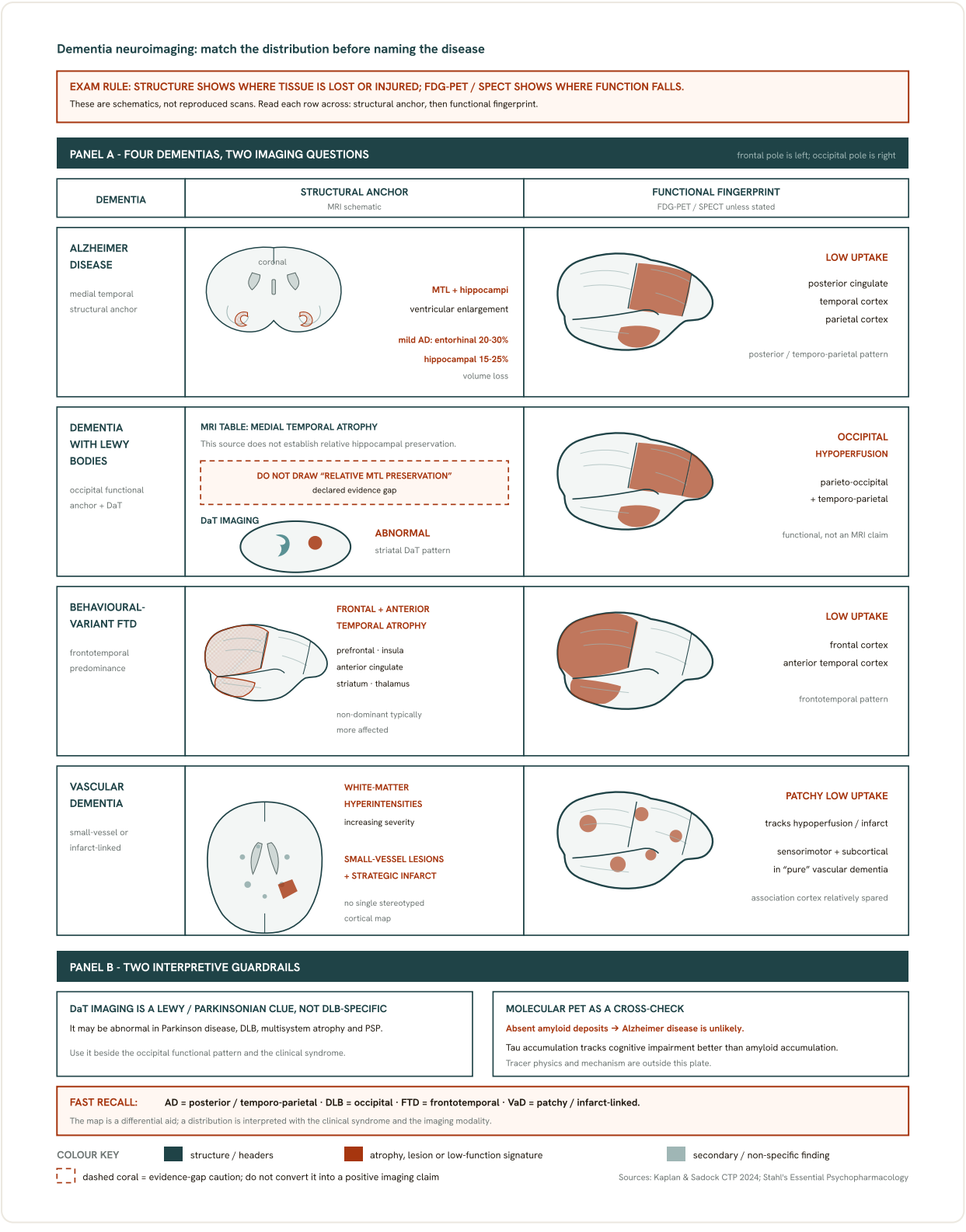

Fig 32.8 Neuroimaging patterns in the dementia differential. Alzheimer disease centres on medial temporal and hippocampal atrophy with posterior cingulate, temporal and parietal functional reduction; DLB adds an occipital functional pattern and abnormal DaT imaging; behavioural-variant F'TD is frontal and anterior temporal; vascular dementia combines white-matter and infarct burden with patchy, lesion-linked functional loss. The DLB schematic does not claim relative hippocampal preservation because that comparison was not grounded in the supplied evidence.

The accompanying figure should be read as a schematic of relative patterns, not as a substitute for viewing or formally reporting patient images. The following table condenses the high-yield differential.

CLINICAL SYNDROME	CHARACTERISTIC FUNCTIONAL PATTERN	HOW TO USE IT
AD	**Posterior cingulate, temporal and parietal reduction**	Supports the characteristic posterior-temporoparietal network pattern when concordant with the phenotype
Vascular dementia	**Patchy reduction corresponding to hypoperfusion or infarct location**	Relate each deficit to the vascular distribution rather than expecting a smooth degenerative pattern
FTD	**Frontal and anterior-temporal reduction**	Seek concordance with behavioural or language-led frontotemporal dysfunction
DLB	**May show occipital hypoperfusion or reduced function**	Use as supportive functional evidence within the full clinical differential

A second description of relatively "pure" vascular dementia adds a **sensorimotor and subcortical pattern with relative association-cortex sparing**, contrasting with the posterior or temporoparietal emphasis of AD. This is not a contradiction with a patchy vascular pattern. It reflects the fact that vascular cognitive syndromes can be expressed through the territory and network disrupted. In an answer, link the functional abnormality to the vascular anatomy instead of presenting vascular dementia as a single uniform metabolic map.

MNEMONIC

Back, Broken, Behaviour, Back-of-head

For the functional differential: AD is predominantly **back** in posterior cingulate and temporoparietal regions; vascular dementia is **broken** or patchy by lesion distribution; FTD follows **behaviour** and language networks in frontal and anterior-temporal regions; DLB may point to the **back of the head** through an occipital pattern.

Pattern reading should proceed in layers. First identify whether the reduction is focal, patchy or network-like. Next name the dominant lobes and whether association cortex appears relatively spared. Then compare the functional map with MRI. Finally, ask whether the patient's phenotype is expected from that network. This disciplined sequence prevents a colourful image from acquiring more authority than its clinical context permits.

A single affected region is usually less informative than the relationship among regions. Posterior cingulate involvement gains meaning when temporal and parietal reduction forms a coherent posterior network. Frontal reduction gains meaning when anterior-temporal involvement and the clinical syndrome point in the same direction. Occipital change gains meaning within the DLB differential rather than as an isolated visual label. Vascular reduction gains meaning through correspondence with hypoperfusion or infarct distribution. In each case, the pattern is the teaching unit. Memorising one lobe without its network context invites false certainty.

21.4 Amyloid-PET and tau-PET: molecular evidence changes probability

Molecular PET addresses pathology more directly than a regional atrophy or metabolism pattern, but its interpretation remains probabilistic. The most important negative inference is that **absence of amyloid deposits** indicates that dementia is not likely to be due to AD. Notice the direction of the statement: a negative amyloid study argues against that aetiology. The converse should not be carelessly rewritten as "a positive scan proves the entire clinical diagnosis." Clinical syndrome, functional effect and alternative explanations still matter.

Tau-specific PET detects hyperphosphorylated tau aggregates described across AD, progressive supranuclear palsy, corticobasal degeneration, frontotemporal lobar degeneration and chronic traumatic encephalopathy. For the candidate, the discriminating point is not merely that amyloid and tau can each be imaged. It is that the degree of tau accumulation correlates better with cognitive impairment than the degree of amyloid accumulation. This **tau burden-cognition relationship** helps explain why a pathological signal and current clinical severity are related but not interchangeable constructs.

The proper mental model is a chain rather than a verdict. Molecular signal addresses the presence of targeted pathology; structural imaging addresses accumulated anatomical effect; functional imaging addresses network dysfunction; clinical assessment addresses lived cognitive and functional consequence. Agreement across these layers increases coherence. Discordance is information: it may indicate timing, co-pathology, a poorly matched phenotype, or a limitation of the test. Without a supported threshold or performance figure, do not invent one in an examination answer.

Negative results also have unequal meanings. The supplied evidence gives a clear negative inference for amyloid imaging, but it does not provide equivalent exclusion rules for every other modality. A non-characteristic FDG pattern, for example, should be described as non-supportive or discordant rather than automatically treated as proof of an alternative dementia. The disciplined answer uses the strongest direction actually established for each test and leaves unsupported reverse inferences alone. This is especially important when a candidate remembers a familiar slogan but cannot state the population, comparator or threshold behind it.

> **GOOD TO REMEMBER**
>
> Read a negative amyloid study in the direction actually supported: it makes AD an unlikely cause of the dementia. Do not reverse that statement into an unqualified claim that any positive study establishes symptomatic AD.

21.5 DAT scan: a supportive test with a deliberately narrow claim

Dopamine-transporter imaging is abnormal in **Parkinson disease, DLB, multisystem atrophy and progressive supranuclear palsy**. Therefore, an abnormal scan is not unique to DLB and cannot by itself separate all disorders in that group. Its value is narrower: in the appropriate clinical differential, it supports the presence of an abnormal dopaminergic imaging signal and should be integrated with the dementia phenotype and neurological examination.

This is a useful example of why "abnormal" and "diagnostic" are not synonyms. A test can discriminate one broad mechanism or disease family while remaining unable to identify a single member of that family. The result must be interpreted against the question asked. If the clinical problem is not a differential in which dopamine-transporter status would change probability, the scan adds little merely by producing another abnormality.

Do not import the neuropsychiatry or treatment algorithms of Parkinson disease into this discussion. Those belong in the Neuropsychiatry of systemic and neurological disease notes. Here, retain only the dementia-imaging point: DLB may show an occipital functional pattern, and dopamine-transporter imaging can be abnormal, but neither statement is a substitute for the full syndrome diagnosis.

21.6 Integrating discordant results

Discordance is a prompt to think, not a reason to average the reports. A structural pattern may be subtle while functional change is convincing; molecular signal may be present without a matching clinical phenotype; vascular injury may coexist with a degenerative distribution. The clinician should identify exactly which layer disagrees and then reconsider the working hypothesis. "Mixed dementia" should not become a wastebasket label for every mismatch.

A practical integration sequence is:

- Restate the dominant clinical syndrome and the unresolved aetiological question.
- Describe MRI by distribution and burden, then ask whether the anatomy explains the phenotype.
- Describe functional imaging by network pattern, not merely as reduced uptake.
- Use molecular or dopamine-transporter imaging only for the probability shift that the test can legitimately provide.

When reports disagree, return to the images and the referral question where possible. Clarify whether the report is describing a definite pattern, a mild non-specific change, or a technically limited study. Compare prior imaging when available to understand progression, but avoid claiming a rate or interval that is not established. The clinical conclusion should state what the imaging supports, what it argues against, and what remains unresolved.

Fluid biomarkers can provide another biological layer, but their dementia-specific directions and emerging blood assays are taught in the dedicated biomarker section. Likewise, cognitive batteries contribute phenotype and severity, while their administration and general scoring belong in the Psychometry, Assessment and Descriptive Psychopathology notes. Imaging is strongest when it is one coherent part of this multimodal formulation.

21.7 Writing the examination answer

A high-scoring answer is organised by modality and clinical purpose. Begin with structural MRI, emphasising distribution of atrophy, ventricular enlargement and vascular white-matter burden. State that MRI is supportive rather than independently diagnostic. Then give the functional differential: posterior cingulate-temporoparietal reduction in AD, patchy lesion-linked reduction

in vascular dementia, frontal and anterior-temporal reduction in FTD, and a possible occipital pattern in DLB. Add the molecular PET principle that absence of amyloid makes AD unlikely and that tau burden tracks cognitive impairment more closely than amyloid burden. Finish with the narrow DAT point and its lack of uniqueness.

The best answer also contains its limitations. It does not teach PET or MRI physics, invent cut-offs, equate every white-matter lesion with vascular dementia, or conceal the conflict in the cited FTD MRI table. It distinguishes a characteristic pattern from a diagnostic criterion and a supportive biomarker from a complete diagnosis. That combination of recall and restraint is the real assessment target.

> Memorise the distributions: AD is posterior cingulate-temporoparietal, vascular dementia is patchy or lesion-linked, FTD is frontal and anterior-temporal, and DLB may be occipital; every pattern remains supportive and phenotype-dependent.

22 · CSF and emerging blood biomarkers (amyloid-beta-42, total and phospho-tau, plasma p-tau217)

Fluid biomarkers answer a biological question that the clinical interview cannot answer alone. They indicate whether a patient's cognitive syndrome is accompanied by a pattern of amyloid deposition, tau pathology or neuronal injury. Their value is greatest when the phenotype, structural assessment and longitudinal course leave a genuine question about the underlying disease process. They do not replace history, informant evidence, examination, cognitive assessment or the search for alternative causes.

The core examination task is to recognise the direction and meaning of the principal cerebrospinal-fluid changes, then place them within the **AT(N) research framework**. The same logic explains why blood testing is attractive: a less invasive sample could make biological assessment easier to deploy. However, an emerging marker is not automatically a stand-alone diagnosis, and a named analyte must not be given an invented threshold or accuracy estimate.

22.1 What a dementia fluid biomarker contributes

A biomarker is evidence about biology, not a synonym for dementia. The clinician begins by establishing whether there is an acquired cognitive decline, determines its pattern and severity, assesses functional consequences, and looks for competing neurological, psychiatric, medical and drug-related explanations. Fluid results then refine the causal formulation. This sequence prevents a laboratory pattern from being mistaken for the clinical syndrome itself.

The useful mental model is to separate the biological questions. Is there evidence of amyloid pathology? Is there evidence of pathological tau aggregation? Is there evidence of **neurodegeneration or neuronal injury**? These questions are related but not interchangeable. A result may speak strongly to an axis while saying little about another. Therefore, the report should be read analyte by analyte before it is compressed into an overall impression.

- **Phenotype:** What cognitive and behavioural syndrome is present, and how convincing is the evidence of decline?
- **Biology:** Which pathological axis does each measured analyte represent?
- **Concordance:** Do the clinical formulation and the biomarker pattern support the same explanation?

RULE **Diagnose the patient, then interpret the biomarker.** A fluid result modifies the probability of a biological process within a clinical formulation; it does not independently establish the patient's syndrome, severity or care needs.

This distinction also clarifies consent. Before testing, the clinician should know what uncertainty the sample is intended to resolve and how a positive, negative or discordant result would alter counselling or further assessment. Testing without a decision question creates information without a plan. It can also produce misplaced certainty when the report is read outside the context in which it was requested.

22.2 The core cerebrospinal-fluid profile

In **Alzheimer disease (AD)**, the characteristic amyloid signal is **low CSF amyloid-beta-42** relative to healthy individuals. The corresponding **CSF amyloid-beta-42/amyloid-beta-40 ratio** is also low. The ratio expresses the disease-relevant amyloid analyte relative to the broader amyloid pool rather than treating the absolute concentration in isolation. For examination purposes, both belong to the amyloid axis and move downward.

The tau side moves in the opposite direction: **CSF total tau** and **CSF phosphorylated tau** are increased relative to healthy individuals. Their shared upward direction should not erase their conceptual difference. Phosphorylated tau represents the tau-pathology axis in the biological framework, whereas total tau is placed with neurodegeneration or neuronal injury. This is why collapsing both measures into a generic tau label earns less than identifying which measure is being discussed and what biological question it answers.

FLUID MEASURE	DIRECTION IN AD	FRAMEWORK MEANING	INTERPRETIVE ROLE
Absolute amyloid measure	Decreased	Amyloid pathology	Read as an amyloid signal, not as a measure of clinical severity
Amyloid ratio	Decreased	Amyloid pathology	Frames the disease-relevant analyte relative to the accompanying amyloid measure
Phosphorylated tau	Increased	Aggregated tau	Answers the tau-pathology question
Total tau	Increased	Neurodegeneration or neuronal injury	Supports an injury signal but is not, by itself, disease-specific

The directions are more examinable than any remembered concentration. A numerical result only acquires meaning through the laboratory's validated method, units, quality controls and reference interpretation. The allowed evidence does not provide universal fluid cut-offs, so none should be memorised from this fragment. The safe answer is the pattern: amyloid measures are low, while both tau measures are high, with phosphorylated and total tau assigned to different biological axes.

Absolute concentration and biological classification also belong at different levels of reasoning. The analyser produces a concentration or ratio; the laboratory compares that result with its validated interpretive system; the clinician decides whether the resulting axis assignment is coherent with the patient. Skipping any of these levels invites error. A raw value copied into a case summary without units or laboratory interpretation is incomplete, while a categorical label copied without the underlying analytes conceals how the conclusion was reached.

MNEMONIC

Amyloid sinks; tau rises

For the core CSF pattern, the amyloid concentration moves down, the amyloid ratio moves down, and total tau and phosphorylated tau move up. Then separate phosphorylated tau as the tau-pathology signal from total tau as the neuronal-injury signal.

The must-memorise CSF pattern is low amyloid concentration and low amyloid ratio, with high total tau and high phosphorylated tau.

22.3 Reading the biological framework correctly

The framework sorts biomarkers into **three** biological axes. It was proposed by the **NIA-AA Research Framework** in **2018**. The conventional abbreviations are **A** for aggregated amyloid, **T** for aggregated tau and **(N)** for neurodegeneration or neuronal injury. The parentheses around the injury axis are meaningful in the notation: injury evidence is useful for characterising the biological state, but it is not specific to the defining protein pathologies.

A	T	(N)
AMYLOID	TAU PATHOLOGY	NEURONAL INJURY

For the fluid panel, the absolute amyloid measure or its ratio supplies A; phosphorylated tau supplies T; and total tau supplies (N). The framework also accommodates imaging correlates on these axes, but imaging selection and interpretation belong with the structural and functional neuroimaging discussion. The physics of those modalities is covered in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

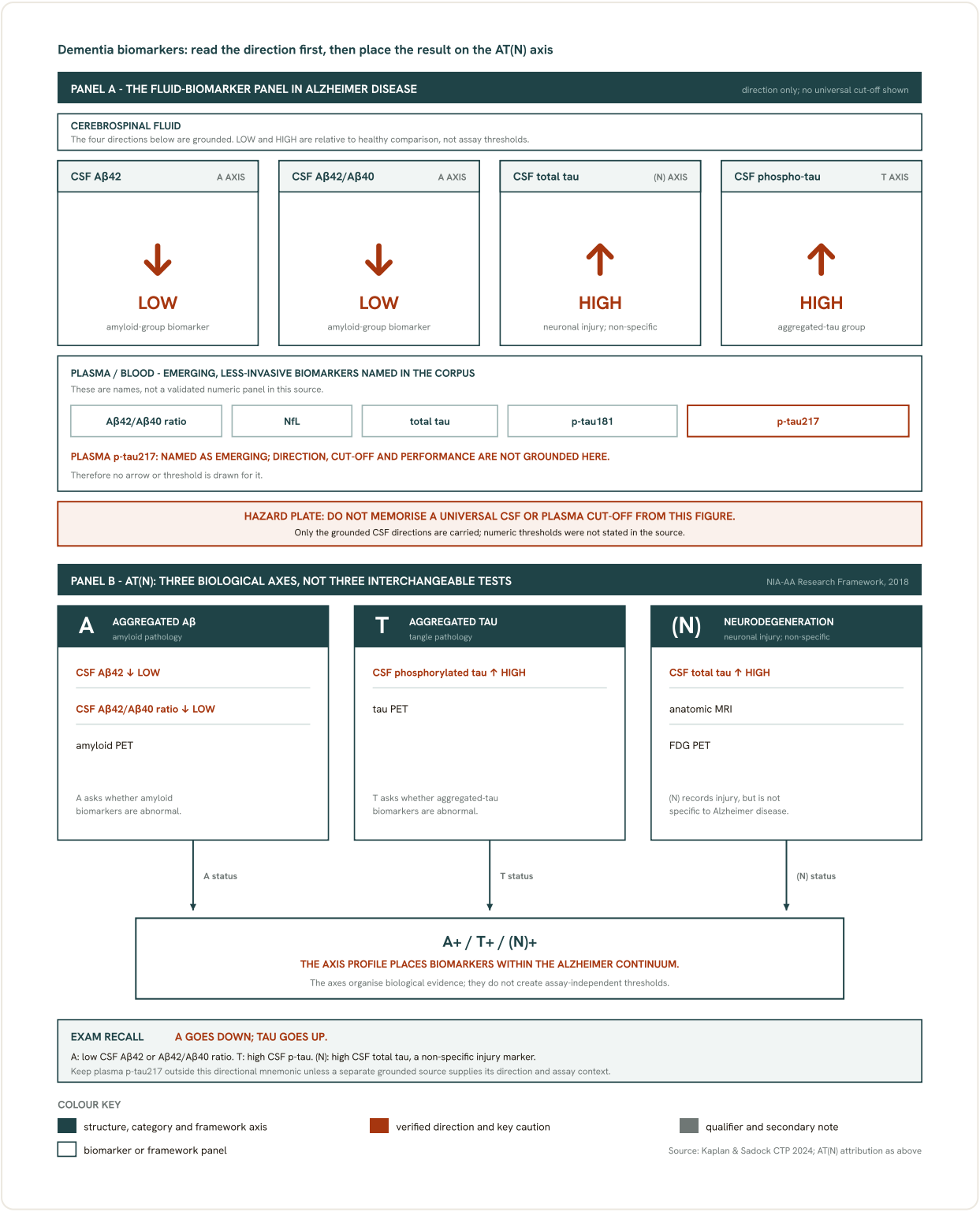

Fig 32.9 Dementia fluid biomarkers and the AT(N) framework. In Alzheimer disease, CSF Aβ42 and the Aβ42/Aβ40 ratio are low, while CSF total tau and phosphorylated tau are high. Plasma p-tau217 is shown only as an emerging named biomarker because the grounded source supplies no direction, cut-off or performance estimate.

The accompanying figure should be used as a translation device. Begin with the analyte, ask which axis owns it, and only then state the direction or implication. This prevents the common mistake of treating all abnormal biomarkers as equivalent evidence. A positive injury signal does not automatically identify the protein pathology producing that injury. Conversely, an amyloid-axis result and a tau-axis result answer more biologically specific but still distinct questions.

The notation can describe combinations of positive and negative axes, but classification should not become a substitute for clinical reasoning. A shorthand combination is a compact biological summary. It does not convey the pattern of memory loss, language impairment, behavioural change, disability, comorbidity or the wishes of the patient and family. Those dimensions still determine whether the finding is clinically coherent and what should happen next.

The framework is best treated as a coordinate system, not a severity ladder. Each axis tells the reader which kind of biology has been detected; it does not, merely by its place in the notation, rank functional impairment. This protects against a subtle but common overreach: turning a research classification into an unsupported statement about prognosis, rate of decline or current decision-making capacity. Those judgments require their own clinical evidence and should remain visible in the formulation.

TRAP **Putting both tau measures under T.** Phosphorylated tau belongs to the aggregated-tau axis, whereas total tau is assigned to (N), the neurodegeneration or neuronal-injury axis. Their concentrations move in the same direction in AD, but their framework meanings differ.

22.4 Pattern interpretation and discordance

A fluid panel should be interpreted as a pattern rather than as a row of isolated flags. Start with the amyloid axis, then the tau-pathology axis, then the injury axis. After that, return to the clinical question. A concordant pattern may strengthen a biological formulation; a discordant pattern should trigger review rather than creative arithmetic.

Discordance has several possible levels. The analytes may disagree with each other, the biological pattern may not match the cognitive phenotype, or the result may not fit the course described by the patient and informant. The correct response is to check what was actually measured, which method and reference interpretation the laboratory used, whether sample quality was acceptable, and whether the original clinical question remains appropriate. It is unsafe to “average” contradictory axes into a vaguely positive panel.

Similarly, a result close to a laboratory decision boundary should not be converted into categorical certainty by rhetoric. Reports may include interpretive language, but the requesting clinician remains responsible for integrating that language with the pre-test formulation. Where the result could materially change counselling or eligibility for a further intervention, discussion with the reporting laboratory or a relevant specialist is preferable to guessing.

PITFALL

Do not import a cut-off from a paper, another laboratory or memory into the current report. Fluid concentrations and ratios require the method-specific reference interpretation supplied by the laboratory. This fragment intentionally teaches direction, not an unverified universal threshold.

There is also a semantic trap in the word “positive.” A positive amyloid-axis classification may correspond to a low measured concentration in CSF. The classification and the raw direction are therefore not synonyms. State both clearly: the measured amyloid signal is reduced, and this

supports positivity of the relevant biological axis according to the laboratory's interpretive framework.

The CSF examination procedure, collection technique and generic constituents are not repeated here; they are covered in the Neurology foundations for psychiatrists notes. For this topic, the psychiatrist's responsibility is to formulate the dementia-specific question, understand the panel's axes, anticipate how the result will be used, and interpret the report without exceeding the evidence it contains.

22.5 Emerging blood biomarkers

Blood biomarkers are attractive because venous sampling is less invasive and potentially easier to repeat or deploy than CSF assessment. The emerging plasma panel includes **amyloid-beta-42/amyloid-beta-40 ratio, neurofilament light, total tau, phosphorylated tau-181 and possibly phosphorylated tau-217**. These candidates span amyloid, tau and neuronal-injury biology rather than representing a generic interchangeable blood test.

The wording “emerging” matters. It signals an evolving clinical role, not permission to assign every candidate the evidentiary status of an established diagnostic standard. In particular, the newest phosphorylated-tau candidate may be named, but the available evidence here does not provide its disease direction, a decision threshold, or diagnostic performance. An answer that supplies such figures from memory is more dangerous than an answer that explicitly states the limitation.

Conceptually, a blood test can occupy different places in a pathway. It may help decide who needs more definitive biological assessment, support a specialist formulation, or contribute to follow-up in a defined service. These are different uses, each requiring its own validation and clinical governance. Evidence for a use cannot automatically be transferred to another. Nor should “measurable in plasma” be paraphrased as “diagnostic in isolation.”

Adoption should therefore proceed from intended use to evidence, rather than from technological availability to indiscriminate ordering. A service needs to decide who is eligible for testing, what result categories mean, how uncertain findings are communicated, and which confirmatory route follows each category. Without that pathway, a convenient sample can generate an inconvenient ambiguity. The appropriate question is not simply whether a marker can be measured, but whether measuring it here will produce a clinically accountable decision.

- Identify the exact plasma analyte and the biological axis it is intended to represent.
- Ask whether the assay and interpretive pathway are validated for the clinical use being proposed.
- Preserve clinical confirmation and an escalation route for unexpected or discordant results.

The blood and CSF names can look deceptively similar. That does not make their numerical values, reference intervals or decision boundaries interchangeable across specimen types. The sample matrix, assay and intended use belong in the interpretation. A clinician should therefore

resist copying a CSF logic statement into a plasma report without checking what the blood assay has actually been validated to mean.

GOOD TO REMEMBER

When a report mentions an emerging plasma marker, document the clinical question, assay name, laboratory interpretation and intended next step. If the result is discordant with the phenotype or would drive a consequential decision, seek specialist or laboratory clarification rather than treating the flag as self-explanatory.

22.6 A practical reporting sequence

A disciplined report can be brief without being simplistic. Begin with the clinical syndrome and the reason biological clarification was sought. Name the specimen and measured analytes. Describe the amyloid, tau-pathology and injury axes separately. Then give an integrated interpretation, including discordance and limitations. Finish with the action the result supports, such as further assessment, review of an alternative explanation, or specialist discussion.

An adequate conclusion should remain traceable. The reader ought to be able to move backwards from the integrated sentence to the axis assignment, from the axis assignment to the measured analyte, and from the analyte to the laboratory's interpretation. Traceability makes disagreement productive: a colleague can identify whether the dispute concerns the clinical phenotype, the biological framework or the analytical result. A conclusion that merely says “biomarker positive” hides all of these distinctions.

Use precise language. “Compatible with” or “supports” is generally safer than wording that implies the laboratory has independently diagnosed the whole clinical disorder. Avoid describing total tau as a disease-specific marker, because its framework role is neuronal injury. Avoid describing phosphorylated tau merely as injury when the relevant framework assigns it to aggregated tau. Avoid calling the plasma panel established merely because its analytes have familiar names.

The pre-test and post-test conversations should mirror each other. Before sampling, explain the question and possible categories of result. After sampling, explain what biological process the result supports, what it does not establish, and whether it changes the working formulation. The patient and family need the clinical meaning, not a recital of abbreviations. Uncertainty should be stated plainly when the phenotype and biomarker pattern do not align.

Quality assurance begins before interpretation. Confirm identity and specimen type, use the reporting laboratory's own reference interpretation, and notice whether any analyte is missing or technically qualified. A partial panel should not be silently treated as a complete biological profile. If serial samples are being compared, the clinician should ensure that the comparison is methodologically meaningful rather than inferring biological change from unexamined laboratory differences.

Finally, keep the framework subordinate to the clinical record. Biomarkers can refine aetiology, but they do not quantify the person's everyday abilities, behavioural burden, safety, decision-

making needs or caregiver strain. Those require direct assessment. The highest-quality answer therefore links biology back to the person: what uncertainty was reduced, what uncertainty remains, and what action is justified now.

22.7 Examination synthesis

A strong short note has a simple spine. Define fluid biomarkers as biological adjuncts to clinical assessment. State the core CSF direction pattern. Explain that the amyloid concentration and ratio represent A, phosphorylated tau represents T, and total tau represents (N). Then name the emerging plasma candidates, including the newest phosphorylated-tau analyte, while explicitly refusing unsupported thresholds or performance claims.

For a long answer, add the distinction between syndrome and biology, explain why the axes must be read separately, describe how discordance is handled, and show how a laboratory report is integrated with phenotype and course. Mention that CSF procedural teaching and imaging physics sit in their respective chapters. This demonstrates ownership of dementia-specific biomarker interpretation without drifting into lumbar-puncture technique or modality science.

The conceptual hierarchy therefore begins with the clinical syndrome, proceeds through the biological axes and individual analytes, and reaches numerical interpretation only within the validated laboratory context. Keeping that order prevents both underuse and overclaiming. The candidate who remembers only “amyloid down, tau up” has the direction; the candidate who also separates T from (N), recognises plasma testing as emerging, and states the limits of the evidence has the complete answer.

23 · Cholinesterase inhibitors and memantine

Why this matters clinically. Cognitive enhancers are among the few dementia drugs that psychiatrists prescribe repeatedly across outpatient follow-up, liaison work and shared care. Examination answers therefore need more than a list of names. A competent answer links the transmitter target to the individual drug, matches the drug to the stage and type of dementia, gives a safe titration plan, anticipates adverse effects and explains how benefit will be judged when dramatic improvement is unlikely.

These medicines are symptomatic treatments. Their value is assessed through the patient's cognition, everyday function, behaviour relevant to care, tolerability and the caregiver's account of change. A small apparent gain on a test does not rescue a regimen that causes vomiting, syncope or loss of adherence; equally, absence of visible improvement does not by itself prove absence of benefit when the clinical aim may be preservation of function. Prescribing is therefore a structured therapeutic trial rather than an automatic response to a diagnostic label.

CHOLINERGIC	GLUTAMATE	TITRATE	REVIEW
AMPLIFY SIGNAL	LIMIT EXCESS	BY TOLERABILITY	FUNCTION AND SAFETY

23.1 Therapeutic logic and mechanisms

The **cholinergic hypothesis** proposes that progressive loss of cholinergic neurons and declining acetylcholine contribute to cognitive deterioration in Alzheimer dementia. Acetylcholinesterase

and butyrylcholinesterase both degrade acetylcholine. Inhibiting this degradation prolongs the availability of acetylcholine at functioning synapses. This is a rational symptomatic strategy, but cholinergic depletion is not considered the sole explanation of Alzheimer disease. The mechanism therefore supports modest therapeutic expectations, not a claim that the underlying neurodegenerative process has been removed.

Donepezil is a selective, reversible acetylcholinesterase inhibitor. **Rivastigmine** inhibits both acetylcholinesterase and butyrylcholinesterase and is described as a reversible, non-competitive inhibitor. **Galantamine** is a competitive, reversible and selective acetylcholinesterase inhibitor with additional nicotinic-receptor agonist properties. These distinctions are examinable because they explain why the drugs belong to the same therapeutic family without being pharmacologically identical.

Memantine acts through a different transmitter system. It is a low-to-moderate-affinity, non-competitive antagonist at N-methyl-D-aspartate receptors. Preferential binding to open receptor-operated calcium channels makes the block activity dependent: pathological glutamatergic activation and excessive ion flux are restrained while ordinary signalling is less indiscriminately suppressed than it would be by a high-affinity, persistent block. The therapeutic concept is attenuation of excitotoxic glutamate activity, not enhancement of acetylcholine.

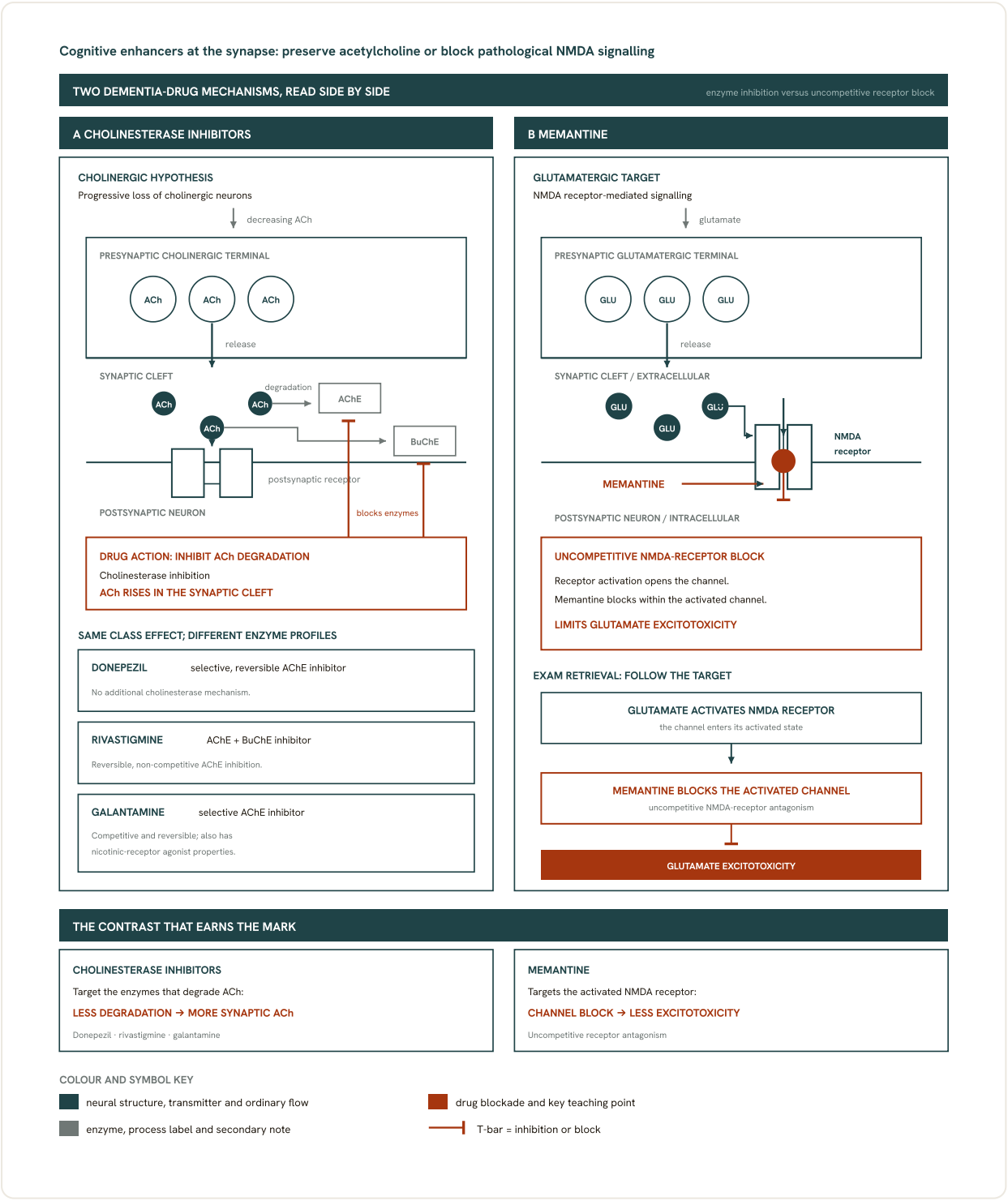

Fig 32.10 Cognitive enhancers at the synapse. Cholinesterase inhibitors raise synaptic acetylcholine by preventing its degradation: donepezil selectively and reversibly inhibits AChE; rivastigmine inhibits AChE and BuChE; galantamine competitively and reversibly inhibits AChE and also has nicotinic-receptor agonist properties. Memantine instead produces uncompetitive NMDA-receptor block, limiting glutamate excitotoxicity. (Maudsley Prescribing Guidelines in Psychiatry, 15th ed.)

The accompanying figure should be read as parallel symptomatic strategies at the synapse. Cholinesterase inhibition increases persistence of available acetylcholine; memantine modifies excessive receptor-mediated glutamatergic flux. The different mechanisms also explain why concurrent use can be rational in the appropriate stage of Alzheimer dementia.

AGENT	PRIMARY PHARMACOLOGICAL ACTION	CLINICAL IMPLICATION
Donepezil	Selective reversible acetylcholinesterase inhibition	Oral cholinergic strategy with simple daily administration
Rivastigmine	Acetylcholinesterase plus butyrylcholinesterase inhibition	Oral and transdermal routes allow route-based individualisation
Galantamine	Selective reversible acetylcholinesterase inhibition plus nicotinic activity	Oral cholinergic strategy in extended-release or solution form
Memantine	Activity-dependent N-methyl-D-aspartate receptor antagonism	Non-cholinergic option for later-stage Alzheimer dementia and combination treatment

RULE **Mechanism determines the therapeutic family; stage, tolerability and route determine the prescription.** Do not choose among these agents merely by remembering that all are called cognitive enhancers.

23.2 Indications and choosing an initial strategy

The **cholinesterase-inhibitor indication envelope** includes donepezil, rivastigmine and galantamine for mild-to-moderate dementia due to Alzheimer disease, with recommendations also supporting their use in severe Alzheimer disease. Rivastigmine additionally has a licence in some countries for mild-to-moderate dementia associated with Parkinson disease. Jurisdiction matters: a country-specific licence cannot be silently converted into a universal indication.

Within the shared Alzheimer indication, there is no sound clinical reason to present a cholinesterase inhibitor as universally best. Selection is practical and patient centred. Consider whether a daily oral regimen is feasible, whether a caregiver can supervise administration, whether swallowing or gastrointestinal tolerability makes a transdermal route attractive, whether the current medicine burden threatens adherence and whether cardiac history changes the safety threshold. The decision should be documented as an individual therapeutic trial with an agreed method of review.

A **sustained-release high-dose donepezil formulation** has United States regulatory approval for moderate-to-severe Alzheimer disease, carries a greater early gastrointestinal adverse-effect burden than the usual formulation and is not approved in the United Kingdom. The important lesson is not to import a formulation or titration practice from another jurisdiction without checking current country-specific product information. Higher dose is not a synonym for better individual treatment.

The **memantine indication** is moderate-to-severe dementia due to Alzheimer disease. NICE positions it as an option in moderate Alzheimer disease when acetylcholinesterase inhibitors are contraindicated or not tolerated, and as treatment in severe Alzheimer disease. Thus memantine may be an alternative when a cholinergic strategy cannot be used, or part of a later-stage regimen rather than a routine substitute at every stage.

TRAP **Do not write that cholinesterase inhibitors and memantine are interchangeable.** They differ in mechanism and stage-related indication. Memantine is not simply the "stronger" cognitive enhancer, and severe disease does not automatically require stopping a tolerated cholinesterase inhibitor.

23.3 Initiation and titration

Titration is part of treatment, not administrative detail. Before starting, establish what the caregiver will observe, record relevant baseline function, review pulse and cardiovascular history, examine the full medicine list, and decide who will supervise dosing. Avoid simultaneous changes to cognitive enhancers where possible. This makes emerging nausea, dizziness, insomnia or syncope interpretable and prevents disease progression from being confused with a treatment effect.

DRUG AND DEMENTIA INDICATION	STARTING, USUAL AND TITRATION REGIMEN
Donepezil for Alzheimer dementia	**Start 5 mg once daily; usual dose 10 mg once daily; increase by 5 mg daily only after at least 4 weeks.**
Rivastigmine for Alzheimer dementia	**Start oral treatment at 1.5 mg twice daily, or use the 4.6 mg per 24 hours patch. The usual oral dose is 3-6 mg twice daily, increased by 1.5 mg twice daily at intervals of at least 2 weeks; the usual patch is 9.5 mg per 24 hours after at least 4 weeks. A 13.3 mg per 24 hours patch may be considered after 6 months. An oral dose above 6 mg daily may be switched directly to the 9.5 mg per 24 hours patch.**
Galantamine for Alzheimer dementia	**Start extended-release treatment at 8 mg once daily, or solution at 4 mg twice daily. The usual extended-release dose is 16-24 mg once daily, increased by 8 mg daily after at least 4 weeks; the usual solution dose is 8-12 mg twice daily, increased by 4 mg twice daily after at least 4 weeks.**
Memantine for moderate-to-severe Alzheimer dementia	**Start 5 mg once daily; the usual dose is 20 mg daily, either once daily or as 10 mg twice daily; increase by 5 mg at intervals of at least 1 week.**

The table gives the regimen, but good prescribing adds method. Explain the formulation clearly, especially when oral solution or a patch is used. Confirm that the caregiver understands which previous formulation is being replaced. At every increase, ask whether the previous dose was actually tolerated and taken. A nominal schedule should never force escalation through clinically important adverse effects.

A formulation switch should be treated as a prescribing event, not as clerical substitution. Reconcile the previous oral or patch regimen, write the replacement route unambiguously and verify that the superseded supply will not continue by mistake. At follow-up, ask how the medicine is actually given rather than asking only whether the patient is "on" it. This detects

duplicate administration, missed doses, misunderstanding of solution volumes and practical failure of caregiver supervision without assuming deliberate non-adherence.

- Define the treatment target in observable terms, including everyday tasks and the level of prompting required.
- Record the formulation, route, supervisor and intended review point.
- At review, separate adherence failure, adverse effects, intercurrent illness and progression of dementia.
- If benefit and harm are uncertain, reconstruct the timeline with the caregiver before changing several medicines.

GOOD TO REMEMBER

The caregiver is part of the pharmacological intervention. A technically correct prescription fails if nobody can describe how it is administered, what changed after titration, or which new symptom should trigger review.

23.4 Cholinergic adverse effects and their interpretation

Cholinergic adverse effects commonly include nausea, vomiting, diarrhoea, dizziness and insomnia; urinary incontinence has also been reported. They are most likely near treatment initiation or after a dose increase, are dose related and are often transient. This temporal pattern is clinically useful. A symptom that appears after escalation should initially be treated as a possible drug effect rather than automatically labelled deterioration of dementia.

Management begins by grading severity and consequence. Mild transient nausea in a patient who remains hydrated and adherent poses a different problem from persistent vomiting, postural instability or diarrhoea causing frailty. Review when the symptom began, which formulation was used, whether a dosing error occurred and whether another medicine or illness offers a better explanation. The response may be to pause escalation, return to a previously tolerated regimen, reconsider route or reconsider the drug. The purpose is not to “push through” toxicity to reach a table dose.

MNEMONIC

Gut, sleep, bladder, beat

For cholinesterase inhibitors, remember gastrointestinal symptoms, insomnia, urinary incontinence and slowing of the cardiac beat. Dizziness may be the presenting clue that links the autonomic and cardiac consequences.

Adverse effects can masquerade as the illness being treated. Insomnia may worsen daytime cognition; dizziness may reduce mobility; urinary incontinence may be misread as loss of functional stage; and vomiting may produce apparent global decline. The correct response is a medication timeline and physical assessment, not reflex escalation of dementia treatment.

PITFALL

Do not attribute new vomiting, syncope or falls to “advanced dementia” without checking the recent cholinesterase-inhibitor start or dose increase. That shortcut can convert a reversible adverse effect into injury and further disability.

23.5 Cardiovascular safety and the patient at higher risk

The clinically important vagotonic effect is slowing of heart rate. **Bradycardia and syncope** are the most prominent cardiovascular adverse effects of cholinesterase inhibitors. Their consequences extend beyond a pulse reading: syncope may lead to falls or fractures, and clinically significant bradyarrhythmia may result in pacemaker placement. Patients with sick sinus syndrome or conduction disturbance require particular caution. People with dementia with Lewy bodies may be especially susceptible to bradyarrhythmic effects.

Cardiovascular screening should be proportionate rather than ritualistic. Take a history of syncope, unexplained falls, palpitations and known conduction disease; examine the pulse; and review drugs that also slow heart rate. An electrocardiogram is advised when cardiovascular disease is present or when concomitant negative-chronotropic medicines are used. If syncope develops, assess it as a potentially consequential cardiac event rather than merely recording “dizziness”.

Risk assessment continues after initiation. A normal baseline assessment does not guarantee future tolerance after dose escalation or addition of another rate-slowing drug. Conversely, a risk factor is not an automatic prohibition. It changes the threshold for investigation, shared decision-making, titration and review. The practical question is whether the expected cognitive or functional value justifies the cardiovascular uncertainty for this patient.

The signal around galantamine in mild cognitive impairment is a separate safety lesson, not an Alzheimer-dementia mortality estimate. In trials involving mild cognitive impairment, mortality was **1.5% with galantamine versus 0.5% with placebo**, with cardiovascular deaths contributing substantially. This led to a United States regulatory warning restricting galantamine use in mild cognitive impairment; the relevance of that signal to Alzheimer dementia remains unclear. The examination error is to transfer the result to a different population without preserving its qualifier.

23.6 Memantine tolerability and combination treatment

Memantine tolerability is generally favourable, but adverse effects still require active inquiry. Reported common effects include somnolence, dizziness, balance disturbance, constipation, headache, hypertension, dyspnoea and elevated liver-function values. Warnings particularly concern severe hepatic impairment and epilepsy or seizures. When a patient becomes more sleepy, unsteady or constipated after initiation, the change should not be absorbed into a vague narrative of dementia progression.

The adverse-effect profile differs from cholinergic toxicity, which helps when memantine is used because a cholinesterase inhibitor was not tolerated. It does not make memantine risk free.

Balance disturbance and dizziness may be functionally important even when the drug is otherwise easy to take. The review should ask what the symptom costs in mobility, supervision and safety, not merely whether it appears on a checklist.

The **cholinesterase-inhibitor plus memantine combination** is recommended by NICE over cholinesterase-inhibitor monotherapy in moderate-to-severe Alzheimer disease: addition may be considered in moderate disease and should be offered in severe disease. There are no pharmacokinetic or pharmacodynamic interactions between these classes. This permits rational concurrent treatment, but it does not eliminate the need to identify which agent is associated with a new adverse effect.

Combination treatment should retain a clear rationale. The patient should have a stage-appropriate indication, a tolerable existing regimen and a practical plan for observing change after the added medicine. If several drugs are changed together, later attribution becomes difficult. The absence of a class interaction means co-prescribing is pharmacologically permissible; it does not mean that every patient will derive enough additional value to justify indefinite treatment.

23.7 Longitudinal prescribing: LOCUS, FOCUS and MODUS

LOCUS. Initiation and routine review usually belong in organised outpatient or memory-service care with a reliable caregiver and access to physical monitoring. Acute assessment becomes appropriate when there is syncope, clinically important bradycardia, repeated vomiting, marked dehydration, sudden loss of balance or another change that cannot safely wait for routine follow-up. The care setting should follow the immediate risk, not the prestige of the clinic that started treatment.

FOCUS. Early treatment focuses on tolerability, correct administration and a trustworthy baseline. Short-term review focuses on adverse effects and whether titration remains justified. Later review focuses on cognition in context, everyday function, caregiver-observed change, falls, adherence and evolving treatment goals. A score can contribute evidence, but it cannot independently decide continuation or withdrawal.

MODUS. Drug treatment sits inside a broader care plan. Prescribing work includes explanation, caregiver training, formulation choice, medication reconciliation, physical monitoring and coordination with the clinician managing cardiovascular or neurological comorbidity. The relevant guidance should be checked before prescribing: current country-specific product information governs available formulations and licensing, while NICE guidance supplies a clear stage-based framework for memantine and for combination treatment. Local institutional policy should determine practical monitoring and responsibility for follow-up.

A useful review reconstructs a sequence: what the patient could do before treatment, what changed after initiation, what changed after each increase, which adverse effects appeared, and what happened to caregiver burden and supervision. This is more informative than a binary question about whether memory “improved”. It also protects against opposing errors: stopping a

tolerated drug solely because dementia continues to progress, and continuing a harmful drug solely because deterioration is expected from the disease.

Continuation and withdrawal deserve the same discipline as initiation. Review the original indication, current stage, adherence, adverse effects and the functional observations that matter to the patient and caregiver. Avoid treating progression alone as proof that the medicine has no value, because the counterfactual course is not directly observable. Equally, avoid indefinite continuation when administration has become burdensome, harms are prominent or the regimen no longer serves the agreed goals. Where change is planned, communicate what will be observed and who will respond if clinically important deterioration or relief of adverse effects follows.

Shared decisions should acknowledge uncertainty without becoming vague. State the intended benefit, the harms that would prompt early contact, the method of administration and who will observe the outcome. When tolerability is poor, reassess dose, route and drug choice rather than assuming the class has failed. When treatment seems ineffective, verify adherence and intercurrent illness before drawing a conclusion. When goals of care change, reconsider whether the current regimen still serves the patient's function and comfort.

> The must-memorise principle: choose by indication and route, titrate only after tolerability is established, and judge treatment by function and safety as well as cognition.

24 · Behavioural and psychological symptoms of dementia: assessment, management and antipsychotic risk

The marks lie in the sequence, not in a drug list. The candidate must recognise the syndrome, search for what the person may be communicating, formulate the interaction between illness, body, environment and care, and use medication only when the target and the risk justify it. **Behavioural and psychological symptoms of dementia** include aggression, agitation, vocalisation, distress during care, disinhibition, hallucinations, delusions, apathy, low mood and anxiety. They are common across the course of dementia and vary greatly in form, severity and meaning.

These symptoms occur to some degree in **over 90% of people with dementia**. That prevalence should not turn them into an automatic indication for sedation. The central clinical task is to translate a broad label into an observable target, a plausible formulation and a proportionate plan. Management is anchored in Maudsley prescribing guidance for person-centred non-drug care and in the Kaplan and Sadock risk synthesis when antipsychotics are considered.

ASSESS	FORMULATE	REVIEW
DEFINE THE TARGET	FIND THE DRIVER	CONTINUE ONLY WITH BENEFIT

24.1 From a label to a target syndrome

BPSD is an umbrella description, not a unitary diagnosis. “Agitation” may refer to pacing, repeated calling, resistance during bathing or striking a caregiver. “Psychosis” may refer to a fixed false belief, a perceptual experience, a misinterpretation of the surroundings or frightened speech

that has been incompletely elicited. Apathy, low mood and anxiety can look superficially similar because each may present as withdrawal. The assessment must therefore move from the caregiver's summary to a description of what actually happens.

Characterise the behaviour in neutral language: its form, context, apparent trigger, consequence, variability and impact. Establish whose distress is being treated. A behaviour may endanger the person or another individual; it may instead be inconvenient to a rigid routine without being harmful. This distinction matters because the burden of drug adverse effects falls on the person with dementia, even when the immediate request for treatment comes from others.

RULE **Name the target before naming the medicine.** "BPSD" is too broad for a treatment trial; the prescription must be tied to a specific, observable and consequential symptom.

The same outward behaviour may have different meanings in different people. Repeated attempts to leave may express a familiar life routine, fear, discomfort or a need for contact. Resistance during care may be an understandable response to unfamiliar touch or rushed communication. This is why phenomenology and biography sit beside the physical examination rather than after it.

24.2 Structured assessment: body, context and sequence

Begin with a safety and medical screen. Look for pain, infection, constipation and adverse effects of medication before concluding that the dementia itself has worsened. Review sensory difficulty, mobility and falls vulnerability. Observe the person directly when possible, because caregiver language can compress several different events into a single term. If the change appears acute, delirium must be considered; its detailed assessment belongs in the Stroke, TBI, delirium and focal brain syndromes notes.

Next, reconstruct the event. Record what happened before the behaviour, the behaviour itself and what followed. An antecedent-behaviour-consequence chart is useful because consequences may inadvertently maintain a pattern: the person may escape an overwhelming task, gain reassurance or encounter escalating confrontation. The chart is not a blame instrument. It turns impressions into testable observations and permits comparison after a change in care.

OBSERVED PRESENTATION	QUESTIONS THAT SHARPEN THE TARGET	USEFUL FORMULATION OUTPUT
Agitation, aggression or vocalisation	What precedes it, who is present, and what ends it?	Trigger, function, risk and a measurable behavioural target
Distress during care	Which task, approach, touch or pace is associated with distress?	A modified care interaction rather than a reflex prescription
Hallucinations or delusions	What exactly is experienced or believed, and how distressing is it?	Phenomenology, associated risk and need for treatment
Apathy, low mood or anxiety	Is there loss of initiative, subjective distress, fear or avoidance?	A discriminated emotional or motivational target
Disinhibition	In which settings does it occur and what consequences follow?	Environmental, supervisory and behavioural safeguards
Variable sleep or pain behaviour	What pattern appears across observation and care records?	A temporal clue to a physical or environmental driver

Life history adds meaning to the sequence. Familiar routines, preferences, occupation, language and prior responses to stress can explain why an apparently irrational event is coherent from the person's perspective. Sleep and pain records, direct observation and a shared formulation meeting convert these data into a care plan that caregivers can apply and review. This unmet-need formulation reframes "problem behaviour" as an expression of distress until evidence suggests otherwise.

24.3 Formulation and risk: deciding what requires action

A useful formulation has predisposing vulnerability, immediate precipitants, perpetuating responses and protective resources, but it remains practical. It should answer what is happening, why it may be happening now, what harm could follow, and what change can be tested. The output is not merely a diagnosis. It is a shared hypothesis linking an intervention to an observable outcome.

Risk assessment separates urgency from annoyance. Consider danger to the person, danger to others, interruption of essential care, inability to meet basic needs and the cumulative effect of sustained distress. Also examine how staff or family responses alter the event. Fear, argument, rapid commands and inconsistent limits can intensify an interaction without anyone intending harm. Conversely, a calm approach, adequate time and predictable sequencing may allow necessary care without medication.

MNEMONIC

PAIN before prescription

Physical illness and pain; **A**dverse medication effects; **I**mpaired sensory input; **N**eeds, narrative and the care context. It is a compact prompt for formulation, not a substitute for examination or observation.

Document the baseline in terms the team can recognise. “Less agitated” is weak; a description of the relevant care episode, its severity and its consequences is clinically usable. Agree in advance what improvement would count as meaningful, which adverse outcomes will prompt reconsideration, and who will review the plan. This prevents an intervention from continuing simply because it has become part of the medication chart.

24.4 Management architecture: LOCUS, FOCUS and MODUS

LOCUS asks where safe care can occur. Outpatient or home-based care is appropriate when risk can be contained and caregivers can implement the plan. Inpatient care may be needed when assessment, containment or treatment cannot be delivered safely in the usual setting. An emergency presentation requires immediate protection and a search for reversible physical or environmental drivers, followed by reassessment once the crisis has settled.

FOCUS changes with phase. In an acute crisis the target is immediate safety and relief of severe distress. Over the short term, the task is to identify precipitants and make the care environment workable. In the middle term, behavioural learning, caregiver consistency and restoration of tolerable routines become central. Long-term care aims to preserve function and dignity while repeatedly removing interventions that no longer have a clear benefit.

MODUS means that management is genuinely multimodal: treatment of physical contributors, communication and environmental modification, behavioural intervention, caregiver psychoeducation, selected psychological or sensory approaches, social support and, only when justified, medication. The evidence favours **first-line personalised multicomponent non-drug care** delivered with caregivers. Drug evidence is less secure and several agents carry serious adverse effects.

- Define the priority target and the harm or distress attached to it.
- Correct contributory physical and sensory factors before escalating treatment.
- Choose an intervention that follows directly from the formulation.
- Teach caregivers how to apply the plan consistently across settings.
- Record response and adverse effects, then revise rather than merely add treatment.

24.5 Non-pharmacological treatment in practice

At this management stage, **LOCUS** determines feasibility: a home plan must fit the household, while a ward plan must survive shift changes. **FOCUS** is the target behaviour and the unmet need inferred from assessment. **MODUS** begins with changing the interaction or environment, not trying to suppress the person. Simplify demands, pace care, use familiar routines, reduce avoidable confrontation and build pleasant engagement around the person’s history and preferences.

Behavioural management and caregiver psychoeducation are generally successful, and their effects can persist for months. Their strength lies in repeated application: caregivers learn to recognise antecedents, alter their approach and notice early escalation. A written care plan should

specify what helps, what worsens the situation and how to respond consistently. Review remains necessary because the person's cognition, health and environment change.

Among sensory-stimulation approaches, **music therapy** has the most convincing evidence for reducing agitation and aggressive behaviour. Multicomponent interventions, animal-assisted therapy, doll therapy, bright light therapy and aerobic exercise may help. Aromatherapy has not shown benefit. These findings should guide selection without turning any modality into a ritual. An intervention is useful when it suits the person, is deliverable in the actual locus of care and changes the agreed target.

Pain assessment and effective treatment deserve special attention because pain may be expressed behaviourally when self-report is limited. Even without overt pain, an analgesic trial, usually with paracetamol, may be worthwhile. The trial still requires a target and review: improved comfort during movement or care is more informative than indefinite continuation without observed benefit.

> **GOOD TO REMEMBER**
>
> Ask the caregiver to show you the difficult interaction or describe it step by step. A direct account often reveals a modifiable trigger that disappears inside the single word "agitation".

24.6 When medication enters the plan

Medication is not the next rung after reassurance fails. In the relevant **LOCUS**, establish beforehand that physical illness, pain, constipation, medication effects and sensory deficits have been addressed. The **FOCUS** must be severe distress, serious risk of physical harm or another clearly consequential target, rather than wandering, calling out or care resistance considered in isolation. The **MODUS** remains combined: a drug trial supplements a person-centred plan and does not replace it.

Antipsychotic use for BPSD is discouraged as routine practice because average benefit is small, tolerability is poor and mortality is increased. Conventional agents other than haloperidol have not shown efficacy in the evidence summarised here. Among newer agents, risperidone has evidence for psychosis, agitation and overall BPSD; olanzapine for agitation; and aripiprazole for overall BPSD. Quetiapine has generally failed to show effectiveness except at doses that may be poorly tolerated. These are evidence signals, not instructions to cycle through agents.

Before prescribing, discuss the expected target, uncertainty of benefit, material risks and the intended stopping plan with the caregiver. Assess falls vulnerability and stroke risk factors. Record why the situation crosses the medication threshold and why less hazardous measures are insufficient. If the presentation does not involve severe distress or serious risk of physical harm, neither risperidone nor olanzapine should be used merely to make care easier.

TRAP **"Agitation in dementia" is not itself an antipsychotic indication.** The high-scoring answer states the target, excludes physical and environmental drivers, documents non-drug measures, and then explains why risk or severe distress makes a time-limited trial proportionate.

24.7 Agent selection and dementia-scoped dosing

For **persistent aggression in moderate to severe Alzheimer dementia** that has not responded to non-pharmacological approaches and carries risk of harm, risperidone is the preferred licensed option in the referenced UK guidance. Its indication is short term, **up to 6 weeks**. Haloperidol is also licensed there, but its dangers make risperidone the preferred agent. Licensing is jurisdiction-specific and should never be silently transferred to Indian practice.

Dosing must remain indication-bound. The optimal risperidone dose described for BPSD in dementia is **500 micrograms twice daily (1 mg/day); it is licensed up to 1 mg twice daily**. This is deliberately a dementia-scoped low-dose approach. Schizophrenia-range doses do not belong in this section. The broader teaching of antipsychotic pharmacology and extrapyramidal and metabolic adverse effects belongs in the Schizophrenia: management, antipsychotics and adverse effects notes.

The same indication discipline applies if another antipsychotic is considered: use dementia-specific low-dose ranges and do not import a dose from a different disorder. Choice should be driven by the target for which an agent has evidence, the person's vulnerabilities, likely tolerability and the capacity to review promptly. A long medication list is not sophistication. It usually means that targets and stopping decisions have become blurred.

Between-agent mortality comparisons do not provide a simple "safe antipsychotic". Haloperidol has generally been associated with greater mortality, while quetiapine users showed lower risk in some comparative evidence. Clinically meaningful differences were not found for several other agents, and another comparative analysis did not find significant differences among commonly used newer antipsychotics. Risk appeared strongest soon after initiation, and higher dose was generally associated with greater mortality except in the quetiapine findings. These observations support caution, not substitution by reputation.

24.8 Boxed warning, cerebrovascular risk and review

The decisive safety fact is the **antipsychotic boxed warning in dementia**. Placebo-controlled evidence underlying the warning found a **1.6 to 1.7-fold increase in all-cause mortality versus placebo** among people with dementia taking atypical antipsychotics. Deaths were attributed to cardiac events, including heart failure and sudden death, or to infections, most often pneumonia. The benefit for aggression or psychosis is modest and short term, while the adverse outcome is potentially fatal.

Product labelling also warns of possible **cerebrovascular events** when antipsychotics are used in dementia, and the warnings now apply across the class. Do not attach a remembered numerical stroke estimate to this statement: the permitted evidence gives a quantitative mortality estimate but no quantitative relative risk specifically for stroke. Mortality and cerebrovascular risk are related safety concerns, not interchangeable numbers.

In any **LOCUS**, the **FOCUS** of review is benefit against the original target, emerging harm and whether the indication still exists. The **MODUS** is active deprescribing, not passive renewal. Use the **lowest effective dose with repeated stopping review**. Review at **4 to 6 weeks, and taper**

or withdraw when there has been no significant response after 4 weeks. Consider stopping at every review even when some benefit is reported.

> **PITFALL**
> A drug started during an inpatient crisis may remain on the discharge prescription after the trigger has resolved. The transition of care must carry the original target, observed response, adverse effects and a stopping plan, not merely the medicine name.

24.9 Other drug options and the final hierarchy

Other medicines do not remove the need for formulation. In the chosen **LOCUS**, set a symptom-specific **FOCUS** and retain psychosocial measures as the surrounding **MODUS**. **Non-antipsychotic drug options** have uneven evidence. Valproate trials for dementia-related behaviour have been disappointing. Selective serotonin reuptake inhibitors are most helpful for agitation, with citalopram having the strongest evidence, but its cardiac repolarisation risk constrains use in older people. Benzodiazepines are poorly supported and are associated with cognitive decline, pneumonia, all-cause mortality, falls and hip fractures.

Brexpiprazole, a dopamine partial agonist, improved agitation in Alzheimer dementia compared with placebo and is the only medicine approved by the United States regulator specifically for agitation associated with dementia due to Alzheimer disease. It is not available in the UK. Regulatory approval does not cancel class risk, replace non-pharmacological care or convert every episode of agitation into a prescribing indication. Availability and approval in India require current local verification.

The management hierarchy is therefore coherent. Begin by defining the behaviour and the person's distress. Then treat bodily contributors, understand the sequence, change care and environment, and work with caregivers. If a medicine becomes proportionate, choose it for a named target, use a dementia-scoped low dose, explain mortality and cerebrovascular warnings, and make withdrawal part of the original prescription. A careful decision not to prescribe is active treatment when the formulation points elsewhere.

> In BPSD, personalised non-drug care is the default; an antipsychotic is a low-dose, target-bound, time-limited trial whose mortality and cerebrovascular risks must be explained and repeatedly reviewed.

25 · Caregiver support, psychosocial interventions and end-of-life care in dementia

Dementia care is delivered through a relationship, not to an isolated brain. The person with dementia remains the centre of care, but the caregiver commonly becomes the observer, interpreter, organiser and practical carrier of the treatment plan. **Caregiver stress, isolation and burden** may include psychological, physical and financial problems. Caring for cognitive impairment also creates greater psychological strain than caring for medical illness, even though the caregiver remains the key resource through whom most interventions are implemented. This combination of indispensability and vulnerability defines the clinical task.

The examination answer therefore needs more than an instruction to "counsel the family". It should show how the clinician assesses caregiver burden, builds an active support package, uses the caregiver to make psychosocial treatment workable, and changes the goal of care when advanced disease makes comfort and dignity paramount. The strongest answer treats support as part of treatment architecture. It also keeps the boundary clear: detailed assessment and prescribing for behavioural and psychological symptoms belong in the corresponding management section, while this section concentrates on the caregiver and psychosocial system around the patient.

NOTICE	EQUIP	SUSTAIN	COMFORT
BURDEN AND RESOURCES	KNOWLEDGE AND SKILLS	SUPPORT AND RESPITE	DIGNITY AT THE END

25.1 The caregiver as co-recipient and implementation partner

A caregiver is simultaneously a person with legitimate support needs and the person expected to translate recommendations into daily practice. When the support need is overlooked, the consultation becomes extractive: information and labour are requested from someone whose capacity to continue is never assessed. When implementation is overlooked, support may remain sympathetic but disconnected from the practical demands of care. A sound formulation holds these positions together.

The caregiver's account supplies history that a brief encounter cannot. It is also shaped by fatigue, fear, relationship history and competing duties. This does not make it unreliable. The clinician must listen for patient information as well as caregiver distress. "Nothing works" may describe a care problem, an exhausted implementation system, or their interaction. Clarify what is happening, what has been tried, what is realistic, and what support would make the plan possible.

RULE **Link the patient outcome to the caregiver outcome.** Ask what should improve for the person with dementia and what must become more manageable for the caregiver who will carry the plan.

The phrase **caregiver as the key intervention resource** should never be mistaken for unlimited availability. Capacity fluctuates with sleep, health, employment, finances, family conflict and the amount of help available. A technically elegant intervention fails if it assumes time, privacy, physical strength or cooperation that the household does not possess. Feasibility is therefore a clinical property of the intervention, not a moral test of the family.

25.2 Assessing burden without reducing it to a score

Assessment begins by identifying who actually provides care. The named relative in the record may not be the person supervising meals, accompanying consultations or managing difficult evenings. Map the tasks, the people carrying them, the points at which responsibility changes hands, and the gaps where nobody is reliably available. Ask separately about emotional strain, physical demands, social isolation and financial pressure because a global question about "coping" often invites a socially acceptable answer.

Then examine the relationship between burden and the care situation. Which task is hardest? Which period feels least manageable? What behaviour evokes fear, anger, shame or helplessness? What has the caregiver stopped doing? What support is offered but unusable, and what support is absent? The aim is not to grade devotion. It is to identify the mechanisms by which strain is produced and the resources that may interrupt them.

ASSESSMENT DOMAIN	CLINICAL ENQUIRY	PLAN GENERATED
Care tasks	What must be done, by whom, and at which difficult points?	A realistic map of labour and supervision
Psychological strain	What emotions, thoughts or interactions are becoming hard to bear?	Support directed at the actual source of distress
Physical impact	How is caregiving affecting rest, health and bodily capacity?	Protection of the caregiver's ability to continue safely
Isolation	Which relationships, roles or activities have narrowed or disappeared?	Reconnection with usable social support
Financial pressure	Which care demands create direct or indirect economic difficulty?	A plan that does not assume unavailable resources
Knowledge and confidence	What is poorly understood, feared or difficult to perform?	Targeted education, rehearsal and feedback

Assessment should also identify strengths. These may include a calm communication style, an effective routine, a cooperative relative, a meaningful relationship or prior success with a behavioural strategy. Strengths are not decorative positives added after listing problems. They show where an intervention can attach. The clinician can reinforce what already works, reduce unnecessary complexity and reserve scarce caregiver effort for the change most likely to matter.

Revisit burden when care demands, health or living arrangements change. A feasible plan may become exhausting, while competence may grow with practice. Reassessment prevents the chart from freezing the caregiver into a permanent label such as "coping well" or "poor support".

25.3 What makes a caregiver intervention effective

Structured caregiver intervention is active treatment, not a loose collection of reassuring remarks. Group approaches work best when techniques are structured and intensive, caregivers participate actively, and the programme combines education, support and respite with knowledge transfer, skill building and competency. Individual support strengthens this package. Each component answers a different failure point in the care system, so merely naming them is not enough.

- **Education** gives the caregiver a coherent explanation of the care problem and the purpose of the plan.

- **Active participation** turns the caregiver from a passive recipient of advice into a collaborator who can test and refine it.
- **Skill building** converts general principles into observable actions that can be rehearsed and corrected.
- **Competency** means the caregiver can apply the skill in the real situation, not merely repeat the teaching point.
- **Support** creates space for distress, ambivalence and relationship strain without treating these reactions as failure.
- **Respite** interrupts continuous demand and helps preserve the person who is sustaining care.

The clinical sequence is explain, demonstrate, rehearse, adapt and review. Explanation without practice often produces apparent agreement but little change at home. Practice without explanation can feel controlling and may be abandoned when the situation varies. Review closes the loop by asking what the caregiver tried, what happened, what became easier, and where the technique broke down. The answer may require simplifying the skill, changing the environment or redistributing a task rather than repeating the same advice more forcefully.

MNEMONIC

CARE

Clarify the burden and target; **A**ctively involve the caregiver; **R**ehearse skills and arrange respite; **E**valuate competence, feasibility and support. The mnemonic keeps the intervention active and reviewable.

Group caregiver work offers shared learning and support, but it is not the whole intervention. A general strategy may remain difficult in a particular relationship or emotionally charged task. **Individual support** permits formulation at that level and discussion of shame, resentment, grief or conflict that may not be voiced in a group. The formats are complementary when linked by common goals.

25.4 Psychoeducation that changes behaviour

Psychoeducation should reduce confusion and increase usable agency. It begins with the caregiver's current model: what does the caregiver think the patient is doing, why is it happening, and what response seems sensible? If the caregiver sees every failure as deliberate refusal, repeated confrontation may follow. A more useful formulation can change the response without dismissing the caregiver's frustration. The teaching must remain specific to the person and the difficult situation.

Effective teaching uses plain explanation, an actionable target, demonstration and feedback. Ask the caregiver to describe the plan back and anticipate obstacles. Written instructions should identify what to do, what to avoid and how to judge benefit. "Maintain routine" is too abstract unless the caregiver knows which routine and how to adapt it.

Knowledge transfer, skill building and competency form a progression. Knowledge answers why. Skill answers how. Competency answers whether the caregiver can carry out the action under real conditions. This progression protects against a common clinical illusion: information was delivered, therefore care was improved. The meaningful endpoint is not the amount said in the consultation but the change the household can sustain.

> **GOOD TO REMEMBER**
> Before adding advice, ask the caregiver to take you through the hardest care episode from beginning to end. The point where the interaction becomes unmanageable usually gives a more useful teaching target than a broad request for "stress management".

Respite should be discussed as a treatment component rather than as permission to abandon responsibility. Caregivers may refuse help because the available arrangement feels unsafe, the patient rejects unfamiliar care, family expectations are rigid, or organising relief creates more work than it removes. The clinician should explore these barriers without moralising. A respite plan becomes real only when the caregiver can identify what demand will pause and who can safely hold it.

25.5 Caregiver-supported psychosocial care for the person with dementia

Psychosocial care becomes effective when it is personalised, multicomponent and embedded in the patient's ordinary environment. For behavioural and psychological symptoms, this caregiver-centred non-drug approach occupies the **first-line position**. The caregiver helps identify the target behaviour, the context in which it occurs, and the responses that may calm, worsen or maintain it. The clinician then converts this information into a plan that can be applied consistently.

Behavioural management with caregiver psychoeducation is centred on the individual patient's behaviour. Its logic is formulation rather than suppression: define what happens, observe the setting and sequence, modify the interaction or environment, and review the result. A personalised plan is more defensible than a generic activity prescription because it connects the intervention to an observed problem and to the person who must implement it.

Structured psychosocial intervention is better implemented when caregivers are supported. This is not merely because encouragement improves morale. Support protects attention, consistency and willingness to persist through imperfect early attempts. It also gives the caregiver a place to report that the plan is unrealistic or that the behaviour has changed. Behavioural management and caregiver psychoeducation are generally successful, and effects may persist for **months**, but durability still depends on continued fit between the plan, the patient and the caregiver's capacity.

TRAP **Do not write "family counselling" as the psychosocial plan.** A complete answer names the target behaviour, active caregiver role, structured education, skills practice, support, respite and review of feasibility.

The boundary with the BPSD management section matters. This section does not repeat symptom-specific drug choices or their risks. Its contribution is to explain why non-drug treatment is carried through the caregiver system and why unsupported caregivers cannot be expected to deliver complex behavioural plans reliably. When medication is considered elsewhere, caregiver observation remains important for describing the target, detecting change and reporting harm, but pharmacological teaching belongs with BPSD management.

25.6 Management architecture: LOCUS, FOCUS and MODUS

LOCUS asks where care is actually happening and who is available there. A plan for a household, outpatient service or inpatient setting must match its staffing, routines, privacy and capacity for follow-up. The clinician should not export a ward strategy into a home without checking whether the available caregiver can carry it. Movement between settings is a vulnerable point because advice may travel without the practical knowledge of what has worked.

FOCUS changes with the care phase. In an acute difficulty, protect the patient and caregiver while clarifying the immediate source of distress. In the short term, make the most difficult care task manageable and restore a workable routine. In the middle term, consolidate skills, share labour and prevent isolation from deepening. In the long term, sustain the caregiver system, revisit goals and prepare for increasing dependence without pretending that the earlier plan will remain sufficient.

MODUS must remain multicomponent. It includes education, behavioural and psychological work, individual and group support, respite, social and practical assistance, medical review of the patient, and palliative care when the goal changes. These modes are coordinated around a shared formulation. Adding services without deciding what each component is meant to change creates activity but not treatment.

PLANNING AXIS	IMMEDIATE QUESTION	CLINICAL OUTPUT
LOCUS	Where will the plan be used and who can carry it?	A setting-specific, feasible care arrangement
FOCUS: acute	What threatens safety or makes care impossible now?	Containment, clarification and immediate support
FOCUS: short term	Which task or interaction should become manageable?	A defined behavioural and caregiver target
FOCUS: middle term	Which skills and supports need consolidation?	Competency, shared work and respite
FOCUS: long term	How will the plan adapt as dependence grows?	Reassessment, continuity and goal revision
MODUS	Which psychological, social, medical and palliative modes fit?	A coordinated multicomponent plan

Review the original targets. Has the patient's distress changed? Is the caregiver more confident or better supported? Can the household still deliver the intervention, and has respite occurred?

Attendance or information delivery alone does not establish benefit. The outcome lies in the functioning of the care relationship.

25.7 Recognising the transition to end-of-life care

In the final stages of **Alzheimer disease**, patients become bedridden and develop **swallowing impairment**. Pneumonia and other infections commonly become the illnesses through which death occurs. These changes should prompt an explicit shift in clinical attention. The question is no longer only what deficit can be corrected, but what burdens can be relieved and what form of care best preserves comfort and dignity.

The **LOCUS** of end-of-life care must be able to provide comfort and support the family. **FOCUS** moves toward distress, bodily comfort, communication and the emotional needs surrounding dying. **MODUS** becomes palliative and family-centred while retaining ordinary clinical attentiveness. The shift should not be interpreted as withdrawal of care. It is a change in the purpose by which each intervention is judged.

Communication is central because caregivers may experience the transition as failure, abandonment or a demand that they make impossible decisions. The clinician should explain the observed change, acknowledge uncertainty, elicit the patient's known values and help the family understand the goal of comfort. Language should be direct enough to permit preparation and gentle enough to leave room for grief. Avoid presenting a complex decision as though there were a morally correct answer obvious to every family.

> **PITFALL**
>
> Do not continue a restorative style of care by inertia after the clinical goal has become comfort. Equally, do not use the word "palliative" to justify inattentive care. The plan still requires observation, explanation, symptom relief and active family support.

The caregiver's role also changes. Earlier, the emphasis may have been on learning techniques and sustaining routines. Near the end of life, the caregiver may need permission to relinquish performance goals, help in recognising comfort, and support while witnessing decline. Clinical review should ask not only what the family can do, but what should no longer be demanded of them.

25.8 Palliative care, dignity and support for the family

Palliative care in end-stage dementia is helpful because it organises treatment around comfort and supports the family in seeking a peaceful and dignified death. Dignity is expressed through the manner of care: explaining before touch, preserving privacy, responding to distress, avoiding unnecessary disruption and continuing to address the person as a person. Severe cognitive impairment does not remove relational needs or the ethical importance of ordinary respect.

The palliative plan should be coherent across clinicians and caregivers. Each proposed intervention is considered against the current goal, its likely burden and the comfort it may offer. Decisions should not be fragmented into isolated technical choices while the family remains unclear about the overall direction. A shared account of the goal allows different members of the

team to communicate consistently and prevents the caregiver from repeatedly carrying the same explanation between services.

Family support includes anticipatory explanation, space for grief and ambivalence, and recognition of the long period of labour that may precede death. Relief, sadness, guilt, exhaustion and affection can coexist. The clinician need not force these reactions into a uniform narrative. The therapeutic task is to validate the complexity, correct avoidable misunderstanding and make sure that the caregiver is not left alone with practical and emotional responsibility.

After the goal has shifted, caregiver support remains structured. Ask what the family understands, what they fear, who needs to be involved, what care is feasible in the chosen locus, and where additional help is required. Revisit the plan as the patient's condition changes. Consistency does not mean rigidity; it means that adaptations remain visibly tied to comfort, dignity and family support.

The principle is continuous. Caregivers must be noticed, educated, equipped and relieved. Psychosocial treatment works through support, not instructions alone. In advanced disease, the focus moves toward comfort, family support and a dignified death. The caregiver is never merely an informant, and palliative care is not merely absence of curative intent.

> Support the caregiver as a person under strain and as the key treatment partner; when dementia reaches its end stage, reorganise care around comfort, family support and dignity.

26 · Disease-modifying anti-amyloid antibodies: lecanemab, donanemab and the aducanumab debate

Why this topic matters. Anti-amyloid antibodies have changed the Alzheimer treatment question from whether plaques can be removed to whether removing them produces enough clinical benefit to justify infusion, biomarker confirmation, imaging surveillance and haemorrhagic risk. The examination marks therefore lie in interpretation, not in merely listing drug names. A strong answer separates biological action from patient-important benefit, identifies the early symptomatic population in which benefit was studied, explains amyloid-related imaging abnormalities, and uses the regulatory history of aducanumab to show why plaque clearance alone cannot settle efficacy.

These drugs are not conventional symptomatic cognitive enhancers. They intervene in the pathological amyloid pathway and may slow deterioration in selected patients, but they do not imply restoration of lost cognition or a cure. Their use consequently begins before a prescription is written: the clinical syndrome, stage and amyloid evidence must fit the evidence base, while the patient and family must understand the scale and uncertainty of benefit as well as the monitoring burden.

Target	Entry	Outcome	Constraint
AMYLOID	BIOMARKER PROOF	SLOWER DECLINE	ARIA

26.1 Therapeutic logic: from amyloid biology to immunotherapy

Anti-amyloid therapy rests on a pathological sequence in which secretase cleavage of amyloid precursor protein yields beta-amyloid, pathological beta-amyloid accumulates and plaques contain this material; therapeutic development has consequently pursued secretase inhibition, inhibition of beta-amyloid aggregation and beta-amyloid immunotherapy. The antibodies discussed here belong to the immunotherapy strategy. This classification is useful because it prevents the common error of treating all "anti-amyloid" agents as pharmacologically interchangeable.

An antibody can engage a particular physical form of beta-amyloid and reduce plaque burden. That is a biological effect. Disease modification, however, is a clinical claim: the treated group should deteriorate less than an appropriate comparator on outcomes that reflect cognition or function. These are related claims, but they are not synonyms. Plaque removal supports target engagement; it does not by itself tell the clinician how much longer a person will preserve independence, whether an individual patient will perceive improvement, or whether risk outweighs benefit.

RULE **Separate target engagement from clinical benefit.** Amyloid reduction answers "did the drug affect its target?"; comparative cognitive and functional outcomes answer "did that biological effect matter clinically?"

The same distinction shapes consent. "Slowing decline" means a difference in trajectories between groups while disease continues to progress. It should not be translated into "memory improves" or "dementia is reversed." A modest average separation can still matter to some patients, but its value depends on baseline stage, goals, treatment burden, imaging risk and the uncertainty of applying a trial mean to an individual patient.

26.2 Lecanemab: target, evidence and interpretation

Lecanemab lowers brain beta-amyloid plaque burden by binding soluble beta-amyloid protofibrils, with variable binding to other beta-amyloid forms. The molecular target matters because the drug is not simply a nonspecific plaque solvent. Its rationale is directed engagement of an amyloid species within a pathway that culminates in plaque accumulation.

The pivotal evidence enrolled people with mild cognitive impairment or early Alzheimer disease whose amyloid pathology had been confirmed by positron-emission tomography or cerebrospinal fluid. In that setting, **the trial included 1795 participants and compared lecanemab 10 mg/kg by intravenous infusion every 2 weeks with matched placebo**. This sentence carries the clinically important scope: the dose belongs to early symptomatic Alzheimer disease with amyloid confirmation, not to unselected cognitive complaints or advanced dementia.

On the **Clinical Dementia Rating Sum of Boxes**, **lecanemab reduced decline by 27% relative to placebo over 18 months, an absolute difference of 0.45 points, with changes of 1.21 and 1.66 respectively**. Key secondary outcomes also favoured treatment. The relative figure sounds larger than the absolute separation because they express different things. The relative result describes proportional slowing against the comparator trajectory; the absolute

result shows how far apart the groups actually were on the scale. An exam answer should state both concepts and should never convert slowing into improvement.

The appropriate reading is therefore neither dismissal nor triumphalism. The trial demonstrated amyloid reduction accompanied by statistically supported slowing of measured decline in the studied population. It did not establish that every treated patient notices benefit, and it does not justify extending the claim beyond the stage and biomarker conditions studied. Selection is part of the treatment, not an administrative prelude to it.

GOOD TO REMEMBER

When explaining lecanemab, separate the message into clear statements: amyloid is confirmed; the drug slows average decline rather than improving established deficits; imaging risk and infusion burden remain part of the treatment decision.

26.3 Donanemab: plaque clearance and clinical slowing

Donanemab is a high-potency anti-amyloid treatment given by intravenous infusion whose pivotal study concerned early symptomatic Alzheimer disease, including mild cognitive impairment and mild dementia, with amyloid pathology and tau-pathology strata demonstrated on positron-emission tomography. This reinforces the class lesson: biological confirmation and early clinical stage define the evidentiary population.

Compared with placebo, **donanemab slowed cognitive and functional decline by approximately 35% over 18 months in the primary target population, while 52% of treated participants became amyloid-PET negative by 12 months**. The pairing of these results is instructive. Conversion to an amyloid-negative scan is a striking marker of target effect; slowing on cognitive and functional outcomes is the clinically relevant companion result. The scan outcome cannot be substituted for the clinical outcome, even when both move in the expected direction.

Donanemab also illustrates why a treatment programme is more than the act of infusion. The clinician must establish that the syndrome and stage correspond to those studied, demonstrate amyloid pathology, interpret tau information where it forms part of the treatment pathway, obtain suitable baseline imaging, discuss realistic benefit and arrange continuing safety surveillance. The allowed evidence supports an intravenous schedule but does not supply a numeric maintenance amount; that absence should remain explicit rather than being filled from memory.

Comparing donanemab with lecanemab by placing headline percentages side by side is tempting but methodologically weak. Different trial populations, outcome frameworks and biomarker selection can change apparent effect sizes. The safe conclusion is that each antibody showed slowing against its own placebo group in an early, biomarker-confirmed population. A direct claim that either is clinically superior requires comparative evidence not contained in these trial summaries.

26.4 ARIA: the class-defining imaging hazard

Amyloid-related imaging abnormalities, abbreviated ARIA, refer to brain swelling or bleeding seen in association with these treatments. The useful clinical distinction is between oedematous change and haemorrhagic change. ARIA may be discovered on surveillance imaging even without symptoms, but it can also become clinically important. The possibility of an asymptomatic lesion is exactly why symptom-triggered scanning alone is an inadequate conceptual model.

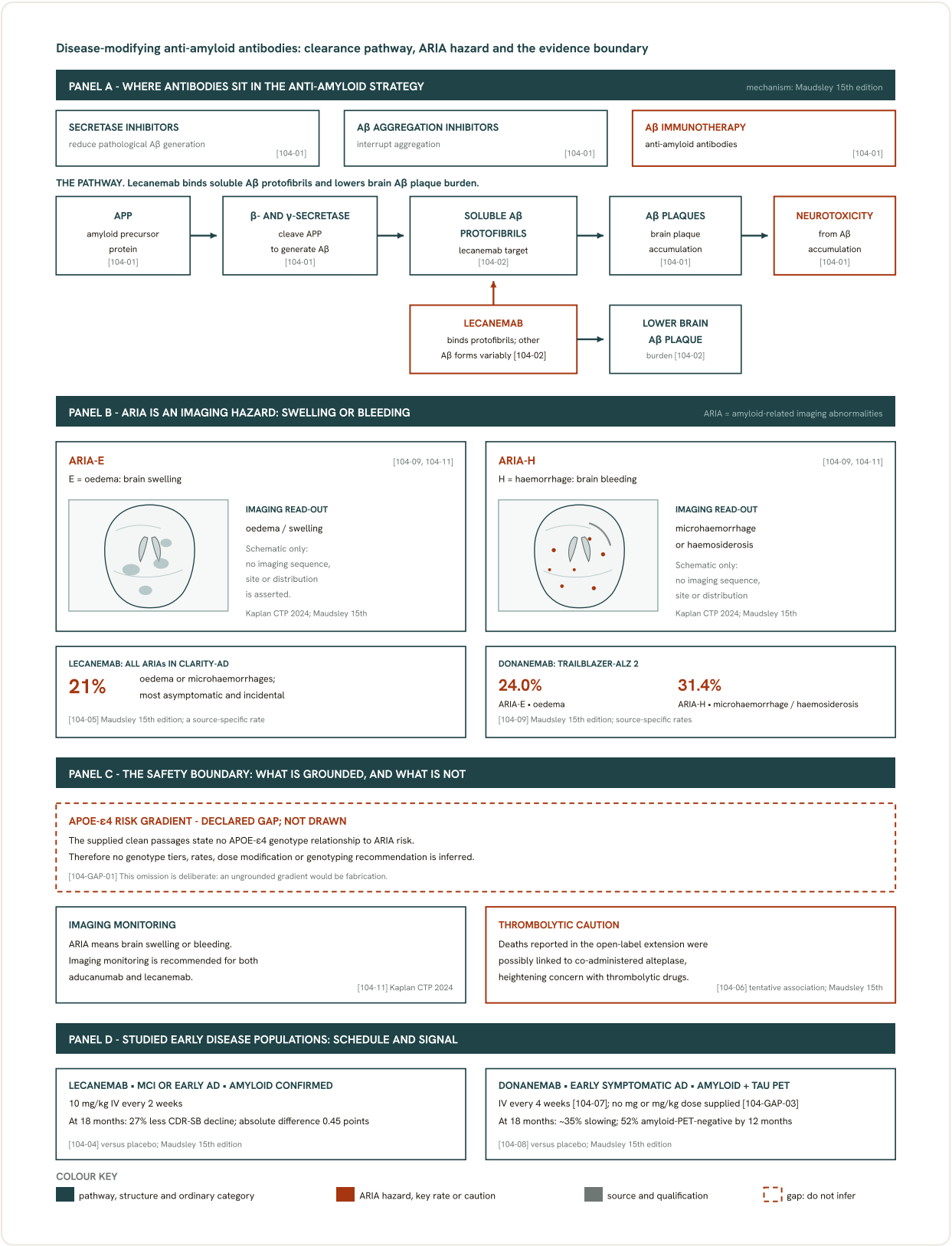

Fig 32.11 Anti-amyloid antibodies and amyloid-related imaging abnormalities (ARIA). Lecanemab binds soluble Aβ protofibrils and lowers plaque burden; ARIA-E denotes oedema and ARIA-H denotes haemorrhagic findings. The rates shown remain attached to their own trial and source rows. The requested APOE-ε4 risk gradient is not drawn because the supplied evidence contains no genotype-risk relationship. (Maudsley Prescribing Guidelines in Psychiatry, 15th ed.; Kaplan and Sadock's Comprehensive Textbook of Psychiatry, 2024.)

The accompanying figure links amyloid clearance with the distinct imaging patterns. ARIA-E denotes the oedematous pattern, while ARIA-H denotes microhaemorrhage or haemosiderosis. In

the donanemab study, **ARIA-E occurred in 24.0% and ARIA-H in 31.4% of treated participants**. These categories are not interchangeable, and their percentages should not be added as if they represented mutually exclusive patients.

With lecanemab, ARIA affected a substantial minority of the treated group; **asymptomatic radiological detection** accounted for most reported cases. This is a practical warning against equating "no complaint" with "no adverse effect." Imaging surveillance is recommended for lecanemab and aducanumab because ARIA is fundamentally an imaging-defined safety problem. Exact scan timing, thresholds for interruption and criteria for resumption must come from the applicable current protocol rather than from an unsourced generic schedule.

A separate safety signal concerns **thrombolytic co-administration**: deaths reported during open-label extension treatment were considered possibly linked to co-administration of alteplase. The wording must remain cautious: this is a possible association, not proof that alteplase caused every event. Nevertheless, acute-care teams need to know that a patient is receiving anti-amyloid therapy when evaluating neurological deterioration or a reperfusion decision.

PITFALL

Do not reassure solely because the patient is asymptomatic. ARIA can be an incidental imaging finding, so safe treatment depends on planned surveillance and a clear pathway for responding to new neurological symptoms or radiological change.

MNEMONIC

Plaque proof, Benefit modest, Radiology matters

Plaque proof defines entry into the evidence base; **Benefit modest** prevents "slowing" from becoming "reversal"; **Radiology matters** keeps ARIA surveillance inside the treatment plan.

26.5 Comparative frame: what can and cannot be concluded

QUESTION	LECANEMAB	DONANEMAB	ADUCANUMAB
Amyloid action	Binds soluble protofibrils and lowers plaque burden	Potent anti-amyloid action with substantial plaque clearance	Preferentially binds aggregated beta-amyloid and reduces plaques
Evidence population	Early symptomatic disease with amyloid confirmation	Early symptomatic disease with amyloid and tau imaging characterisation	Mild cognitive impairment or mild dementia due to Alzheimer disease
Clinical evidence	Slower decline than placebo on cognitive and secondary outcomes	Slower cognitive and functional decline than placebo	Conflicting clinical-decline results underlay the regulatory dispute
Biomarker evidence	Reduced brain amyloid	Many treated participants reached amyloid-negative imaging status	Plaque reduction formed the surrogate basis of approval
Central safety issue	ARIA, often detected without symptoms	Both oedematous and haemorrhagic ARIA patterns	ARIA drove concern about the risk-benefit balance
Core interpretation	Target engagement plus demonstrated slowing in the studied population	Marked plaque effect plus demonstrated slowing in the studied population	Target engagement did not resolve uncertainty about clinical benefit

The table should be read across rows, not as a league table. These agents engage amyloid, yet their evidentiary stories differ. Lecanemab and donanemab are taught through concordance between biomarker change and slower decline against placebo. Aducanumab is taught through discordance: convincing plaque reduction existed alongside disputed clinical evidence. That contrast is the conceptual centre of the debate.

Several conclusions are unsafe. Plaque clearance does not establish cure. A larger relative percentage from a trial does not prove superiority over another drug. Absence of symptoms does not exclude ARIA. Approval does not mean that uncertainty has disappeared. Conversely, controversy surrounding an antibody does not invalidate the entire therapeutic target; each agent requires appraisal of its own target, population, clinical endpoint and safety evidence.

26.6 Aducanumab: mechanism and the approval controversy

Aducanumab targets beta-amyloid and preferentially binds aggregated beta-amyloid, reducing its accumulation and plaque number. After titration it is administered as **maintenance intravenous therapy**. Mechanistically, therefore, it has an intelligible disease-modifying rationale and clear evidence of biological target engagement. The controversy was not about whether amyloid plaques could fall. It was about whether the available clinical evidence justified inferring meaningful benefit and accepting the associated harms.

Development was initially stopped after futility analysis in parallel late-stage trials. The manufacturer's later **reanalysis** included participants who had continued beyond the futility cut-

off, reported a significant finding in part of the programme with supporting evidence elsewhere, and preceded an application for United States approval; conditional accelerated approval followed, while approval was not granted in Europe. This sequence explains why the dispute cannot be reduced to "the trial was positive" or "the trial was negative." The interpretation changed after additional data and post hoc analysis, while consistency across trials remained a central concern.

The United States decision used reduction of beta-amyloid plaque as a **surrogate endpoint** because clinical-decline findings conflicted. Accelerated approval therefore carried an obligation to verify clinical benefit after approval. It was historically important as a disease-modifying approval, but historical importance and evidentiary certainty are different judgments.

Experts questioned both the extent of clinical benefit and the **risk-benefit profile**, particularly because ARIA may include vasogenic oedema, sulcal effusion or microhaemorrhage; the drug was directed to mild cognitive impairment and mild dementia due to Alzheimer disease, not to dementia of any cause or severity. The scientifically fair position is neither that plaque reduction is worthless nor that it is sufficient. It is useful evidence about mechanism, but clinical benefit must be demonstrated on clinical outcomes.

TRAP **Do not turn an internally variable approval date into false precision.** Parallel textbook passages describe lecanemab accelerated approval as **January 2023** and as early in the same year. Preserve that wording difference, distinguish accelerated from later traditional approval, and focus the answer on the confirmatory demonstration of clinical benefit.

26.7 Clinical deployment: LOCUS, FOCUS and MODUS

LOCUS. Initiation belongs in a specialist outpatient service able to confirm the syndrome and amyloid pathology, deliver intravenous therapy, review brain imaging and coordinate urgent assessment. Hospital or emergency care becomes the relevant locus when new neurological symptoms raise concern for oedema or bleeding. The service must communicate treatment status across memory, radiology, neurology and acute-care teams because an infusion decision made in a particular setting can alter risk assessment elsewhere.

FOCUS. Before treatment, the focus is eligibility: early symptomatic Alzheimer disease, evidence of amyloid pathology, a baseline clinical and imaging picture suitable for later comparison, and goals realistic enough for informed consent. During treatment, the focus shifts to preserving function by slowing decline, maintaining adherence to infusions and surveillance, and detecting imaging or neurological adverse effects. Over longer follow-up, the focus is whether ongoing burden and risk remain proportionate to observed course and patient priorities.

MODUS. The mode is not drug-only care. It combines intravenous antibody treatment, biomarker-supported selection, serial clinical review, imaging surveillance, adverse-event pathways, education and shared decision-making. Supportive dementia care continues; disease modification does not replace attention to function, comorbidity, caregiver needs, safety or advance planning. Current jurisdiction-specific product information and clinical guidance must

supply exact imaging schedules, interruption rules and eligibility exclusions because these operational details are not interchangeable between antibodies.

- **Before starting:** confirm that the clinical stage and amyloid evidence match the studied population; document baseline cognition, function and imaging; discuss slowing rather than recovery.
- **During treatment:** preserve infusion and imaging continuity; ask about new neurological symptoms; ensure radiological findings reach the prescribing team promptly.
- **Across settings:** make anti-amyloid treatment visible to acute-care clinicians, especially when haemorrhage or oedema enters the differential; the lecanemab safety signal with a thrombolytic is a specific caution worth extending prudently to the class, given the shared haemorrhagic risk of ARIA.

Guidelines-first practice here means using the current local label and specialist protocol rather than memorising an attractive universal schedule. The supplied evidence establishes that imaging monitoring is recommended, but it does not provide the complete timing or stop-and-restart algorithm. A safe textbook answer states that boundary explicitly.

26.8 Consent, viva framing and final synthesis

Consent should be organised around decisions rather than data dumping. The patient and family need to understand the treatment aim, the biomarker requirement, the expected direction of benefit, infusion and imaging burden, ARIA, uncertainty about individual response and the possibility that treatment may be paused or stopped. Cognitive impairment makes supported decision-making especially important, but support should clarify the person's values rather than replace them.

A concise viva answer can follow a linked sequence:

1. Define the class as beta-amyloid immunotherapy, then state that lecanemab and donanemab reduced amyloid and slowed decline against placebo in selected early symptomatic, biomarker-confirmed populations.
2. Explain ARIA as oedematous or haemorrhagic imaging abnormalities; because they occur with each of these antibodies, at their highest rates with donanemab, imaging surveillance is integral to treatment, with the monitoring recommendation stated explicitly for aducanumab and lecanemab.
3. Use aducanumab to distinguish surrogate plaque reduction from verified clinical benefit and to explain accelerated-approval controversy.

This structure also prevents a fragmented answer. Mechanism leads to selection, selection leads to efficacy, efficacy must be balanced against ARIA, and the approval debate tests whether the candidate understands the hierarchy of evidence. If time is short, preserve that chain rather than reciting isolated brand facts. It demonstrates both pharmacology and clinical judgment.

The mature conclusion is balanced. Anti-amyloid antibodies are a genuine advance because biological target engagement has been accompanied, for some agents, by slower cognitive or functional decline in the populations studied. Their benefits remain modest at group level, their administration is resource-intensive, and imaging harm is central rather than incidental. The correct candidate is therefore not “anyone with dementia” but a person whose phenotype, stage, biomarker status, safety profile, care setting and preferences fit the evidence and the applicable protocol.

> Anti-amyloid antibodies may slow decline in selected early, amyloid-confirmed Alzheimer disease, but plaque clearance is not cure and ARIA surveillance is part of the treatment itself.

27 · Down syndrome and early-onset Alzheimer's disease: chromosome 21, amyloid and assessment of decline in intellectual disability

The marks lie in connecting chromosome, gene dosage, tissue change and acquired dementia without collapsing them into one claim. **Down syndrome** provides a clinically important bridge between a developmental chromosomal disorder and an Alzheimer-like neurodegenerative syndrome. The bridge is not merely an association. The cited account links the chromosomal substrate to extra copies of a gene involved in amyloid biology, and links the later clinical syndrome to plaques, tangles and amyloid accumulation. A strong answer preserves every step in that chain and also preserves the uncertainty around the proposed mechanism.

The diagnostic problem is equally important. Intellectual disability is a pre-existing developmental condition, whereas dementia denotes an acquired clinical disorder. The chromosomal diagnosis, the proposed molecular mechanism, the presence of characteristic tissue changes and the clinical diagnosis answer different questions. None should be used as a shortcut for another. Intellectual disability and Down syndrome as a developmental syndrome are taught in the Intellectual disability and autism spectrum disorder notes; this section remains focused on the later dementia relationship.

Chromosome 21	3 APP COPIES	BY 50 YEARS	6D85.9
CHROMOSOMAL SUBSTRATE	PROPOSED GENE-DOSAGE LINK	ALMOST UNIFORM COMPLICATION	ICD-11 CATEGORY

27.1 Chromosomal basis: state the cause precisely

The central genetic fact is involvement of chromosome 21. In the cited clinical-neurology account, **90%** of cases arise from **nondisjunction during gametogenesis**, while a **chromosomal translocation** is responsible in **5% or less**. These figures should be quoted with their mechanisms attached. A percentage without the corresponding chromosomal process is inert recall; a process named without its stated scope may falsely imply that it explains every case.

Nondisjunction and translocation are therefore alternative causal routes within the supplied account, not interchangeable words for the same event. The safe formulation is that the developmental syndrome is caused by a chromosomal abnormality involving chromosome 21,

with nondisjunction during gamete formation accounting for the great majority and translocation for a much smaller proportion. The supplied figures do not form an exhaustive genetic catalogue. Their total should not be manipulated to invent an unnamed residual category or an unsupported percentage.

This precision matters later. The amyloid theory depends on increased dosage of a particular gene situated on the same chromosome. The chromosomal cause and the later molecular hypothesis are connected, but they remain distinct propositions. The causal statement concerns why the developmental syndrome occurs. The gene-dosage statement proposes why people with that syndrome tend to develop an Alzheimer-like dementia. Keeping those propositions separate prevents circular reasoning.

RULE **Move from chromosome to gene dosage to amyloid to the clinical syndrome.** Each link answers a different question, and no link by itself proves the whole chain in an individual patient.

27.2 Parental age: association is not individual causation

The incidence of the developmental syndrome correlates with increasing **maternal age**, with the association especially noted **after 40 years**. Increasing paternal age is also associated with greater incidence, but the relation is less marked than the maternal-age association. The direction of comparison must be retained: paternal age is not stated to have an equal effect, and maternal age is not presented as the only population correlate.

These are incidence associations. They describe how occurrence varies across groups and should not be rewritten as a deterministic rule for a particular pregnancy or family. Maternal age is neither the chromosomal mechanism itself nor a retrospective assignment of responsibility. The mechanism in the supplied account is nondisjunction of chromosome 21 during gametogenesis in most cases, or translocation in a smaller group. Parental age and chromosomal mechanism belong at different explanatory levels.

The same distinction protects later dementia reasoning. A factor associated with occurrence of Down syndrome should not automatically be presented as a factor governing the timing or certainty of the later dementia. The allowed evidence supports an age association for incidence of the developmental condition and a separate age-linked statement about the Alzheimer-like complication. It does not establish that parental age predicts the later cognitive course, neuropathological burden or clinical severity. That inference must not be smuggled into an otherwise correct genetic answer.

PITFALL

Do not use a population association to assign blame to parents or to predict the later dementia trajectory. State the maternal-age association, acknowledge the weaker paternal-age association, and then return to the chromosomal mechanism actually supplied.

27.3 The amyloid gene-dosage hypothesis

The mechanistic centre of the topic is the **amyloid precursor protein gene**. The cited source frames the explanation as one theory: people with Down syndrome have **three copies** of the gene, which is situated on chromosome 21, and this extra gene dosage is proposed to cause **amyloid overproduction**. The wording “one theory” is not decorative caution. It is part of the factual claim and must survive into the answer.

The logic is attractive because it creates a continuous biological narrative. The chromosomal disorder changes gene copy number; the relevant gene lies on the affected chromosome; greater dosage is proposed to increase amyloid production; and the later dementia is accompanied by amyloid accumulation. This is a mechanism-level explanation, not merely a juxtaposition of facts. It explains why the association has particular importance for understanding the wider disease biology.

Nevertheless, coherence is not the same as complete proof. The allowed evidence does not say that gene dosage is the sole pathway, that amyloid alone is sufficient for clinical dementia, or that the clinical timing can be calculated from copy number. It also supplies no mutation catalogue, laboratory threshold or individual predictive test. A disciplined answer therefore says “one theory holds” or “the proposed mechanism is” rather than presenting the chain as an exclusive settled cause.

The direction of reasoning also matters. The theory begins with the known chromosomal state and proposes a downstream consequence for amyloid production. It should not be reversed into the claim that finding amyloid proves Down syndrome, or that any Alzheimer-like presentation must arise through the same chromosomal route. The model explains a particular association in a defined population. It is not a universal diagnostic rule for dementia and it does not erase the need to establish the clinical syndrome.

Gene dosage, pathology and phenotype are therefore related but non-equivalent levels of explanation. Gene dosage is the proposed upstream driver. Amyloid overproduction is the proposed molecular consequence. Plaques, tangles and amyloid accumulation are the associated tissue findings. Alzheimer-like dementia is the clinical phenotype. An examination answer becomes more accurate, not less confident, when it names these levels and keeps the source's uncertainty attached to the mechanistic step.

EXPLANATORY LEVEL	WHAT THE SUPPLIED EVIDENCE SUPPORTS	WHAT MUST NOT BE INFERRED
Chromosomal cause	Down syndrome usually follows nondisjunction involving chromosome 21; translocation accounts for a smaller proportion	That the listed mechanisms exhaust every possible case
Gene dosage	The amyloid precursor protein gene is on chromosome 21, and affected individuals have an extra copy	That copy number alone diagnoses dementia
Proposed molecular effect	Extra gene dosage is theorised to increase amyloid production	That the theory is the only mechanism or predicts an individual's course
Tissue phenotype	The later syndrome is associated with plaques, tangles and amyloid accumulation	That a qualitative pathological association supplies a clinical prevalence estimate
Clinical phenotype	An Alzheimer-like dementia becomes an almost uniform complication by the age stated in the source	That every person at a younger age already has clinical dementia
Classification	ICD-11 lists dementia due to Down syndrome as a discrete category	That a category label substitutes for clinical assessment

MNEMONIC

CAPS

Chromosome 21; **A**myloid precursor protein gene dosage; **P**laques and tangles with amyloid accumulation; **S**yndrome of Alzheimer-like dementia. CAPS preserves the causal sequence while leaving room for the source's “one theory” qualification.

27.4 From amyloid accumulation to Alzheimer-like dementia

The clinical-neuropathological link is unusually direct in the supplied account. Down syndrome leads to an **Alzheimer-like dementia** associated with **cerebral plaques**, **neurofibrillary tangles** and accumulation of amyloid. The combination matters. Amyloid is not presented as an isolated laboratory observation; it sits beside characteristic structural lesions and a clinical dementia phenotype.

The temporal statement is also strong: the dementia is described as an almost uniform complication **by age 50 years**. “Almost uniform” should not be silently converted into a percentage, and the age statement should not be converted into an earlier neuropathological threshold. The source gives a qualitative description of near-universality at the specified age and a qualitative account of the associated pathology. It does not provide prevalence by decade or a numerical separation between tissue change and clinical dementia.

This distinction is central to examination answers. A candidate may remember a widely repeated age for pathological change or a prevalence estimate for clinical dementia, but those figures are not supplied here. The defensible answer is narrower and stronger: the later dementia is almost uniform by the stated age and shows plaques, tangles and amyloid accumulation. Nothing is gained by adding an unverified earlier age or an uncited percentage.

The pathological terms should also remain together. Plaques and tangles describe structural lesions, while amyloid accumulation supplies the molecular emphasis that connects back to the gene-dosage theory. Selecting amyloid alone makes the account sound more complete mechanistically than the source permits; listing pathology without the dementia phenotype loses the clinical point. The supported formulation is a linked clinical-pathological syndrome, not an isolated protein abnormality.

The phrase “Alzheimer-like” also deserves care. It communicates close clinical and pathological resemblance while remaining the wording of the cited source. It should not be used to re-teach the entire neuropathology, staging, biomarker profile or treatment of the wider disease. Those constructs are developed in their dedicated sections. Here, the educational point is the specific bridge from the chromosomal disorder to amyloid-related dementia.

TRAP **Do not turn a strong association into an invented prevalence table.** “Almost uniform by the stated age” does not license a clinical percentage for each decade, and qualitative neuropathology does not license an earlier numerical threshold for plaques or amyloid.

27.5 The assessment problem in pre-existing intellectual disability

Assessment is the clinically hardest part, but the supplied evidence does not provide an operational method. The conceptual distinction is clear: the developmental diagnosis and the acquired dementia diagnosis are not synonyms. The available claims establish the genetic substrate, a proposed amyloid mechanism, the later clinical-pathological syndrome and its diagnostic-manual category. They do not establish how decline should be measured against pre-existing intellectual disability.

Accordingly, this fragment does not name a Down-syndrome-specific dementia instrument, reproduce an informant questionnaire, print a threshold, prescribe an assessment interval or provide a rule for interpreting serial scores. It also does not claim that a generic cognitive screen has been validated for this purpose. General cognitive-screen administration and scoring belong in the Psychometry, Assessment and Descriptive Psychopathology notes, but that cross-reference does not fill the missing Down-syndrome-specific evidence.

What can safely be said is a limit on inference. A chromosomal diagnosis demonstrates the developmental condition; it does not by itself demonstrate acquired dementia. The gene-dosage theory supplies biological plausibility; it does not establish current functional decline in an individual. The strong age-related association changes clinical concern; it does not replace assessment. Plaques, tangles and amyloid accumulation explain the pathological resemblance; they do not provide an allowed bedside algorithm in this evidence set.

GOOD TO REMEMBER

When the evidence bundle does not supply an assessment instrument or threshold, do not manufacture one from memory. State the developmental condition and the suspected acquired dementia separately, then identify the need for an appropriate decline assessment without pretending that an unsupported tool or cut-off has been established here.

27.6 Diagnostic formulation and ICD-11 classification

ICD-11 recognises **dementia due to Down syndrome** as a discrete category within the dementia block, coded 6D85.9. The classification has useful implications. It acknowledges a specific etiological relationship rather than forcing the presentation into an unspecified dementia label, and it keeps dementia conceptually distinct from the developmental syndrome itself.

The code should be attached to the complete construct, not memorised as a floating number. “Due to Down syndrome” identifies the etiological attribution, while placement within the dementia block identifies the acquired clinical disorder being classified. The developmental syndrome is not being recoded as dementia. Conversely, the availability of a dedicated category does not mean that every adult with Down syndrome automatically meets the clinical requirements for dementia at every age.

The allowed claim establishes category and code, not the full diagnostic criteria. It does not provide required symptom domains, duration, severity thresholds, exclusion rules or a crosswalk to another diagnostic manual. These should not be reconstructed from memory and placed under the code. In a written answer, use the category to complete the formulation after explaining the genetic and pathological relationship, not as a substitute for that explanation.

A clean etiological formulation therefore has layers. Name the established developmental chromosomal disorder. State that the later syndrome is Alzheimer-like and associated with plaques, tangles and amyloid accumulation. Present extra copies of the amyloid precursor protein gene on chromosome 21 as one proposed mechanism for amyloid overproduction. Then, when the clinical diagnosis has actually been established, use the discrete ICD-11 category. The sequence is more informative than code recall alone.

27.7 Building the final examination answer

A high-quality answer begins with chromosome rather than with a vague statement that dementia is “common”. It gives the supplied chromosomal mechanisms with their properly scoped proportions, then introduces the parental-age association without turning it into personal blame or a dementia predictor. It next explains the amyloid precursor protein gene-dosage theory, explicitly retaining the source's theoretical framing.

The answer then moves to phenotype. It states that Alzheimer-like dementia is an almost uniform complication by the specified age and names the associated plaques, tangles and amyloid accumulation. It distinguishes this supported statement from the unsupported claim that all affected adults have clinical dementia at an earlier age. Finally, it names the dedicated diagnostic-

manual category and acknowledges that the supplied evidence does not furnish an operational protocol for measuring decline in pre-existing intellectual disability.

- **Genetic cause:** name the chromosome 21 abnormality and keep nondisjunction separate from translocation.
- **Epidemiological association:** state the stronger maternal-age relation and the weaker paternal-age relation without extending either to dementia prognosis.
- **Mechanism:** present extra amyloid precursor protein gene dosage as one theory of amyloid overproduction.
- **Phenotype:** link the Alzheimer-like dementia to plaques, tangles and amyloid accumulation, preserving the source's age wording.
- **Diagnostic boundary:** separate developmental syndrome, biological plausibility, tissue phenotype and acquired dementia classification.

The common errors all come from collapsing levels. A candidate may treat parental age as the mechanism, treat the chromosomal diagnosis as proof of dementia, treat gene dosage as a bedside diagnostic test, treat pathology as identical to clinical prevalence, or treat a classification code as complete criteria. The cure is the same each time: state what kind of claim is being made and stop at the limit of the evidence.

That restraint is not thin knowledge. It is the core clinical method in a high-fabrication-risk topic. The causal chain is memorable precisely because it is coherent, but coherence can tempt the writer to fill missing links with familiar figures or named instruments. The mature answer explains the supported links in depth and declares the missing assessment evidence rather than disguising memory as authority.

> Down syndrome links chromosome 21 to an extra amyloid precursor protein gene dose and proposed amyloid overproduction, but dementia remains a distinct acquired clinical diagnosis.

Consolidate and apply

28 · Worked vignettes

A vignette rewards the candidate who can rank evidence, not the candidate who can repeat the stem. Cognitive-disorder cases are deliberately crowded with memory complaints, behavioural observations, medical comorbidity, scan language and family anxiety. The task is to identify which facts establish an acquired cognitive syndrome, which facts define its phenotype and tempo, which facts merely modify performance, and which fact changes what must be done now. A polished answer therefore moves from syndrome to cause to action while preserving uncertainty.

These cases consolidate the chapter without replacing its disease-specific sections. Each vignette is followed by the reasoning that should be audible in a written answer or viva: the diagnostic pivot, the nearest alternative, the missing evidence and the immediate care consequence. Exact criteria, biomarker cut-offs, drug doses and monitoring schedules must be retrieved from their dedicated sections rather than reconstructed from memory.

28.1 Decode the stem before choosing a label

Read a cognitive vignette in passes. Begin by asking whether the stem demonstrates decline from a previous level or only reports a complaint. Identify the dominant cognitive, behavioural or neurological pattern. Establish tempo from concrete changes rather than adjectives such as "recent" or "gradual." Decide whether everyday independence has changed because of cognition. Close the read by identifying a safety issue, active contributor or discordant fact that could alter urgency.

Tempo	Pattern	Function	Safety
SETS THE ROUTE	RANKS CAUSES	SETS THE LEVEL	SETS THE ACTION

The **diagnostic pivot** is the feature, or coherent cluster of features, that most changes the ranking of plausible explanations. It is not always the most dramatic symptom. Repeated forgetting may be less discriminating than the way information is lost, the sequence of behavioural change, genuine fluctuation, focal neurological evidence or a mismatch between reported disability and observed function. State the pivot explicitly. This shows that the answer is reasoned rather than guessed.

A useful opening sentence contains the syndrome, phenotype, tempo and functional effect. The etiological formulation follows and should be qualified by the strength of evidence. Then name the strongest alternative and the observation that would separate it. If the question asks for the next step, do not bury that step beneath a complete differential. Answer the decision being tested.

RULE **Every vignette answer should contain a pivot, a competitor and a consequence.** Say what finding leads, what plausible explanation still competes, and what the formulation changes in assessment, urgency or care.

28.2 Vignette: progressive memory-led decline

A retired teacher is brought because conversations are repeated, recent events are lost and familiar household responsibilities have gradually passed to the spouse. Remote autobiographical material remains readily available. The patient gives plausible explanations for mistakes and regards the family's concern as excessive. Examination shows poor acquisition and retention of new information, while social manner and basic language remain relatively preserved. The history contains neither abrupt change nor prominent fluctuation or a focal neurological event.

The safest answer begins with a **progressive amnestic neurocognitive syndrome**, not an etiological name. The stem supports acquired decline through collateral examples, a memory-led phenotype through the error pattern, and clinically meaningful functional effect through transfer of previously managed responsibilities. Reduced awareness strengthens the need for collateral

evidence but is not itself diagnostic. The absence of an abrupt or fluctuating course makes some alternatives less persuasive, yet it does not establish the pathology.

The next reasoning step is to ask whether memory failure reflects inefficient attention or retrieval, impaired storage, language difficulty, mood-related interference, sensory limitation, medication burden or a broader degenerative process. Observe learning across attempts, delayed retention, recognition, cueing and intrusion errors as a pattern rather than reducing cognition to a total score. General administration and scoring of cognitive instruments belong in the Psychometry, Assessment and Descriptive Psychopathology notes.

A strong answer also asks what has been taken over and why. A spouse may compensate so effectively that outward independence looks preserved. Conversely, retirement or traditional division of household roles may mean the patient never performed the task under discussion. Function must be compared with the person's own baseline and linked to cognition. Investigations should then test the leading formulation, identify contributors and determine whether disease-specific confirmation would change counselling or treatment.

GOOD TO REMEMBER

When a stem says “memory loss,” translate it into an error mechanism. Failure to register, rapid loss after learning, poor retrieval with useful cueing, language-based misunderstanding and inconsistent engagement are not interchangeable. Describe the observed pattern before assigning meaning to it.

28.3 Vignette: fluctuation, perception and motor change

An older adult has periods of strikingly clear conversation alternating with episodes of marked cognitive inefficiency that are not explained by sleep or an acute medical state. The family reports recurrent, well-formed visual experiences and increasingly slow, rigid movement. Memory complaints are present, but visuospatial and attentional failures dominate daily mishaps. A previous sedating prescription produced a disproportionate deterioration in mobility and alertness.

The **cortical synucleinopathy phenotype** is raised by the convergence of cognitive fluctuation, recurrent formed visual phenomena, visuospatial-attentional difficulty and spontaneous extrapyramidal change. An isolated feature should not carry the diagnosis. Fluctuation must be distinguished from ordinary good and bad periods, fatigue, medication timing, sleep disturbance, seizures and delirium. Visual experiences require phenomenological description and assessment of vision, context, distress and insight. Motor findings require direct examination rather than reliance on a family adjective such as “slowness.”

The medication history is a safety pivot. It should prompt review of the drug, the target symptom, temporal relation, concurrent illness and recovery after withdrawal. It does not justify transferring a general antipsychotic algorithm into dementia care. General antipsychotic pharmacology belongs in the Schizophrenia: management, antipsychotics and adverse effects

notes; dementia-specific behavioural prescribing and sensitivity are developed in the relevant chapter sections.

The nearest competitors include an amnestic degenerative disorder with later perceptual symptoms, a primary visual or psychiatric explanation, medication effects, sleep-related phenomena and a superimposed acute confusional state. The distinction rests on chronology, clustering, examination and longitudinal corroboration. Movement-disorder neuropsychiatry without dementia belongs in the Neuropsychiatry of systemic and neurological disease notes. In this vignette, the examination question is the dementia phenotype and its prescribing consequence.

TRAP **Do not let a vivid hallucination become the diagnosis.** The discriminating evidence is the coherent longitudinal cluster, and the clinically important consequence is caution with sedating or dopamine-blocking treatment while causes of deterioration are reassessed.

28.4 Vignettes with executive, behavioural or language-led presentations

A patient develops slowing, impaired planning and loss of organisational ability after recurrent cerebrovascular events, with focal neurological signs and an uneven course. A different patient retains orientation and routine memory but becomes tactless, impulsive, emotionally indifferent and rigid in habits, with progressive failure of social judgement. Another speaks fluently yet increasingly loses word meaning and conceptual knowledge, while practical behaviour initially remains comparatively organised.

These stems test whether the candidate can resist the reflex that all dementias are primarily amnestic. The vascular stem suggests a **vascular executive syndrome** when cognitive change, neurological evidence and vascular chronology cohere. A vascular lesion on imaging is not enough by itself; common abnormalities may be contributory, incidental or insufficient to explain the phenotype. The broader pre-dementia and post-stroke cognitive spectrum is taught in the Stroke, TBI, delirium and focal brain syndromes notes.

The behavioural stem suggests a **frontotemporal syndrome** because progressive change in social cognition, inhibition, empathy and behavioural regulation leads the presentation. A primary psychiatric disorder remains a serious competitor. The answer should therefore seek longitudinal loss from baseline, consistency across settings, stereotyped or compulsive patterns, dietary change, language or motor evolution, neurological signs and imaging concordance. A psychiatric history does not immunise a patient against neurodegeneration, and a late behavioural change does not automatically prove it.

The language-led stem requires the candidate to identify which part of language is failing. Fluency, grammar, motor speech, naming, repetition, individual-word comprehension and semantic knowledge should be separated conceptually. The syndrome label follows the dominant deficit and its progression; disease pathology should not be inferred with more certainty than the evidence permits. Hearing, education, multilingual usage and premorbid vocabulary can distort a superficial language examination.

STEM PATTERN	BEST OPENING FORMULATION	DIAGNOSTIC PIVOT	CLASSIC WRONG TURN
Gradual memory-led loss with functional transfer	Progressive amnestic neurocognitive syndrome	Learning and retention pattern linked to decline	Naming a pathology from "forgetfulness" alone
Fluctuation with visual, attentional and motor features	Cortical synucleinopathy dementia phenotype	Convergent feature cluster and medication sensitivity	Using an isolated perceptual symptom as proof
Executive decline with vascular chronology	Vascular dementia syndrome	Temporal and anatomical coherence	Equating any vascular scan change with cause
Early social and behavioural disintegration	Frontotemporal neurodegenerative syndrome	Progressive change from personality baseline	Choosing psychiatric or neurological causation by stereotype
Progressive language-led impairment	Language-predominant degenerative syndrome	Nature of the language breakdown	Calling every word-finding complaint aphasia
Cognitive complaints embedded in depressive illness	State-related cognitive impairment or coexisting decline	Longitudinal consistency and function	Treating "pseudodementia" as a final diagnosis
Rapid, discordant or medically unstable decline	Urgent cognitive syndrome of uncertain cause	Tempo and evidence of active brain dysfunction	Assuming rapid decline is merely severe chronic dementia

28.5 Vignette: depression, effort and apparent reversibility

A patient with pervasive low mood, loss of interest, sleep disturbance and marked self-criticism reports catastrophic memory failure. Answers are frequently abandoned, yet performance improves with encouragement and structure. Family members describe reduced initiative but disagree about whether established skills have actually been lost. The referral asks whether this is "pseudodementia."

The term **depression-associated cognitive impairment** can describe the clinical problem, but it must not end the reasoning. Depression can impair attention, processing efficiency, retrieval and motivation; neurocognitive disease can present with depression; both can coexist. Distress about failure, variable engagement or ready use of "I do not know" is suggestive only in context. These are not stand-alone discriminators.

The answer should reconstruct premorbid function, establish chronology, seek objective and ecologically valid decline, examine the internal consistency of errors, treat the depressive state and follow cognition longitudinally. Improvement in mood with persistent cognitive or functional decline should reopen the etiological formulation. Improvement in both supports a substantial state-related contribution but does not erase vulnerability or eliminate the need for follow-up when concern remains.

PITFALL

Do not reassure the family that cognition is "only depression" after an initial interview. That phrase can delay recognition of coexisting neurocognitive disease. Record the uncertainty, treat what is treatable, define the functional observations to be followed and obtain collateral information again.

A related stem may describe gait deterioration, urinary symptoms, cognitive slowing and ventricular enlargement, or cognitive decline associated with systemic illness, medication burden, sensory loss or nutritional risk. These patterns should trigger a structured search for treatable contributors rather than a promise of complete reversibility. The endocrine, metabolic and nutritional diseases themselves belong in the Endocrine and metabolic psychiatry notes. The dementia answer owns the workup logic: identify a plausible mechanism, test it appropriately, treat it and reassess what remains.

28.6 Vignette: rapid decline and diagnostic urgency

A previously independent adult develops rapidly worsening cognition, behavioural change, gait instability and abnormal involuntary movements. The course is too fast for the common chronic degenerative pattern suggested in the referral. Mental state and neurological findings vary, and the patient is becoming medically difficult to manage at home. The examination asks for the approach rather than a rare diagnostic label.

The correct response is an **urgent rapidly progressive cognitive syndrome**. Tempo changes both differential weighting and locus of care. The candidate should confirm that the apparent rapidity is real by identifying the previous baseline, earliest unequivocal change and sequence of loss. A long unrecognised decline with recent caregiver collapse is different from genuinely rapid brain dysfunction. Delirium, seizures, toxic exposure, systemic disease, inflammatory or infectious processes and rapidly progressive degenerative disease must be considered according to the clinical context.

Assessment should become targeted and parallel rather than leisurely and serial. Stabilise immediate medical and behavioural risk, review substances and medications, obtain collateral chronology, perform full mental state and neurological examinations, and select laboratory, imaging, electrophysiological or fluid studies to answer specific hypotheses. Imaging physics belongs in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. The cerebrospinal-fluid examination procedure belongs in the Neurology foundations for psychiatrists notes. The autoimmune and limbic encephalitis workup belongs in the Neuropsychiatry of systemic and neurological disease notes.

The key is not to write an encyclopaedic list. Rank possibilities by tempo, systemic context, neurological pattern and treatability. State which diagnoses require immediate exclusion because delay changes outcome. Preserve infection-control, consent and capacity considerations where relevant, but do not invent statutory particulars. If a chronic diagnosis already appears in the notes, it must not be allowed to explain away a new, rapid or fluctuating deterioration.

28.7 Vignette: behaviour, prescribing and caregiver collapse

A person with established dementia begins pacing, shouting and striking out during evening care. The caregiver requests a sedating prescription and says home care may no longer be possible. The patient cannot give a coherent account, has reduced oral intake and appears uncomfortable during movement. The question asks for management.

LOCUS precedes treatment selection. Decide whether the person can be assessed safely in the present setting or needs urgent medical evaluation or a more supported environment. **FOCUS** is not "agitation" in the abstract. It is the immediate danger, distress and probable unmet need, together with caregiver exhaustion. **MODUS** begins with assessment for pain, acute illness, medication effects, sensory overload, communication failure, fear, hunger, toileting needs, sleep disruption and environmental triggers. Behavioural observation and caregiver reconstruction of antecedents and consequences are clinical data.

The **behavioural formulation** should describe what happens, when, with whom, during which task and with what apparent consequence. A label such as aggression compresses too much. If the behaviour is defensive during painful movement or intimate care, sedation may obscure the cause while increasing harm. Modify the task, environment and communication; treat identified contributors; support the caregiver; and define the target behaviour before considering disease-specific medication guidance.

- State the immediate risk to the patient, caregiver and others, and identify what would make the current setting unsafe.
- Look for a new medical, neurological, medication-related, environmental or interpersonal precipitant before calling the behaviour progression.
- Use simple communication, predictable care, sensory aids, meaningful activity and environmental modification matched to the trigger.
- If medication is considered, define the target, expected benefit, major harms, review plan and stopping logic using current dementia-specific guidance.
- Assess caregiver capacity and respite needs directly; "family support" is neither limitless nor clinically neutral.

IN INDIA

A workable plan must identify who actually provides supervision, who can accompany urgent assessment, who controls medicines and money, and what local services are reachable. Joint-family language can conceal that an exhausted relative carries nearly all care. Ask for the real roster and build the least restrictive safe plan around available people, transport, cost and follow-up.

Drug selection, dementia-specific dosing and adverse-event safeguards belong in the dedicated behavioural-management section. The candidate should never improvise a dose from general psychiatric practice. The answer earns marks by showing that medication is considered only after the target, cause, risk and non-drug response are defined, except where immediate danger requires simultaneous containment and assessment.

28.8 Write the final answer with VITALS

Under examination pressure, use a consistent retrieval spine. The aim is not to force different diseases into the same presentation. It is to ensure that the answer does not lose baseline, function, competing explanations or safety while pursuing a recognisable phenotype.

MNEMONIC

VITALS

Verify acquired decline from the person's baseline. **I**dentify the leading cognitive, behavioural and neurological pattern. **T**race tempo, sequence and functional consequence. **A**ssess alternatives, active contributors and acute threats. **L**ink collateral history, examination and targeted investigations into a ranked formulation. **S**tate the safest next step, uncertainty and follow-up plan.

For a diagnosis question, lead with the syndrome and its level of certainty, then justify the most likely cause using the pivot. For a differentiation question, compare the leading formulations on shared axes: onset, tempo, cognitive pattern, associated behaviour, neurological findings, functional trajectory and response to context. For an investigation question, state the hypothesis each test addresses. For a management question, use LOCUS, FOCUS and MODUS, then connect every intervention to a target and review plan.

The **discriminating negative** is an absent expected feature that genuinely weakens a competitor. Use it carefully. Absence is meaningful only when the feature was sought reliably and should be present at the relevant stage. Do not turn silence in a short stem into proof that a symptom is absent. Likewise, do not invent normal findings. State what information is missing and how it would change the ranking.

When investigations disagree with the phenotype, name the discordance. A structural abnormality may not explain the clinical distribution; a disease-associated biomarker may not explain function; a reassuring brief screen may not outweigh credible longitudinal decline. Recheck sampling, context, language, education, sensory function, comorbidity and mixed pathology. General test administration remains in the Psychometry, Assessment and Descriptive Psychopathology notes, while dementia-specific interpretation belongs in this chapter.

End with action. A complete formulation that does not change care is unfinished. Clarify immediate safety, the setting of care, reversible contributors, support for the caregiver, treatment targets, monitoring and what finding should prompt reassessment. This is also the correct response to uncertainty: not false precision, but a safer plan for acquiring better evidence.

In every dementia vignette, verify decline, identify the pattern and tempo, establish functional consequence, rank cause against its strongest competitor, and state the action that cannot safely wait.

29 · Consolidation and quick review

The marks lie in integration, not in reciting isolated lists. A strong answer to a cognitive-disorder question moves in a disciplined direction: establish that there is a cognitive syndrome, define its pattern and tempo, determine whether everyday function has changed, search for reversible or superimposed contributors, formulate the most defensible cause, and convert that formulation into a safe plan. The same sequence protects clinical practice. It prevents a familiar complaint such as forgetfulness from being mistaken for a diagnosis and prevents a familiar scan abnormality from replacing bedside reasoning.

Consolidation means learning a reusable architecture rather than another catalogue. Whether the doorway is a memory complaint, behavioural change, executive failure, an imaging finding or a caregiver's safety question, return to the same questions. What syndrome is present? How secure is the evidence? What explains it? What contributes? What matters now?

29.1 Build the syndrome before naming the disease

The first task is to distinguish a cognitive complaint from a demonstrable **cognitive syndrome**. Subjective concern deserves assessment, but it does not by itself establish objective impairment. Conversely, a patient who minimises difficulty may still have substantial change recognised by family or colleagues. The clinician integrates self-report, collateral account, observed performance and change from the person's previous level. Premorbid ability, education, language, occupation, sensory impairment and opportunity to perform a task all shape what a test result means.

Next determine whether cognition has altered everyday independence. **Functional decline** is not simply inability to perform a task during an interview. It is a change in real-world execution attributable to cognitive difficulty rather than physical illness, poverty, unfamiliarity, lack of opportunity or another psychiatric state. Complex activities often reveal change before basic self-care, but the important issue is the causal link between cognition and function. Ask what the person previously did, what now goes wrong, who compensates, and what would happen without that compensation.

Syndrome	Function	Collateral	Safety
BEFORE SUBTYPE	BEFORE LABEL	BEFORE CERTAINTY	BEFORE ELEGANCE

The syndrome statement should be compact but rich: the dominant cognitive pattern, associated behavioural or neurological change, tempo, functional consequence and any active confounder. Etiology comes after this statement. A disease label given too early creates confirmation bias; subsequent history is then forced to fit it. A syndrome-first formulation leaves room for mixed pathology, treatable contributors and diagnostic revision.

RULE **Name the level and pattern of impairment before naming its cause.** A defensible etiological diagnosis rests on a demonstrated syndrome, meaningful functional evidence and a trajectory that coheres with the proposed explanation.

29.2 Make history longitudinal and collateral

A cross-sectional interview can show how the patient performs today; dementia assessment asks how the person has changed over time. The core evidence is therefore longitudinal. Establish the earliest credible change, the sequence in which difficulties emerged, whether progression has been smooth or stepwise, and whether fluctuations represent genuine variation, environmental demand, fatigue, sleep disruption, medication effects or an acute confusional state. Tempo narrows the differential far more efficiently than an undirected list of causes.

Collateral history is not an optional confirmation of the patient's account. It is an independent source of evidence about decline, compensation and risk. Speak to someone who knows the patient's previous abilities and current routine. Resolve disagreements rather than automatically privileging either narrator. A patient may under-report because of reduced awareness, shame or fear of lost autonomy. A relative may over-report because of anxiety, conflict, burden or unrealistic expectations. The clinician's task is triangulation.

- Map change across memory, language, attention, visuospatial ability, executive control, social cognition and behaviour without assuming that memory must dominate.
- Translate each reported deficit into a concrete event such as missed payments, repeated journeys, unsafe cooking, lost work sequences, altered social judgement or failure to use familiar objects; ask who has silently taken over tasks, because family compensation can conceal clinically important loss of independence.
- Review medical illness, prescribed and non-prescribed substances, sleep, pain, mood, psychosis, sensory loss and environmental disruption as contributors; record driving, medication management, finances, falls, wandering, self-neglect, vulnerability to exploitation and access to weapons or toxic substances as safety domains, not as moral judgements.

The history should also identify the patient's values and the family's explanatory model. Some families present behavioural change as stubbornness, laziness or normal ageing; others interpret ordinary lapses as inevitable dementia. Correcting either error requires examples and functional reasoning, not reassurance alone. Language concordance and culturally familiar tasks improve the validity of the encounter, but cultural sensitivity must not become an excuse for avoiding a clear assessment of impairment.

29.3 Use examination and investigations as converging evidence

The mental state examination, bedside cognition and neurological examination answer different questions. The interview reveals engagement, affect, thought content, perception, insight and behaviour. Cognitive examination samples domains and exposes error patterns. Neurological examination looks for focal, extrapyramidal, cerebellar, gait, motor, sensory or release phenomena that may redirect the formulation. No single component should be treated as a universal arbiter.

The **cognitive phenotype** is the pattern formed by relative strengths, weaknesses and characteristic errors. A total screening score compresses that pattern and can be useful for communication or follow-up, but it cannot explain why the score is low. Performance may be distorted by education, language, poor hearing or vision, anxiety, depression, pain, fatigue and

reduced effort. General administration and scoring of standardised screens belong in the Psychometry, Assessment and Descriptive Psychopathology notes. In a dementia assessment, the relevant question is how screening findings fit the history, function and observed behaviour.

EVIDENCE LAYER	QUESTION IT ANSWERS	COMMON MISUSE	CORRECT INTEGRATION
Patient account	What is experienced and feared?	Treating confidence as accuracy	Compare with previous ability and other evidence
Collateral account	What has changed in daily life?	Accepting family interpretation as fact	Seek examples, sequence, compensation and context
Mental state	What psychiatric state affects cognition?	Calling all poor performance dementia	Separate state effects from enduring decline
Cognitive examination	Which domains and error types are affected?	Using a total score as an etiology	Interpret the profile with language and education
Neurological examination	What accompanying brain-system signs are present?	Ignoring subtle signs after a psychiatric presentation	Use signs to refine localization and differential diagnosis
Laboratory assessment	Is a contributor or mimic present?	Ordering without a clinical question	Link each test to a plausible, actionable hypothesis
Imaging	Is there structural or functional support?	Equating an abnormality with causation	Ask whether distribution and severity fit the syndrome
Fluid biomarker	Does biology support a proposed pathology?	Allowing biology to erase the phenotype	Update diagnostic probability and management eligibility

The physics and general interpretation of imaging modalities belong in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. The cerebrospinal-fluid examination procedure belongs in the Neurology foundations for psychiatrists notes. Here, their dementia-specific purpose is conceptual: investigations test a hypothesis generated at the bedside, exclude important alternatives, and sometimes increase confidence in an underlying pathology. They support a clinical formulation; they do not manufacture one.

29.4 Protect the differential from premature closure

The differential diagnosis is most efficient when organised by tempo, cognitive pattern, associated features and reversibility rather than by a memorised undifferentiated list. Begin by asking whether the presentation is chronic and progressive, acute or fluctuating, rapidly evolving, stepwise, static, or apparently variable with mood and effort. Then ask whether the dominant deficit is amnestic, executive, language-led, visuospatial, behavioural, subcortical or mixed. Finally, identify systemic, neurological, psychiatric, medication-related and environmental explanations that could mimic or worsen the syndrome.

Reversible contributors should be framed carefully. Finding a potentially treatable abnormality does not prove that it explains the whole cognitive syndrome, and treating it does not guarantee restoration of previous cognition. The clinically useful formulation often contains layers: an underlying degenerative or vascular process, a superimposed medical or psychiatric burden, and modifiable factors that amplify disability. This layered model avoids the false choice between "reversible" and "irreversible." The endocrine, metabolic and nutritional diseases themselves are covered in the Endocrine and metabolic psychiatry notes.

Rapidly progressive decline requires urgency because the diagnostic balance shifts toward active neurological, inflammatory, infectious, toxic, metabolic and other potentially actionable processes. The detailed workup of autoimmune and limbic encephalitis belongs in the Neuropsychiatry of systemic and neurological disease notes. Delirium is taught in the Stroke, TBI, delirium and focal brain syndromes notes. The dementia clinician must nevertheless recognise when either possibility changes the locus and urgency of assessment.

Depression can produce prominent cognitive symptoms, and a neurocognitive disorder can coexist with depression. Variable engagement, subjective distress or apparent effort do not settle the question. The distinction depends on longitudinal evidence, internal consistency, functional examples, mental state and response over time. Similarly, vascular brain injury may contribute to a dementia syndrome, while the broader pre-dementia and post-stroke cognitive spectrum belongs in the Stroke, TBI, delirium and focal brain syndromes notes.

TRAP **Do not answer "dementia" when the vignette asks for a cause, and do not answer with a cause before establishing dementia.** Examiners reward the chain from syndrome to phenotype to etiology, with competing explanations explicitly addressed.

29.5 Formulate certainty, mixtures and discordance

A useful diagnostic formulation states not only what is most likely, but why, how certain the clinician is, and what evidence does not fit. The level of cognitive disorder, dominant phenotype, probable cause, contributing conditions, behavioural complications and functional risks should be distinguishable. This structure allows the diagnosis to evolve without making earlier work appear careless. Neurocognitive disorders are often probabilistic clinical constructs, especially when several pathologies or systemic burdens plausibly coexist.

Mixed etiology should not become a refuge for uncertainty. It is appropriate when independent lines of evidence support more than one meaningful contributor. It is weak when used merely because the history is incomplete or the scan contains common abnormalities. State which contributor explains which aspect of the presentation, which evidence is shared, and what future observation could shift the balance.

A **biomarker** changes the probability of a biological process; it does not independently establish the patient's functional state or explain every symptom. Concordance among phenotype, trajectory, examination and biomarker strengthens a formulation. Discordance should trigger a deliberate review of sampling, test limitations, comorbidity, disease stage and the possibility that

more than one process is present. It should not trigger selective forgetting of inconvenient clinical evidence.

GOOD TO REMEMBER

Write the formulation as a hierarchy: syndrome and severity of functional effect; dominant cognitive and behavioural pattern; most likely etiology; contributors and mimics; current risks; and the evidence still needed. This is clinically useful and converts directly into an examination answer.

Diagnostic language should preserve uncertainty without becoming vague. Terms expressing probability are useful only when the evidence behind them is stated. Naming discordant data is mature reasoning. The goal is not maximal certainty; it is maximal defensibility.

29.6 Translate formulation into a whole-care plan

Management begins with **LOCUS**: decide whether assessment and care can proceed in the outpatient setting or whether acute risk, rapid deterioration, severe behavioural disturbance, inability to maintain basic needs, caregiver collapse or diagnostic urgency requires a more supported setting. Locus is dynamic. It changes when risk, supervision, medical stability or available support changes.

FOCUS identifies the targets of care across phases. Immediate priorities are safety, distress, acute medical or psychiatric contributors and communication of the working diagnosis. Subsequent priorities include preserving function, reducing avoidable disability, managing cognitive and behavioural symptoms, supporting the caregiver, planning supervision, and revisiting goals as the illness changes. The target must be explicit. “Treat dementia” is not a treatment target; unsafe wandering, distressing misidentification, medication errors, insomnia, caregiver exhaustion and loss of meaningful activity are.

MODUS ensures that the plan is not reduced to a prescription. Depending on the formulation, modes include disease-specific medication, treatment of contributors, environmental adaptation, psychological strategies, occupational support, rehabilitation, caregiver education, social and legal planning, and palliative approaches. Cognitive enhancers, behavioural and psychological symptoms, antipsychotic risk and disease-modifying anti-amyloid therapy are taught in their dedicated sections of this chapter. General antipsychotic pharmacology belongs in the Schizophrenia: management, antipsychotics and adverse effects notes.

Every intervention needs a reason, a realistic outcome, a monitoring plan and a stopping rule. Benefits should be described in functional or behavioural terms that matter to the patient and family. Risk discussion should include uncertainty and burden, especially when treatment requires repeated monitoring or when the person cannot provide fully informed consent. Capacity is decision-specific and should be assessed in relation to the actual choice rather than inferred globally from the diagnosis.

IN INDIA

Plans must fit the family's actual geography, finances, language, caregiving structure and access to investigations, rehabilitation and follow-up. A theoretically complete plan that cannot be implemented is not superior to a staged plan that addresses danger first, uses available supports and preserves continuity. Ask who will supervise medication, accompany visits, manage money and provide respite; do not write "family support" as if it were an unlimited resource.

29.7 Follow the person, not merely the score

Dementia care is longitudinal. Follow-up should revisit cognition, function, behaviour, neurological change, medical contributors, medication benefit and harm, nutrition, mobility, sleep, continence, pain, sensory function and safety. The relative importance of these domains changes over time. A stable screening score can coexist with meaningful functional deterioration, while a lower score may reflect language, illness, fatigue or testing conditions rather than a true change in trajectory.

The **care dyad** is the patient and the person providing sustained support. Their needs overlap but are not identical. The patient's autonomy, comfort, identity and preferences remain central; the caregiver's health, sleep, burden, knowledge, grief and ability to continue must be assessed directly. A plan that protects the patient by exhausting the caregiver is unstable. Equally, caregiver convenience cannot automatically override the patient's rights and preferences.

- Define what change would count as benefit, deterioration or unacceptable harm before altering treatment, and review adherence and administration rather than assuming that prescribed treatment is received correctly.
- Reassess environmental triggers and unmet needs before attributing every new behaviour to disease progression; update supervision, financial safeguards, mobility support and crisis plans as function changes.
- Revisit communication preferences, future care goals and the caregiver's ability to sustain the plan.

PITFALL

A new behavioural or cognitive deterioration should not be casually labelled "progression." First look for pain, infection, constipation, medication effects, sleep disruption, sensory loss, environmental change, depression and delirium. The label of dementia does not protect a patient from developing another illness.

End-of-life care is not an abrupt final chapter of management. It grows from earlier conversations about values, burdens, comfort, feeding, hospital transfer and acceptable intervention. These discussions require tact, repetition and attention to capacity and family conflict. The therapeutic task is to preserve personhood while making progressively realistic decisions.

29.8 The master retrieval frame

When the vignette feels crowded, return to a fixed retrieval frame. The aim is not to force every case into a slogan. It is to prevent omission under pressure. The frame below follows the natural order of assessment and care, while leaving disease-specific criteria, investigations and treatments to be inserted only when the case supports them.

MNEMONIC

MIND CARE

Map the complaint, baseline and tempo. **I**dentify the cognitive and behavioural pattern. **N**ote functional change, neurological signs and safety. **D**etect delirium, depression, drugs and reversible contributors. **C**orroborate with collateral history, examination and targeted investigations. **A**ssign the syndrome, likely etiology and degree of certainty. **R**espond through LOCUS, FOCUS and MODUS for the patient and caregiver. **E**valuate longitudinally and revise the formulation when evidence changes.

In a long answer, begin with a brief definition of the syndrome in clinical terms, then classify the presentation by level, phenotype, tempo and likely cause. Follow with history, collateral information, mental state, cognition, neurological examination and targeted investigations. Present the differential as a reasoned hierarchy. End with a whole-care plan and follow-up parameters. In a short answer or viva, compress the same sequence rather than substituting an unrelated list.

The boundaries around neighbouring topics should remain visible. General cognitive-screen administration belongs in the Psychometry, Assessment and Descriptive Psychopathology notes. Imaging physics belongs in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. The cerebrospinal-fluid procedure belongs in the Neurology foundations for psychiatrists notes. Delirium belongs in the Stroke, TBI, delirium and focal brain syndromes notes. Movement-disorder neuropsychiatry, inherited movement disorders and autoimmune encephalitis belong in the Neuropsychiatry of systemic and neurological disease notes. Intellectual disability as a developmental condition belongs in the Intellectual disability and autism spectrum disorder notes. Cross-reference these areas without importing their criteria into a dementia answer.

A final answer should sound like clinical reasoning: evidence first, inference second, action third. State what establishes the syndrome, supports the etiology, argues against alternatives, remains modifiable and matters now. If evidence is incomplete, say what remains uncertain and how it would be resolved.

The must-memorise sequence is: establish syndrome, map phenotype and tempo, verify function with collateral evidence, exclude superimposed and treatable contributors, formulate cause and certainty, then plan care for both patient and caregiver.

References

The canonical sources this chapter is grounded in. Every fact-bearing specific in the notes traces to one of these; where a primary paper or a trial is named in the text, it is cited inline. The list is ordered by how much of the chapter rests on each.

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