WEAVE SPRINT

PAPER IV · VOLUME FOUR

MD and DNB psychiatry, theory revision

Neurology, Medicine and Recent Advances

Stroke, Injury and Systemic Disease

What a damaged brain does to a person, and how stroke, injury and delirium separate on the ward. Then the systemic diseases that reach psychiatry.

Dr. Wilfred D'souza · Dr. Niharika Reddy

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WEAVE SPRINT · PAPER IV

Neurology, Medicine and Recent Advances

THE WEAVE SPRINT SERIES

TITLE

Weave Sprint, Paper IV, Volume Four: Stroke, Injury and Systemic Disease

Part of the Weave Sprint series, MD and DNB psychiatry theory revision.

WRITTEN BY

Dr. Wilfred D'souza and Dr. Niharika Reddy

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EDITION

First compiled 2026. Free to read, share and print for study.

The clinical content is written for doctors and doctors in training. It is a study and revision aid, not a substitute for current guidelines or clinical judgement. Verify doses and thresholds against the current references and your local protocols before any clinical use.

For every resident who has ever sat up the night before,
afraid it will not be enough.

ACKNOWLEDGEMENT

A word of thanks

I want to begin by thanking something I cannot quite name. Call it whatever you like. I have never been certain what to call it, and I have stopped needing to be. There is a part of this work that does not feel like mine. The line that arrives before I have thought of it, the connection I did not plan, the steadiness on a morning I had no reason to be steady. I only hold the pen. Something moves through the holding, and I have learned to thank it without asking it for a name.

Someone once asked me why I give all of this away. Why hand out the notes I sat up making, to the very people sitting the same exam beside me. It is a fair question. If I had kept them, I would probably have scored a few marks more than the next person, and I might have been thought of as the better student. I have turned that over honestly, and I have decided it is a small thing to want. What I get instead, by putting the work in your hands, is the chance to take a little of the fear out of a great many nights. That trade is not close. Easing that fear is not a detour on the way to becoming a good psychiatrist. It is the thing itself. I did not come here to be the best student in the room. I came here to be a good psychiatrist.

And to Niharika, who reads everything first and knows when to be honest and when to wait; and to the residents who study from these pages and write back with the corrections and the questions: thank you. The book is better for you, and so am I.

Dr. Wilfred D'souza

Foreword

This fourth volume is the damaged brain and the diseased body. Stroke, injury and delirium each produce psychiatric pictures that a purely psychological formulation will absorb without complaint, and the systemic diseases do the same more slowly. The work in both chapters is learning to notice when the formulation has absorbed something it should have questioned.

The notes were written to be understood, not just revised. Each chapter is a full account of its subject, from the mechanism up to the point the exam tests, so that you can read to learn the first time and read to recall every time after. Where a fact is worth holding exactly, it is marked. Where a mistake is easy to make, it is named before you make it. The colour code on the next pages tells your eye what kind of fact it is looking at before your mind has to decide, and after a few pages it stops being a key you consult and becomes a sense you carry.

Read it in order if you are meeting the material, or open it anywhere if you are returning to it. The contents at the front and the index at the back both jump to the page you want. However you use it, the hope held in these pages is plain: that one ordered, trustworthy place to study from makes the work a little lighter, and that you walk into the hall steadier than you would have otherwise.

HOW TO USE THIS BOOK

The colour memory code

Every note in this volume speaks one visual language, so once you learn it in the first chapter you read the rest without thinking about it.

Concept and rule	The core idea and the principle that follows from it. When a line is petrol, it is the thing to understand, and the thing worth being able to state.
Key number	A figure to hold exactly: a dose, a threshold, a prevalence, a cut-off. Amber means memorise this number, not just the shape of it.
Trap	The mistake the exam is waiting for. When a line is coral, it is warning you off an error that looks right until it costs you the mark.

Hold this is the single line from a topic you must carry out of it. **Good to remember** gathers, for each named thing, what it is, when it matters, and the one number or formula worth keeping. Both help a tired brain find the centre of a dense page fast.

The contents at the front is clickable, and so is the index at the back: every entry jumps to its page. Read to learn once, and to recall as often as you need.

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PART V

V

Stroke, TBI, Delirium and Focal Brain Syndromes

What a damaged brain does to a person, and how the syndromes of stroke, injury and delirium separate on the ward.

01 The cerebrovascular and post-stroke syndromes

02 Traumatic brain injury and its psychiatric sequelae

03 Delirium and the amnestic syndromes

04 The bedside examination and the focal lobe syndromes

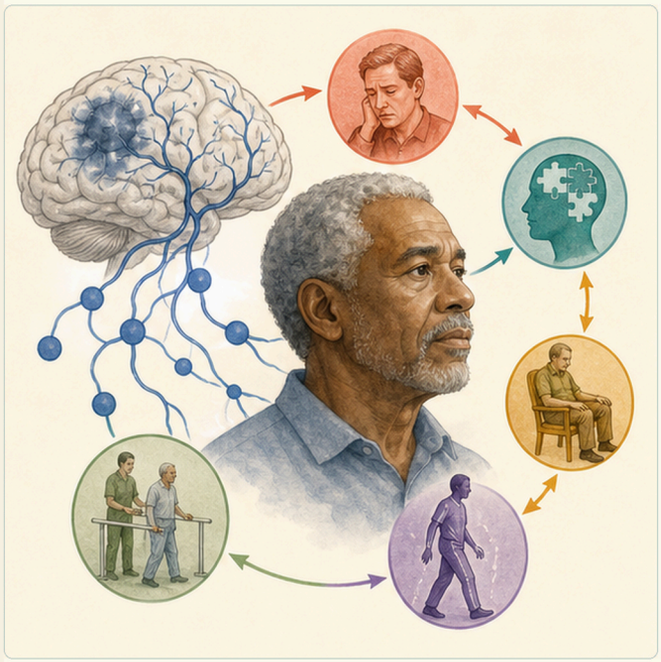
05 Structural lesions and the seizure overlap

06 Consolidate and apply

07 Sources and further reading

PART 5 • Stroke, TBI, Delirium and Focal Brain Syndromes

VISUAL 5.1



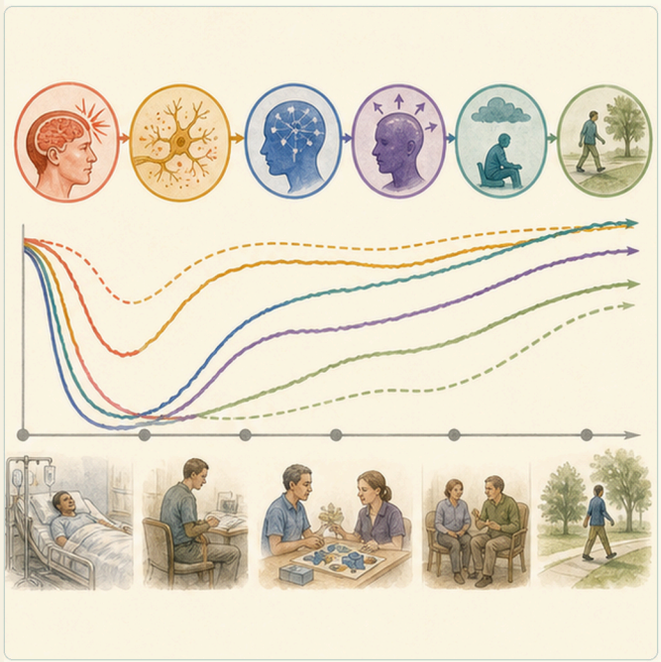
Stroke produces a network of psychiatric outcomes

- Lesion and vascular burden
- Mood
- Cognition
- Behaviour and apathy
- Focal signs
- Rehabilitation

Post-stroke psychiatric outcomes reflect lesion, network disruption, disability, prior vulnerability and recovery context.

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VISUAL 5.2



TBI unfolds from injury into recovery

- Primary injury
- Secondary injury
- Cognition
- Behaviour
- Mood and trauma
- Rehabilitation

Traumatic brain injury begins with primary injury and evolves through secondary processes, neuropsychiatric sequelae and rehabilitation.

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VISUAL 5.3



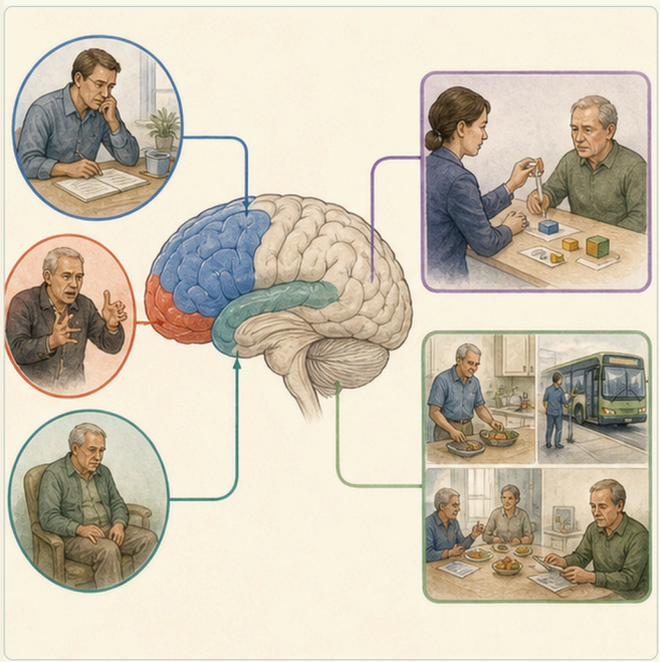
Delirium runs on two simultaneous clocks

- Acute fluctuation
- Detect
- Find and treat causes
- Non-pharmacological care
- Medication restraint
- Prevention

Delirium care treats the underlying cause while supportive environmental measures, risk management and prevention run in parallel.

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VISUAL 5.4



Three frontal syndromes, three functional failures

- Dorsolateral
- Orbitofrontal
- Medial
- Executive testing
- Everyday function

Frontal syndromes are patterns of executive, inhibitory and motivational failure that require bedside testing and functional corroboration.

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PAPER IV

Stroke, TBI, delirium and focal brain syndromes

Five bands . one complete notes document

The cerebrovascular and post-stroke syndromes

1 · Acquired brain injury and focal brain syndromes for the psychiatrist: what this chapter owns, and what it points to

The psychiatric presentation may be the first visible expression of acquired brain dysfunction. A patient may reach the psychiatrist because of altered mood, belief, behaviour, memory, motivation, personality or awareness, while the decisive history is a vascular event, head injury, fluctuating medical state, focal cortical disorder, structural lesion or seizure-related change. The mental state describes the presentation. It does not, by itself, identify the neurological process that produced it.

This orientation provides the **clinical architecture** for the chapter. The dedicated sections teach each syndrome, lesion pattern, criterion set, investigation and treatment in depth. Here the task is to learn the shared method: establish the previous baseline, define the tempo and trigger, identify immediate danger, describe the dominant syndrome, localise only when findings converge, rank causes and consequences, and plan care across medical treatment, psychiatry and rehabilitation. This is where the marks sit, because a long list of associations is not yet a neurological psychiatric formulation.

1.1 Define the territory before naming the disorder

Acquired neurological psychiatry concerns changes in mental state, cognition and behaviour that arise in the context of brain injury, diffuse cerebral dysfunction or structural neurological disease. Its central difficulty is overlap. Affective symptoms, psychosis, apathy, disinhibition, amnesia and functional decline can each occur through several mechanisms, and the same neurological illness can produce different psychiatric phenotypes in different people.

The opening question is therefore not “Which psychiatric diagnosis is this?” It is “What changed, from what baseline, in what neurological and medical context?” This creates an **index problem** that is clinically useful without claiming more than the evidence supports. “New behavioural and cognitive change after a neurological event” preserves the sequence and uncertainty. A premature label such as depression, dementia or psychosis may discard the very observations needed to distinguish neurological injury, systemic disturbance, treatment effect, adaptation and independent psychiatric illness.

The chapter crosses several levels of explanation. At the symptom level, it describes what the patient experiences and what others observe. At the syndrome level, it asks which features cohere. At the anatomical level, it considers diffuse dysfunction, focal injury, disconnection and network disturbance. At the aetiological level, it asks what process caused the state. At the

functional level, it measures the effect on safety, autonomy, rehabilitation and relationships. A defensible answer moves between these levels without confusing them.

This approach also prevents diagnostic overshadowing in either direction. A known psychiatric disorder should not make a new neurological change invisible. Conversely, a visible lesion should not be made responsible for every symptom merely because it is concrete. Pain, sleep disruption, medication, sensory loss, fear, grief, family strain and premorbid vulnerability remain clinically active even when neurological disease is established.

RULE **Describe the change before naming the syndrome, and describe the syndrome before assigning a site or cause.** Each later inference should explain the observations already established rather than replacing them.

1.2 Read the chapter as a set of clinical lenses

The chapter is arranged by the kind of neurological problem confronting the psychiatrist. These are not sealed compartments. A vascular event may produce a focal syndrome, an injured patient may become delirious, a structural lesion may alter cognition, and seizures may complicate several forms of brain injury. The value of the map is to show which lens leads and where detailed teaching is located.

CLINICAL TERRITORY	OPENING QUESTION	DEPTH SUPPLIED BY THE CHAPTER
Cerebrovascular and post-stroke syndromes	What changed after the vascular event, and how securely can it be attributed?	Affective, motivational, psychotic, expressive, awareness-related and vascular cognitive presentations
Traumatic brain injury	How do injury severity, evolving damage and recovery context shape the psychiatric course?	Classification, concussion, psychiatric and personality sequelae, cognition, rehabilitation and pharmacological principles
Delirium and amnestic syndromes	Is the central disturbance an acute unstable state, a persistent memory syndrome or a transient amnesia?	Recognition, mechanisms, investigation, management, prevention, amnestic pathology and confabulation
Bedside and focal brain syndromes	Do cognitive and behavioural findings converge on a cortical, subcortical or disconnection pattern?	Ordered bedside examination and the frontal, temporal, parietal, occipital and disconnection syndromes
Structural lesions and seizure overlap	Could mass effect, altered pressure, an extra-axial collection, tumour, hydrocephalus or seizure-related illness explain the presentation?	Reversible structural differentials, location-related presentations, pressure syndromes and psychiatric implications of seizures

Event	**State**	**Network**	**Impact**
WHAT HAPPENED	HOW THE BRAIN FUNCTIONS NOW	WHERE FINDINGS CONVERGE	WHAT CARE MUST CHANGE

Use the map from either starting point. A known neurological event directs the clinician toward likely psychiatric and cognitive sequelae. An unexplained psychiatric change directs the clinician back toward neurological possibilities that must not be missed. The sections supply depth, but the orientation preserves integration: event, current state, anatomical pattern, cause, function and trajectory belong in the same case formulation.

1.3 Let tempo and trajectory organise the differential

Tempo is the most efficient opening discriminator. Abrupt onset, fluctuation, a stepwise course, gradual progression, episodic recurrence and a stable residual deficit raise different clinical questions. The sequence of features matters as much as their presence. A behavioural change that follows altered alertness, a focal deficit, injury or a seizure-like event is framed differently from a longstanding psychiatric syndrome later accompanied by neurological illness.

Start with the last reliably known baseline. Establish prior cognition, personality, daily function, psychiatric history, substance exposure and treatment. Place neurological, psychiatric, cognitive and systemic changes on one timeline. Mark injuries, procedures, medication changes, intoxication or withdrawal, intercurrent illness, transfers between settings and changes noticed after return home. A family statement that the patient was “normal before” should be unpacked into actual capacities and roles.

Distinguish onset from recognition. Executive or memory difficulty may become visible only when environmental demands increase. A family may date all later problems to a dramatic injury even when some were present beforehand. Conversely, a polished interview may conceal a clear decline from a highly functioning baseline. The patient should be compared with their own previous level rather than with an abstract norm.

State dependence means that performance and behaviour can vary with arousal, pain, fatigue, anxiety, intoxication, withdrawal, medication, sensory impairment and task demands. A snapshot taken during acute illness should not be treated as a fixed estimate of future ability. Serial observation tests the formulation: improvement with medical stabilisation, persistence despite recovery, or emergence under complex demands each changes the causal balance.

The trajectory also guides urgency. Rapid deterioration or fluctuation demands a different response from a stable deficit. The formulation should state what is changing, what appears fixed, what may be reversible, and which uncertainty requires reassessment. Avoid precise prognostic language unless the relevant disease section supplies evidence for it.

1.4 Hold parallel formulations rather than one grand diagnosis

A robust case uses **parallel formulation**. The syndrome, anatomical, aetiological and consequence accounts are developed together, but each answers a different question. They constrain one another without being collapsed. When they do not align, the discrepancy is information, not an invitation to force certainty.

The **syndrome formulation** describes the dominant pattern in clinical language: altered arousal and attention, amnesia, executive-behavioural change, a focal higher-function deficit, affective or

psychotic symptoms, or a mixed presentation. It separates observed behaviour from inferred intention. Sparse speech, inactivity, emotional display or inaccurate recall should be described before being interpreted.

The **anatomical formulation** asks whether the pattern suggests diffuse cerebral dysfunction, a lateralised deficit, a focal cortical syndrome, disconnection, subcortical network involvement or pressure-related compromise. The hypothesis becomes stronger when several findings converge and weaker when it rests on an isolated test error or an imaging abnormality without clinical correspondence.

The **aetiological formulation** ranks direct injury, evolving complications, systemic illness, medication and substances, seizures, structural disease and independent psychiatric conditions by urgency, probability and reversibility. More than one cause may be active. A common explanation may lead the probability list while a less likely but dangerous alternative leads the action list.

The **consequence formulation** covers risk, decision-making, self-care, treatment adherence, caregiver burden, rehabilitation participation and social role. It prevents a diagnostically elegant answer from ignoring what must change today. It also exposes cases where a seemingly mild symptom has major functional effect, or a conspicuous symptom causes distress without equivalent loss of independence.

> **PITFALL**
>
> Inferring intention from impaired performance. “Refusal,” “lack of effort” or “uncooperativeness” may instead reflect poor comprehension, weakness, pain, fatigue, altered awareness, fear or inability to execute the requested act. Record what happened and what the task required before assigning motive.

1.5 Know what this chapter owns and what it hands over

Neurological psychiatry touches constructs that are taught elsewhere in full. A disciplined answer names the interface and cross-refers; it does not reproduce another chapter’s criteria, scoring table or pharmacology. This boundary is part of clinical competence because it keeps the answer centred on the neurological question actually asked.

- The ordered bedside cognitive examination is taught here, while standardised cognitive instruments, their item content and scoring belong to the Psychotherapies, clinical assessment, MSE and nosology notes. Use instruments without reproducing their proprietary or chapter-owned detail.
- Vascular and post-injury cognitive presentations are taught here through their neurological lens. The general dementia syndrome and its full diagnostic workup belong to the Dementias and neurocognitive disorders notes.
- Substance-withdrawal delirium is placed within the delirium differential here, while withdrawal timelines, severity scoring and regimen detail belong to the Substance use

disorders notes. Nutritional emergencies that precede persistent amnesia are treated in the Endocrine and metabolic psychiatry notes.

- The psychiatric implications of post-injury and post-stroke seizures are taught here. Seizure classification and anticonvulsant pharmacology belong to the Epilepsy and psychiatry notes, while antidepressant pharmacology and general drug selection belong to the Mood disorders: pharmacotherapy notes.

The same discipline applies within this chapter. Post-stroke affective syndromes, traumatic brain injury classification, delirium criteria, amnestic pathology, focal lobe syndromes, structural lesions and seizure-related presentations each have one teaching home. An orientation may name them and explain how to approach the territory, but their numbers, criteria, mechanisms and treatment evidence remain with the owning section.

A useful handover sentence does real work: name the neighbouring construct, identify why it matters to the current case, and point to its owning chapter. Then return to the neurological lens. This is shorter and more accurate than inserting a generic dementia workup, a copied cognitive test, a withdrawal regimen or a drug-selection essay into every answer that happens to touch them.

1.6 Localise cautiously and think in networks

Network localisation is a hypothesis built from converging observations. Begin with the descriptive phenotype and neurological findings, then ask whether they form a coherent pattern. A localising account should explain the combination rather than match one dramatic feature. An isolated bedside error is insufficient because performance may be distorted by demands outside the ability being examined.

Structural imaging contributes evidence about lesion location, vascular burden, mass effect and other pathology, but it does not replace bedside description. An abnormal scan may be causally important, contributory or incidental. Concordance among tempo, phenotype, examination and imaging is what makes attribution persuasive. When these disagree, preserve the discrepancy and reconsider the formulation.

Psychiatric syndromes rarely map onto one anatomical point in a deterministic way. Focal injury can disturb connected regions, diffuse injury can produce apparently focal deficits, and similar behaviours can arise through different network failures. Premorbid organisation, reserve, sensory and motor disability, medication and environment shape expression. This is why lesion associations should generate and test hypotheses rather than end discussion.

TRAP **Do not turn an association into a localisation law.** A remembered side, lobe or structure may support an answer, but it cannot substitute for phenomenology, tempo, neurological examination and competing explanations.

The bedside cognitive method, executive testing and focal higher-function examination are taught in their dedicated sections. The orientation contributes only the interpretive rule: before calling a deficit localising, confirm that the observed performance is valid for the ability being

inferred. When validity is uncertain, seek converging observations rather than forcing a site from the task.

1.7 Assess safety and manage across the recovery pathway

Assessment begins with immediate safety rather than diagnostic elegance. Physiological instability, reduced or fluctuating consciousness, rapid deterioration, a new focal change, seizure-like events, recent injury or other evidence of an evolving neurological or systemic emergency should move care toward urgent medical evaluation. These are escalation signals, not diagnoses. Seek collateral information when the neurological or cognitive state may make the history unreliable.

Management follows the shared spine. **LOCUS** asks where care can safely occur: outpatient and rehabilitation settings for stable patients with adequate support, inpatient care when medical or behavioural needs exceed community capacity, and emergency or higher-dependency care when instability or deterioration demands it. The setting should match the most urgent active problem, not the specialty of the clinician who first received the referral.

FOCUS orders targets over time. Acute work addresses stabilisation, the underlying cause, immediate risk and behaviour that prevents essential treatment. Shorter-term work supports sleep, pain control, communication, mobilisation and participation in rehabilitation. Continuing care addresses residual cognitive, affective and behavioural problems, recurrence prevention, social reintegration, occupational goals and caregiver strain. Targets should be observable and linked to function.

MODUS ensures that care is not reduced to prescribing. Cause-directed medical treatment, cautious symptom treatment, psychological support, rehabilitation, environmental adaptation, nursing strategies, family work and social intervention may all be required. Procedural treatment belongs where the underlying neurological condition indicates it. Current guidance and local protocols should direct disease-specific decisions; no named guideline is available to this orientation.

> **GOOD TO REMEMBER**
>
> Ask what the patient can do across a normal day, not only what can be demonstrated in a quiet interview. Nursing, therapy and caregiver observations often reveal participation, supervision needs and risk more clearly than a symptom label does.

Monitoring should cover benefit and harm. Define the target behaviour or function, identify who can observe it, and state what worsening prompts reassessment. Avoid unnecessary sedation and other interventions that obscure examination or reduce rehabilitation participation. Family involvement is essential, but clinical responsibility should not be transferred to caregivers without support, explanation and a workable follow-up route.

1.8 Use the NEURAL scaffold in essays and cases

Under examination pressure, preserve the order of reasoning. The master mnemonic is **NEURAL**. It is an educational scaffold rather than a diagnostic instrument. It can organise a vascular case, head injury, delirium, amnestic presentation, focal syndrome, structural lesion or seizure-related psychiatric problem without replacing the disease-specific knowledge in the relevant section.

MNEMONIC

NEURAL

New change from baseline: describe what altered and what was present before. **E**volution and event: reconstruct tempo, trigger, sequence and trajectory. **U**rgency: identify instability, deterioration and immediate risk. **R**egional or network hypothesis: localise only when findings converge. **A**etiology and alternatives: rank direct injury, complications, systemic causes, treatment effects and independent illness. **L**ife impact and locus: connect function, rehabilitation, setting, treatment modes and follow-up.

For a short case, compress NEURAL into a problem representation, leading formulation, dangerous alternative, discriminating findings and immediate plan. For a long essay, expand each element and insert disease-specific epidemiology, criteria, investigations and treatment from the owning section. In a viva, make calibration audible: state what is observed, what is inferred, what remains uncertain and which finding would change the ranking.

The enduring habit is integration without overreach. Psychiatric symptoms can be neurologically meaningful without being anatomically unique. A lesion can be clinically important without explaining the whole patient. A fluent conversation can coexist with substantial cognitive or functional impairment. A dramatic behaviour can be less urgent than quiet deterioration. A good answer keeps these tensions visible and resolves them through collateral history, ordered examination, appropriate investigation and serial review.

NEURAL: define the new change, reconstruct evolution and event, detect urgency, build a regional or network hypothesis, rank aetiology and alternatives, then plan for life impact and locus of care.

2 · Post-stroke depression: epidemiology, lesion correlates, diagnosis and treatment

Why it matters clinically. Post-stroke depression is not an understandable sadness that can be dismissed as an inevitable reaction to disability. It is a depressive syndrome occurring in the biological, psychological and social aftermath of stroke, with consequences for quality of life, disability and survival. The examiner therefore expects more than a prevalence figure: define the syndrome, show why detection is difficult, present lesion evidence without false certainty, and separate treatment of depression from attempts to improve neurological recovery.

IN INDIA

Screen for and treat post-stroke depression as a disorder in its own right, choosing an SSRI such as sertraline or escitalopram, and do not wait for neurological recovery before addressing the mood.

The accompanying figure situates depression among the wider post-stroke neuropsychiatric syndromes. Post-stroke mania, anxiety, apathy, fatigue, psychosis, emotional incontinence and denial of deficit are named here only because they enter the differential; their phenomenology and treatment belong in their dedicated sections. Vascular cognitive impairment is likewise a separate construct.

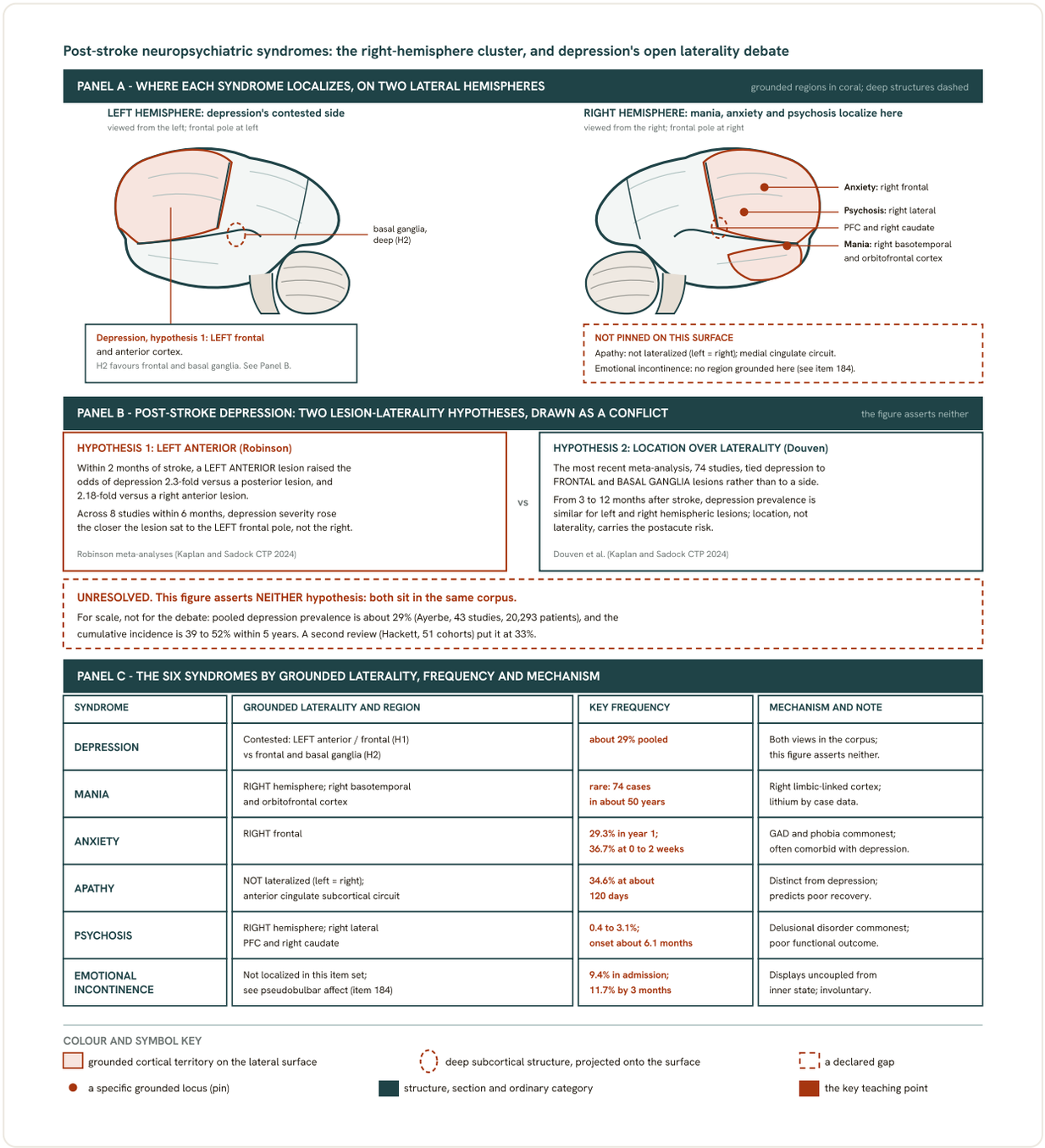


Fig 34.1 **The post-stroke neuropsychiatric map.** Mania, anxiety and psychosis cluster in the RIGHT hemisphere (right basotemporal and orbitofrontal for mania, right frontal for anxiety, right lateral prefrontal cortex and right caudate for psychosis); apathy is not lateralized and emotional incontinence has no region grounded in this item set. Depression is the one open laterality question, shown as a labelled conflict between the left-anterior hypothesis and the location-over-laterality view, with neither asserted. (Kaplan and Sadock Comprehensive Textbook of Psychiatry 2024; Tasman Psychiatry; Cognitive Assessment for Clinicians, Hodges.)

RULE **Diagnose a depressive syndrome, establish its relationship to stroke, and treat the mood disorder as a clinically important outcome in its own right.** Do not require a particular lesion side, and do not promise neurological recovery merely because depression responds.

2.1 Epidemiology: common, persistent and method-dependent

Post-stroke depression is common across the stroke pathway rather than confined to one ward or one phase. In the review by Ayerbe and colleagues, pooled prevalence at any assessed time was **29%**; prevalence did not differ significantly across time points or settings in that synthesis.

Cumulative incidence reached 39% to 52% within 5 years, showing that a patient who is well during initial rehabilitation remains at later risk.

29%	33%	39% to 52%	5 years
POOLED PREVALENCE	SECOND LARGE REVIEW	CUMULATIVE INCIDENCE	INCIDENCE WINDOW

A second large review by Hackett and colleagues estimated depression in 33% of stroke patients. The closeness of the pooled estimates is useful, but neither should be treated as a universal ward rate. The denominator, care setting, assessment method and inclusion of syndromal versus subsyndromal depression change what is counted. Prevalence is therefore best presented as a range of evidence, followed by the reasons for heterogeneity.

CARE SETTING	MAJOR DEPRESSION	MINOR DEPRESSION	INTERPRETIVE POINT
Community-based samples	14.1%	9.1%	Community estimates need not resemble hospital case-mix.
Acute or rehabilitation hospitals	21.6%	20.0%	Active medical and rehabilitation settings contain substantial syndromal and subsyndromal morbidity.
Outpatient studies	24.0%	23.9%	Ongoing surveillance remains necessary after discharge.

These setting-specific estimates come from the systematic review by Robinson and coinvestigators. Their practical lesson is not that one setting is intrinsically more depressogenic, but that sampling and clinical context shape the observed rate. A good answer therefore states that depression is frequent, gives a defensible pooled estimate, and then explains heterogeneity rather than averaging unlike populations.

2.2 Time course, disability and mortality

Risk begins early but does not end with acute admission. Depression is particularly frequent during hospitalisation and the early post-stroke period, while observed rates may remain stable for as long as 10 years. This coexistence of early frequency and long persistence explains why a single negative screen is insufficient. Case finding must recur when function, dependence, living circumstances or engagement with rehabilitation changes.

The course is heterogeneous. In one longitudinal estimate, mean duration was 39.0 plus or minus 31.8 weeks for major depression and 12.2 plus or minus 18.2 weeks for minor depression. Another study found a shorter mean duration for major depression but a longer mean course for minor depression, showing that the labels do not determine an individual trajectory. Among patients depressed at 3 months, **50% had recovered by 1 year**; across a meta-analysis, recovery at that point ranged from 15% to 57%. Variation reflects more than symptom severity: ascertainment, recurrence, medical course and follow-up loss all influence the observed pattern.

Outcome associations are clinically weighty. Post-stroke depression is associated with poorer quality of life, greater disability and later mortality. In one long follow-up, major or minor depression was associated with a **3.4-fold increase in the odds of mortality** compared with no depression. In another cohort, depression assessed early after stroke was associated with 50% higher mortality at 1 year. These observational associations do not by themselves establish a single causal pathway, but they make therapeutic nihilism unsafe.

GOOD TO REMEMBER

Repeat assessment across transitions of care. Ask again when the patient returns home, rehabilitation stalls, dependence becomes clearer, or the caregiver reports withdrawal. A negative interview during acute admission does not close the diagnostic window.

2.3 Lesion correlates: the high-yield unresolved debate

The classic account linked depression to anterior left-hemisphere injury. In a meta-analysis examining depression within 2 months of stroke, a **left anterior lesion** increased the odds of depression by 2.3 compared with a left posterior lesion and by 2.18 compared with a right anterior lesion. A separate synthesis found that depression severity increased as lesions lay closer to the left frontal pole, without the same relation to the right frontal pole. This became the memorable left-anterior hypothesis.

Later synthesis makes a simple laterality rule difficult to defend. The most recent meta-analysis described in the available evidence included 74 studies and identified clearer risk with **frontal and basal ganglia lesions**. An associated imaging review emphasised lesion location rather than laterality or lesion type in the postacute phase. In studies conducted 3 to 12 months after stroke, prevalence was similar after left- and right-hemisphere lesions, although lesion location appeared more relevant during the earlier months.

The defensible synthesis is phase-sensitive and probabilistic. Frontal-subcortical systems plausibly connect affect regulation, motivation, cognition and behavioural initiation, so disruption may contribute to depressive expression. Yet stroke also alters disability, communication, identity, relationships and reinforcement. Lesion anatomy is therefore one component of a biopsychosocial formulation, not a bedside diagnostic test.

TRAP **Do not answer "post-stroke depression equals a left frontal lesion."** The classic left-anterior association and the later location-over-laterality synthesis are genuinely in tension. State both, preserve their time windows, and conclude that no single hemispheric rule is adequate.

Equally, absence of a frontal or basal ganglia lesion does not exclude depression. Imaging can support the neurological formulation and may help explain associated deficits, but the depressive diagnosis rests on phenomenology, course, impairment and causal judgement. Anatomical correlation should never replace direct enquiry about mood, pleasure, hopelessness and safety.

2.4 Phenomenology and diagnostic classification

Comparative studies suggest that the phenomenology of post-stroke depression resembles depression in the general population and that **the same diagnostic criteria** can be used. This is important because clinicians sometimes invent a reduced "organic depression" syndrome consisting only of tearfulness and poor rehabilitation. The assessment should instead seek the full depressive pattern, including mood change, loss of interest, cognitive and neurovegetative symptoms, and associated distress or impairment, while interpreting each symptom in its neurological context.

Formal current classification should lead with ICD-11; the verified DSM-5 formulation here is a cross-map rather than a replacement for primary ICD wording. DSM-5 places the syndrome among depressive disorders due to another medical condition. When the post-stroke syndrome meets full criteria for a major depressive episode, the formulation is **depressive disorder due to stroke, with major depressive-like episode**. Subsyndromal depression is classified as depressive disorder due to stroke, with depressive features; the description supplied here requires more than two but fewer than five relevant symptoms persisting for at least 2 weeks.

The crucial attribution method is **etiological symptom counting**: a symptom is counted only when it is not judged to be caused by the physical illness itself. This avoids both extremes. Counting every post-stroke sleep, appetite, energy or concentration change as depressive can overdiagnose; automatically discarding every somatic or cognitive symptom can underdiagnose. The clinician asks whether the symptom belongs to a coherent depressive syndrome, whether it changed with affective experience, and whether a neurological, medical or environmental explanation is better.

MNEMONIC

M-I-N-D

Mood and interest are assessed directly; **I**mpairment is described against the post-stroke baseline; **N**eurological overlap is judged symptom by symptom; **D**anger, including hopelessness, self-neglect and suicidal thinking, is assessed rather than inferred from appearance.

2.5 Bedside diagnosis and differential diagnosis

The interview must be adapted, not abandoned. Aphasia, dysarthria, slowed processing, sensory loss, motor disability and fatigue can reduce the amount or speed of information obtained. Use brief language, allow response time, establish a reliable communication mode, obtain collateral history and compare behaviour with the premorbid and immediate post-stroke baseline. Communication difficulty lowers confidence in a negative interview; it does not prove absence of depression.

The examination should integrate several evidence streams:

- Directly elicit persistent mood change, reduced interest or pleasure, hopelessness, guilt, worthlessness and thoughts of death or self-harm.

- Describe biological and cognitive symptoms, then judge whether each is better explained by the stroke, another medical problem, treatment burden or the depressive syndrome.
- Ask the family about withdrawal, loss of initiative, reduced emotional responsiveness, self-neglect and change from the patient's usual coping style.
- Assess capacity to participate in treatment, current supports, caregiver strain, adherence barriers and the effect of mood on rehabilitation goals.

Apathy, fatigue, emotional incontinence, delirium and vascular cognitive impairment can coexist with or be mistaken for depression. Name them in the differential, but assess each through its dedicated section rather than importing its phenomenology into the depressive formulation. The immediate task here is to decide whether a coherent depressive syndrome is present in addition to the neurological condition.

PITFALL

Do not diagnose or exclude depression from facial expression, crying or rehabilitation performance alone. Neurological impairment can alter expression and performance in either direction. The diagnosis requires triangulation across subjective experience, observed behaviour, collateral change, neurological findings and longitudinal course.

Safety assessment remains explicit even when communication is impaired. Explore suicidal thinking, intent, self-neglect, refusal of essential care and access to support using the most reliable communication method available. If the patient cannot participate adequately, document the limitation, increase observation and collateral assessment, and reassess. The mortality association strengthens the case for active detection but should not be misrepresented as proof that every death is directly caused by depression.

2.6 Management framework: locus, focus and modus

Locus. Most medically stable patients can be assessed and treated through coordinated outpatient stroke, rehabilitation and mental health care. Inpatient care is appropriate when stroke-related medical needs, severe depression, inability to maintain safety, profound self-neglect or inability to participate in essential care require close supervision. Emergency assessment is required for immediate danger, rapidly changing neurological status or an acute confusional presentation. The site of care should be revised as medical stability, communication and social support change.

Focus. In the acute phase, establish the syndrome, exclude urgent mimics, address safety and preserve engagement with stroke care. Over the short term, target depressive symptoms, sleep-wake routine, distress, treatment participation and caregiver understanding. In the middle phase, review response, adherence, residual disability, role loss and rehabilitation goals. Over the long term, monitor recurrence, persistent symptoms, social isolation and transitions in support. Mood outcome and neurological outcome should be documented separately.

Modus. Treatment is multimodal: psychoeducation, collaborative goal setting, psychological intervention, social and caregiver support, rehabilitation coordination and antidepressant

treatment when indicated. Communication adaptations and supported decision-making allow psychological work to continue despite disability. Problem-solving approaches can address practical losses and reduced reinforcement without implying that the depression is merely situational. Current stroke and prescribing guidance should be consulted for patient-specific safety, interactions and monitoring.

The post-stroke evidence supports treating clinically significant depression, particularly severe illness. It does not remove the need to individualise choice against age, medical comorbidity, concomitant treatment, swallowing, cognition, previous response and the patient's priorities. General antidepressant mechanisms, comparative selection and broader prescribing principles belong in the Mood disorders: pharmacotherapy notes; the present section owns their use and evidence after stroke.

2.7 Antidepressant and psychological treatment evidence

Controlled trials establish that depressive symptoms after stroke can respond to medication. The early nortriptyline trial found greater improvement in depression ratings with nortriptyline 50 to 100 mg/day for post-stroke depression than with placebo over 6 weeks. The first placebo-controlled SSRI trial likewise found greater improvement with citalopram, using citalopram 20 mg/day under age 65 and 10 mg/day over age 65 for post-stroke depression, assessed over 6 weeks. These are trial regimens for this indication, not universal prescriptions.

EVIDENCE QUESTION	FINDING	CLINICAL INTERPRETATION
Nortriptyline versus placebo	Greater reduction in depression ratings	Supports antidepressant efficacy in established post-stroke depression.
Citalopram versus placebo	Greater reduction in depression ratings	Provides controlled SSRI evidence for the mood indication.
Pharmacotherapy versus control	Meta-analysis favoured pharmacological treatment	Supports treatment, particularly for severe depression.
SSRIs in later meta-analysis	Mood benefit remained evident	Reinforces mood efficacy without proving neurological benefit.
Problem-solving therapy for prevention	Lower incidence than placebo	Psychological treatment has preventive evidence in a selected nondepressed acute-stroke sample.
Antidepressant treatment and survival	Higher survival at extended follow-up	Suggestive long-term association, not a reason to promise survival benefit to an individual.

The pharmacotherapy synthesis included 16 trials and 1,655 participants and favoured active treatment with an odds ratio of 0.47. A later meta-analysis including 5,370 patients reported a relative risk of 0.78 for patients taking SSRIs. These estimates support efficacy for depression, but response still requires repeated measurement of symptoms, function, tolerability and safety.

A follow-up of patients treated with nortriptyline or fluoxetine for 12 weeks found survival of 59.2% among actively treated patients and 36.4% among placebo recipients at extended follow-up. This finding is clinically interesting but should be expressed cautiously: treatment allocation, later health and comorbidity complicate causal interpretation. The immediate evidence-based reason to treat remains relief of depression and restoration of engagement, not a guaranteed mortality effect.

2.8 Prevention and the functional-recovery controversy

Prevention is distinct from treatment of established depression. In nondepressed acute-stroke patients, a trial used escitalopram 5 mg/day over age 65 and 10 mg/day under age 65 for prevention of post-stroke depression over 1 year. Depression developed in 8.5% of the escitalopram group, 11.9% of the problem-solving therapy group and 22.4% of the placebo group. The result shows preventive efficacy in that trial population, but it does not mean every stroke survivor should automatically receive medication. Baseline depression status, risk, preference, comorbidity and monitoring capacity still matter.

The more important examination distinction is between mood treatment and neurological recovery. Some earlier findings associated fluoxetine 20 mg/day for post-stroke recovery, given for 3 months or nortriptyline 100 mg/day for post-stroke recovery, given for 3 months with improvement assessed later, independent of depression. However, the later systematic review concluded that SSRIs do not appear to improve functional recovery from neurological impairment after stroke. These findings are discordant, so the safest conclusion is deliberately narrow.

Prescribe an antidepressant to treat or, in selected circumstances, prevent depression. Do not present it as a routine neurorestorative treatment. Rehabilitation continues according to neurological and functional need, while mood response is assessed on its own axis. If improvement in participation follows relief of depression, that is clinically valuable, but it is not equivalent to a direct drug effect on motor recovery.

A high-scoring synthesis therefore moves in a disciplined sequence: establish the substantial and persistent burden; state that ordinary depressive phenomenology remains valid; apply etiological judgement to overlapping symptoms; present the left-anterior hypothesis alongside later location-focused evidence; assess safety and mimics; and use coordinated psychological, social, rehabilitation and pharmacological care. Close by separating three questions that are often confused: treatment of established depression, prevention in a nondepressed patient, and enhancement of neurological recovery.

> Post-stroke depression is common, diagnostically clinical and treatable; lesion side is not a rule, and antidepressant mood efficacy must not be converted into a claim of neurological recovery.

3 · Post-stroke mania, anxiety, apathy and fatigue

Why this cluster matters. A survivor who is restless, fearful, inactive or exhausted may be showing a direct neuropsychiatric consequence of stroke, an understandable response to disability, a coexisting depressive syndrome, a medical complication, or several of these at once. The examination marks lie in separating syndromes that look superficially alike: excess drive in mania, threat anticipation in anxiety, reduced initiation in apathy, and reduced capacity in fatigue. The clinical marks lie in making the same distinction before choosing treatment.

IN INDIA

If secondary post-stroke mania needs pharmacotherapy, lithium may be used in selected patients; a specialist opinion and appropriate baseline monitoring are worthwhile before starting.

Post-stroke mania is striking but rare; **post-stroke anxiety** and **post-stroke apathy** are much more frequent. Fatigue is also a central clinical complaint, but a defensible prevalence or time-course estimate is not available in the evidence represented here. Do not fill that gap with a remembered figure. Across all four presentations, diagnosis requires a syndrome-level description, temporal relation to stroke, functional effect, collateral history and a deliberate search for competing explanations.

74	29.3%	34.6%	23
ADULT MANIA CASES REPORTED OVER ABOUT 50 YEARS	POOLED ANXIETY PREVALENCE IN THE FIRST YEAR	MEAN APATHY PREVALENCE AT A 120-DAY MEDIAN	PATIENTS IN THE LONGITUDINAL MANIA COURSE STUDY

3.1 A four-syndrome clinical map

Begin with the patient's dominant change, not with a diagnostic label. Mania is an activated state: mood, speech, thought, sleep and behaviour move together towards excess. Anxiety is organised around threat, uncertainty, bodily alarm or avoidance. Apathy is a disorder of spontaneous goal direction: the patient does less because initiation, interest or emotional engagement has diminished. Fatigue is experienced as excessive effort, low endurance or a need to stop. A patient can therefore be inactive while distressed, inactive while indifferent, or motivated but unable to sustain effort. Those are different clinical problems.

PRESENTATION	CORE BEDSIDE QUESTION	WHAT THE OBSERVER NOTICES	MAIN DISCRIMINATOR
Mania	Has activation increased across several domains?	Accelerated speech, reduced sleep, expansive or irritable behaviour	Excess drive rather than simple agitation
Anxiety	What danger is anticipated, and what is avoided?	Reassurance seeking, vigilance, autonomic distress, reluctance to engage	Fear-linked cognition and behaviour
Apathy	Does action begin without external prompting?	Low initiation, sparse spontaneous activity, reduced interest	Reduced goal direction, not necessarily sadness
Fatigue	Is the wish to act present but effort cannot be sustained?	Slowing, rest seeking, limited endurance	Capacity failure despite intention

MNEMONIC

High drive, high alarm, low drive, low energy

Use that sequence to organise mania, anxiety, apathy and fatigue. It is a starting map, not a substitute for assessing mixed states, cognition, sleep, pain, medication effects and the neurological deficit.

RULE **Describe activation, threat, initiation and endurance separately.** "Not coping" is not a syndrome, and "not participating" does not tell you whether the barrier is fear, absent drive, exhaustion, impaired comprehension or motor disability.

3.2 Post-stroke mania: recognition and diagnosis

Secondary mania may resemble primary mania closely. In a comparative series, elation, pressured speech, flight of ideas, grandiose ideas, insomnia, hallucinations and paranoid delusions occurred with similar frequency in brain-injury-related mania and primary mania when the syndromes were compared. Neurological causation therefore cannot be inferred from an unusual symptom profile. The causal formulation rests instead on the relation to stroke, lesion evidence, age and history, absence or presence of previous mood episodes, exposure to activating substances or medicines, and exclusion of an acute confusional state.

The typical profile reported in the systematic literature was a man with vascular risk, no personal or family psychiatric history and a right-sided cerebral infarct without subcortical atrophy in the reviewed cases. This is a probabilistic profile, not a criterion set. Women, people with psychiatric histories and patients with other lesion patterns still require assessment when the syndrome is convincing. Collateral history is essential because reduced need for sleep, new financial or sexual risk-taking, intrusive sociability and altered premorbid judgement may be clearer to family than to the patient.

Document whether the patient has a full **manic-like episode** or only manic features, and state why stroke is considered causal. The source formulation reserves "with manic features" for presentations that do not meet the full manic syndrome while retaining a stroke-related bipolar formulation. In practice, the note should separate observed behaviour from causal inference: first describe the syndrome, then the temporal and anatomical evidence, then the alternatives considered. This prevents a lesion scan from replacing psychopathology.

TRAP **Writing "right hemisphere equals mania."** Right-sided lesions are an association, not a diagnostic test. The syndrome must still be established clinically, and delirium, disinhibition without mood change, medication effects and primary bipolar illness must be considered.

3.3 Mania: lesion model, course and evidence limits

The exam-salient anatomical contrast is right-sided mania versus the left frontal or basal-ganglia tendency described in post-stroke major depression. In the lesion study, **12 of 17** patients with mania had unilateral right-hemispheric lesions; associated sites included basotemporal and orbitofrontal cortex, frontal white matter, basal ganglia and thalamus across cortical and subcortical lesions. The broad distribution is best understood as a network effect rather than a single "mania centre."

The proposed network is the **right basotemporal-orbitofrontal circuit**, linked to limbic regulation. Direct right basotemporal injury and remote reduction of activity in that region after a subcortical lesion have both been associated with secondary mania. Metabolic imaging found focal right basotemporal hypometabolism in manic patients with right subcortical lesions, supporting a diaschisis account. The conceptual move is important: a structurally distant lesion can disturb mood regulation by disconnecting or suppressing a connected node.

The treatment literature is weak. No randomised controlled treatment study was identified, so apparent efficacy cannot be separated confidently from selection, spontaneous recovery or publication bias in the available evidence. The longitudinal series indicated that most episodes remitted within a few months after post-stroke mania. This should support periodic review of continuing need, not therapeutic passivity during dangerous activation.

PITFALL

Do not treat a new manic syndrome solely from the psychiatric interview. Recheck the neurological course, intercurrent illness, cognition, prescribed and non-prescribed substances, sleep disruption, capacity, vulnerability and immediate behavioural risk. A correct syndrome label can coexist with a wrong causal assumption.

3.4 Post-stroke anxiety: burden, pattern and comorbidity

Anxiety is common enough to require active enquiry, particularly early after stroke. The pooled estimate was highest immediately after the event: 36.7% at 0 to 2 weeks, falling to 24.1% from 2 weeks to 3 months and 23.8% from 3 to 12 months. This pattern supports early screening, but a different meta-analysis suggested a modest rise across later assessment periods. The estimates are

not interchangeable because case definition, setting and measurement method alter who is counted.

That methodological point is visible in the second synthesis: the pooled prevalence was **18% by clinical interview versus 25% by rating scale**. Phobic disorders and generalised anxiety disorder were the most common diagnostic forms in that analysis. Rating scales identify symptom burden; interviews establish whether symptoms form a disorder and whether they are better explained by depression, cognition, communication difficulty or the medical situation. A high scale score is therefore a prompt for formulation, not a self-executing diagnosis.

Anxiety and depression frequently coexist, but neither should be assumed from the other. A review found both **generalised anxiety without depression** and generalised anxiety comorbid with major depression. Setting mattered: community samples and hospital or outpatient samples showed different distributions of anxiety alone and anxiety with depression across the reviewed data. At the bedside, ask separately about fear, worry, avoidance, anhedonia, hopelessness and biological change. Post-stroke depression, including its lesion and treatment evidence, is covered under “Post-stroke depression: epidemiology, lesion correlates, diagnosis and treatment.”

An imaging cohort associated anxiety with right-frontal infarcts even after relevant variables were controlled. This is an association, not a locator. Anxiety can also be sustained psychologically by uncertainty, fear of recurrence, altered bodily sensations and loss of independence. A useful formulation can hold both propositions at once: stroke may disturb circuits involved in emotional regulation, while the meaning and consequences of stroke shape the content of fear.

3.5 Apathy: construct, epidemiology and longitudinal course

Apathy is diminished goal-directed activity arising from reduced motivation. It may be expressed in behaviour, cognition and emotional responsiveness, but the practical bedside sign is lack of self-generated action. The patient may answer correctly, agree that rehabilitation matters and still fail to initiate. Prompting may transiently improve performance because capacity is present but spontaneous mobilisation is weak. This is why an interview conducted entirely through direct questions can miss the syndrome.

Apathy is related to depression but not reducible to it. In the meta-analysis, depression was present in 40.1% of patients with apathy, and the estimated relative risk of depression among apathetic patients was 1.8. The majority of apathetic patients in those data therefore did not have depression. Look for sadness, guilt, hopelessness, negative self-appraisal and distress rather than inferring depression from inactivity alone. Conversely, the absence of visible distress does not make apathy benign.

Course data reinforce the need for repeated assessment. In a longitudinal study, **41.1%** met diagnostic criteria for apathy during the first year after stroke. Mean onset was 3.8 plus or minus 3.3 months, and mean duration was 5.6 plus or minus 2.3 months. Except for a few cases, onset occurred within the first 5 months and the syndrome lasted almost 6 months. A normal early

interview therefore does not close the question, and apparent later “non-compliance” may represent an emerging motivational syndrome.

Older age, depression and cognitive impairment were correlates of apathy, whereas frequency did not differ by sex, stroke type or left versus right hemisphere in the meta-analysis. This non-lateralisation is a useful contrast with the right-sided association described for mania and the right-frontal association described for anxiety. It also warns against using lesion side to dismiss clinically evident apathy.

3.6 Apathy: circuit model and functional importance

The leading anatomical account is disruption of the **anterior cingulate subcortical circuit**. Associated lesions have involved the cingulate region and frontal cortex, ventral striatum, ventral pallidum and magnocellular dorsomedial thalamus. Other reported sites include pons, basal ganglia, dorsal thalamus, posterior limb of the internal capsule and temporal cortex within a distributed circuit model. The shared function is not simple movement but the translation of salience and intention into sustained goal-directed behaviour.

This model explains why apathy can coexist with preserved elementary motor power and why external structure can reveal more ability than spontaneous ward behaviour suggests. It also prevents a moralising interpretation. The person is not necessarily refusing rehabilitation; the neural machinery that assigns value, initiates action and sustains effort may be disrupted. Assessment should therefore compare self-initiated activity with performance after cueing and should obtain observations across settings, not only during a highly structured consultation.

Apathy has prognostic weight. In one cohort, it was a stronger predictor of poor **functional recovery** than depression. A prospective cohort similarly found less recovery in cognition and activities of daily living among apathetic patients during the first year, even after major alternative influences were controlled in the analysis. The clinical implication is direct: recognising apathy changes rehabilitation planning. Goals need to be concrete, initiation may need external scaffolding, progress should be observed rather than inferred from verbal agreement, and caregivers need an explanation that avoids blame.

GOOD TO REMEMBER

Ask the rehabilitation team one question: “What does the patient begin without prompting?” The answer often discriminates apathy more effectively than a polished clinic interview. Then ask what happens after cueing, because improved engagement with structure suggests a target for rehabilitation design.

3.7 Post-stroke fatigue: a disciplined clinical formulation

Post-stroke fatigue should be treated as a real symptom requiring formulation, while resisting unsupported numerical claims. Operationally, ask whether the patient wants to act but experiences effort as excessive, endurance as reduced, or recovery after activity as inadequate. Clarify whether the complaint is mental, physical or both; constant or activity-linked; present on

waking or emerging with exertion; and whether rest restores function. This description is more useful than the word “tired.”

The key distinction from apathy is intention. In fatigue, the patient commonly describes a wish to continue but an inability to sustain output. In apathy, initiation itself is reduced and the lack of activity may not generate equivalent concern. Depression may contribute low energy, but it also requires its own affective and cognitive evidence. Anxiety may consume effort through vigilance and avoidance. Neurological disability may make an ordinary task metabolically and attentively demanding. These formulations can coexist, so forcing the complaint into a single box is often clinically artificial.

Assessment should review the stroke course and functional demands, sleep quality and schedule, pain, nutrition and hydration, intercurrent medical symptoms, medication timing, mood and anxiety, cognition, deconditioning and the balance between activity and rest. Examination and investigations should be directed by the history and neurological context rather than ordered as an undifferentiated panel. Ask the family and therapists whether performance declines predictably, whether the patient can be activated by cueing, and whether apparent fatigue actually follows fear, frustration or cognitive overload.

Management begins by validating the symptom without promising a single cause. Correct remediable contributors, simplify competing demands, pace activity, place important tasks in the patient’s better periods, build rest deliberately into rehabilitation and increase activity according to observed tolerance. Review the response using concrete functional goals. There is no supported prevalence, time-course figure or dedicated treatment trial in the present evidence base, so the academically correct answer is to state the gap rather than manufacture precision.

3.8 Integrated management: locus, focus and modus

Current stroke and liaison-psychiatry guidance should frame care, but the syndrome-specific trial evidence here is limited. Management must remain collaborative with neurology, rehabilitation, general medicine, nursing and caregivers. It should also be phase-sensitive: contain immediate danger first, then restore sleep and participation, then review persistence, recurrence and treatment burden.

Locus. Emergency or inpatient care is appropriate when mania produces dangerous activation, severe behavioural disturbance, inability to cooperate with essential stroke care, marked vulnerability or doubtful decision-making capacity. Medically stable anxiety, apathy and fatigue can often be managed in outpatient or rehabilitation settings, provided risk, function and caregiver capacity are adequate. The locus should change when neurological status, medical stability or behavioural risk changes.

Focus. In the acute phase, target safety, sleep-wake disruption, distress, behavioural containment and participation in essential treatment. Over the short and middle term, target syndrome-specific barriers to rehabilitation: escalating activation in mania, avoidance in anxiety, absent initiation in apathy and limited endurance in fatigue. Longer-term review asks whether the

syndrome has remitted, whether treatment is still needed, whether recurrence risk has changed and whether caregiver burden or social vulnerability persists.

Modus. Combine medical correction, environmental organisation, psychological support, rehabilitation methods, caregiver work and medication when indicated. Use calm structure and reduced stimulation for mania; graded re-engagement and formulation-based psychological work for anxiety; external cueing, scheduled activity and meaningful goals for apathy; and pacing with correction of contributors for fatigue. Preserve autonomy while matching supervision to capacity and risk. For antidepressant pharmacology and drug selection, see the Mood disorders: pharmacotherapy notes.

For mania, case data support a trial of lithium in selected patients, but non-response to lithium and carbamazepine has also been reported, and no randomised treatment evidence exists for post-stroke mania. Choice and monitoring therefore require individual assessment of medical status, interactions, cognition, adherence and rehabilitation goals. Do not copy a primary-bipolar algorithm into a medically complex stroke survivor without reconsidering risk and the likely course.

For anxiety, merged double-blind data comparing nortriptyline with placebo in comorbid anxiety and depression found anxiety ratings improved more rapidly than depressive ratings with nortriptyline. However, the systematic review conclusion was that evidence remained insufficient to guide treatment of post-stroke anxiety. Use that evidence to justify humility, not nihilism: treat clinically important anxiety, define the target, choose an intervention compatible with the patient's medical and cognitive context, and review actual benefit.

For apathy, nortriptyline, bromocriptine, methylphenidate, amantadine, selegiline and tacrine have been used with some success. Nefiracetam at **900 mg/day for post-stroke apathy** outperformed placebo on apathy ratings in a double-blind trial, but it is not approved by the FDA for any indication. These data do not create a routine prescription hierarchy. Off-label treatment requires explicit targets, risk review, informed discussion and withdrawal when meaningful functional benefit is absent.

- Define the target syndrome and the behaviour that will show improvement.
- Record neurological, medical, cognitive, psychological and social contributors.
- Match supervision and treatment setting to risk, capacity and rehabilitation needs.
- Review function with the patient, caregiver and rehabilitation team, not symptoms in isolation.

After stroke, reduced activity is not synonymous with depression: separate fear, loss of initiation and loss of endurance before treating the label.

4 · Post-stroke psychosis, emotional incontinence and denial of deficit

Why these syndromes belong together. After stroke, disturbed reality testing, involuntary emotional display, collapse under challenge and unawareness of disability may all be reported as "behavioural change." That phrase is clinically inadequate. Each phenomenon concerns a different psychological operation: psychosis concerns belief or perception; emotional incontinence concerns control of expression; the catastrophic reaction concerns coping when impaired performance is exposed; and anosognosia concerns awareness of deficit. The marks lie in defining the operation that has failed, then relating it to time course, lesion pattern and function without turning an association into a diagnostic rule.

IN INDIA

Reserve antipsychotic treatment for genuine psychotic risk and use the lowest effective dose, since older stroke patients tolerate these agents poorly and are prone to falls. No specific agent is established for post-stroke psychosis, so choose cautiously and review early.

These distinctions also determine bedside conduct. A fixed false belief requires assessment of its content and consequences. Incongruent laughing or crying requires separation of outward display from inner mood. An outburst during a difficult task may reflect overload rather than sustained hostility. A patient who denies paralysis cannot be assumed to understand safety advice merely because language is fluent. Collateral observation, longitudinal review and direct comparison between what the patient says and does are therefore central throughout this section.

0.4% to 3.1%	6.1 MONTHS	19%	32.3%
REGISTRY FREQUENCY OF POST-STROKE PSYCHOSIS	MEDIAN ONSET AFTER STROKE IN REGISTRY DATA	CATASTROPHIC REACTION IN AN ACUTE-STROKE SURVEY	ANOSOGNOSIA WITH COMPLETE CONTRALATERAL MOTOR IMPAIRMENT

4.1 The syndrome map

The safest opening question is not "Is this psychiatric?" but "What exactly is abnormal?" A syndrome may be apparent in the content of thought, the form of emotional expression, the response to task failure or the appraisal of bodily function. This descriptive step prevents several common category errors. Crying does not automatically establish depressed mood; shouting during testing does not automatically establish a persistent aggressive syndrome; denial of paralysis is not simply poor motivation; and a delusion is not explained merely by the presence of a brain lesion.

SYNDROME	DISTURBED OPERATION	CHARACTERISTIC BEDSIDE CLUE	KEY DISCRIMINATION
Post-stroke psychosis	Reality appraisal	Delusion or hallucination emerging in relation to stroke	Establish psychosis, then assess neurological attribution and competing causes
Emotional incontinence	Control of emotional expression	Involuntary laughing or crying that does not match reported inner feeling	Expression is not equivalent to mood
Catastrophic reaction	Coping under challenge	Brief outburst when a deficit is exposed by a demanding situation	Provoked overload is not the same as sustained aggression
Anosognosia	Awareness of deficit	Statements and behaviour show failure to recognise impairment	Unawareness differs from indifference and from spatial inattention
Anosodiaphoria	Emotional concern about deficit	The deficit is admitted but treated with striking unconcern	Knowledge is present; appropriate concern is reduced

MNEMONIC

Reality, expression, overload, awareness

Use this sequence to localise the clinical problem: reality is altered in psychosis; expression escapes voluntary control in emotional incontinence; overload provokes the catastrophic reaction; awareness fails in anosognosia. Anosodiaphoria sits beside awareness because the deficit is known but not regarded with expected concern.

RULE **Name the disturbed operation before naming the diagnosis.** The same visible behaviour can arise from altered belief, uncontrolled expression, task-related distress or absent insight, and management follows the mechanism suggested by that distinction.

4.2 Post-stroke psychosis: phenotype and epidemiology

Post-stroke psychosis is rare and is identified principally by delusions or hallucinations arising after stroke. Registry estimates vary substantially: hospital studies reported frequencies of 0.4% and 3.1%, with an incidence of **1.1 per 1,000 person-years**. The reported median interval from stroke to onset was 6.1 months. Delayed emergence is therefore entirely compatible with the syndrome; a symptom-free acute admission does not close the later diagnostic window.

The broader systematic review included **76 studies** and found an average age of 66.6 years. Delayed onset was common. **Delusional disorder** was the most frequent psychotic presentation, followed by schizophrenia-like psychosis and mood disorder with psychotic features. Estimated prevalences were 4.67% for delusions and 5.05% for hallucinations; the reported 12-year incidence was 6.7%. These figures come from different study designs and constructs, so they should be presented as complementary estimates rather than forced into a single rate.

Phenomenology still comes before attribution. Describe the belief or perceptual experience in ordinary psychiatric terms: its content, conviction, preoccupation, associated affect, behavioural consequences and effect on care. Ask whether the patient acts on it, whether it concerns staff or family, whether it impairs eating, medication acceptance or rehabilitation, and whether collateral observers confirm a change from baseline. A neurological event does not make psychopathology self-explanatory.

A practical assessment sequence is to establish whether a delusion, hallucination or psychotic mood syndrome is actually present; reconstruct onset in relation to the stroke, recovery setting and later transitions of care; seek collateral evidence about premorbid beliefs, previous episodes, behaviour and functional consequences; and assess immediate risk arising from fear, command experiences, misidentification, refusal or unsafe action.

4.3 Lesion model, causal formulation and prognosis

The recurring anatomical association is the right hemisphere. Reported lesions have involved right frontal, temporal and parietal regions and the right caudate nucleus. In a study of five patients, every patient had a right-hemispheric lesion, mainly in frontoparietal regions. Neuroimaging analyses further associate delusional belief with the **right lateral prefrontal cortex**, either through a lesion in that region or disruption of connectivity to it.

This evidence supports a network formulation rather than a crude "psychosis centre." A focal lesion may disturb appraisal, belief evaluation and the integration of internally generated experience with external evidence. Connectivity findings matter because the decisive functional disruption need not be confined to the visibly damaged tissue. Right-hemispheric injury, particularly involving or disconnecting lateral prefrontal systems, together with seizures and subcortical brain atrophy, has been implicated in pathogenesis. The association increases plausibility; it does not establish causation in an individual.

Causal formulation should therefore integrate syndrome, chronology, neurological evidence and alternatives. Consider an acute confusional state, a mood syndrome with psychotic features, a primary psychotic illness, seizure-related phenomena, substance or medication effects, sensory impairment and a pre-existing cognitive disorder. These are differential labels here, not substitute mini-chapters. The clinician should document which observations support stroke attribution and which uncertainty remains.

TRAP **"Right hemisphere lesion equals post-stroke psychosis."** The laterality and network findings are associations. Diagnosis still requires psychotic phenomenology, a defensible temporal and causal relation, and active exclusion of better explanations.

Prognosis deserves explicit weight. Post-stroke psychosis has been associated with poor functional outcomes and high mortality, adding substantially to the burden of stroke. That association should prompt careful follow-up and coordination, but it should not be converted into deterministic counselling. Functional outcome is shaped by neurological disability, psychiatric symptoms, treatment engagement, environment and support. Record psychiatric and

neurological trajectories separately so improvement in a psychiatric domain is not mistaken for neurological recovery.

4.4 Emotional incontinence in the post-stroke setting

Emotional incontinence denotes involuntary, uncontrollable laughing or crying that may arise spontaneously or after minor provocation and is characteristically unrelated to the patient's reported internal emotional state. Other names include pathological laughter and crying, emotional lability, pathological emotionalism, involuntary emotional expression disorder and pseudobulbar affect. No established DSM-5 diagnostic criteria are provided for the phenomenon.

The core clinical move is to separate display from experience. Observe the episode, then ask how the patient felt before, during and after it. Explore whether the expression was wanted, controllable, congruent with thought content and proportionate to the trigger. Emotional incontinence can be distressing and socially disabling even when the patient denies sustained sadness or mirth. Conversely, genuine depressed mood may coexist with involuntary crying. The visible act alone cannot settle the mood diagnosis.

Post-stroke estimates vary with timing and informant method. Among 508 consecutive patients with ischaemic stroke, pathological emotions affected 9.4% during acute admission and 11.7% three months later. Another study of 516 patients assessed three months after stroke estimated pseudobulbar affect at 7.6%. In 127 patients assessed at the same post-stroke interval, prevalence was **17.9% with caregiver involvement versus 6.3% by patient report alone**.

> **GOOD TO REMEMBER**
>
> Ask the caregiver what the episode looked like, what triggered it and whether it matched the patient's stated feeling. The large informant-related difference in observed prevalence shows why patient report alone can miss involuntary emotional expression after stroke.

This section owns the post-stroke context and recognition of emotional incontinence. Its detailed phenomenology, pathophysiology and treatment are covered under "Pseudobulbar affect: phenomenology, pathophysiology and treatment." Keeping that boundary clear also prevents treatment material from being duplicated or reconstructed from memory.

4.5 Catastrophic reaction: failure under challenge

Catastrophic reaction, first described by Kurt Goldstein, is a provoked emotional outburst containing varying mixtures of anger, frustration, depressed affect, tearfulness, refusal, shouting, swearing, displacement, renunciation, aggression or compensatory boasting. The original account interpreted it as failure of the person to cope when confronted with a serious physical or cognitive defect. Stressful situations such as cognitive testing commonly provoke it, and it usually settles within a few minutes. No formal DSM-5 diagnostic criteria are established.

The time-locked relation to challenge is the bedside clue. The patient may begin a task, encounter evidence of impaired performance and rapidly shift into distress, refusal or anger. The response may look disproportionate if the observer attends only to the immediate test item; it becomes intelligible when understood as exposure of lost capacity. The examiner should stop escalating

demand, acknowledge distress, simplify communication and return later with a graded task. Arguing about the behaviour while the patient is overwhelmed usually supplies more challenge rather than more understanding.

In a survey of 62 consecutive patients with acute stroke using the Catastrophic Reaction Scale, 12 patients, or 19%, showed catastrophic reactions. Of those affected, 9, or 75%, met criteria for major depression and a further 2, or 17%, had minor depression. A larger prospective study assessed 202 consecutive patients within 4 days of stroke; anger occurred in 71 patients, or 35%, and 26 were severely angry. These findings make depressive assessment necessary, but the reaction itself should not be relabelled automatically as depression.

Lesion evidence points towards anterior subcortical systems. Patients with catastrophic reactions had more basal-ganglia lesions than acute-stroke controls. Among depressed patients, those with a catastrophic reaction had more anterior, mainly subcortical lesions: 8 of 9 had subcortical lesions compared with 3 of 9 depressed patients without the reaction. Laterality was not specified in that evidence and should not be invented.

4.6 Anosognosia and anosodiaphoria

Anosognosia, a term introduced by Joseph Babinski, originally referred to lack of awareness of hemiplegia. Its use has extended to unawareness of other post-stroke deficits, including cortical blindness, hemianopia and amnesia. The deficit is behavioural as well as verbal: a patient may deny weakness, attempt an impossible action or plan discharge without accommodating the impairment. A polished explanation of the stroke does not prove awareness if behaviour contradicts it.

Anosodiaphoria is different. Here the patient admits the deficit but appears unconcerned about it. The distinction is between absent knowledge and altered concern. It is also important not to merge anosognosia with hemispatial neglect. Neglect concerns allocation of spatial attention and is covered in the dedicated parietal-lobe syndromes section; anosognosia concerns awareness of the deficit itself. The syndromes may be encountered together, but they are not synonyms.

The evidence base is heterogeneous and timing dependent. A meta-analysis by Lorenzo Pia and colleagues identified 52 studies conducted from 1938 to 2001. Frequency of anosognosia for hemiplegia ranged from 20% to 44%, depending on when assessment occurred relative to stroke. Among patients with complete contralateral motor impairment, prevalence was **32.3%**. Anosognosia is uncommon beyond 3 months after stroke, so repeated reassessment is appropriate rather than treating the acute finding as a fixed personality trait.

Laterality is exam-salient but not absolute. Denial of hemiplegia is associated particularly with right-hemisphere damage producing denial of left-sided paralysis. The underlying functions are not strongly lateralised, yet deficits are more common and more severe after right-hemisphere injury. The correct formulation is therefore “right-sided predominance,” not “right-sided requirement.”

4.7 Bedside assessment and differential reasoning

Triangulate words, behaviour and collateral evidence. Direct questioning alone is especially weak when awareness, expression or coping is the very function under examination. Ask the patient to describe the stroke and its consequences, then observe whether choices and attempted actions incorporate those consequences. Ask relatives and rehabilitation staff about change from baseline, episodes outside the interview and the conditions that trigger them. Repeat assessment because psychosis may emerge after delay, emotional displays may be under-reported, catastrophic reactions are situation dependent and anosognosia often changes with time.

- **For psychosis:** document belief or perception, conviction, distress, action and relation to the neurological course.
- **For emotional incontinence:** compare outward display with reported inner affect, trigger, voluntariness and control.
- **For catastrophic reaction:** reconstruct the task demand, moment of failure, emotional sequence and recovery after the challenge ends.
- **For anosognosia:** compare verbal acknowledgement with practical behaviour, safety decisions and response to demonstration of the deficit.
- **Across syndromes:** assess communication, cognition, sensory impairment, mood, an acute confusional state, medication or substance effects and the possibility of coexisting syndromes.

> **PITFALL**
>
> Do not confront denial by repeatedly forcing proof of failure. Demonstration may be informative, but escalating challenge can provoke distress or a catastrophic reaction and may damage engagement. Use graded observation, collateral information, environmental safeguards and repeated review.

Capacity and awareness must also be kept conceptually separate. A patient may lack awareness of a focal deficit yet reason adequately about an unrelated decision; another may verbally admit weakness while failing to appreciate its practical consequences. Decision-making should therefore be assessed for the actual choice at hand, using communication support and concrete information. The label “poor insight” is too broad to replace this analysis.

4.8 Management framework: locus, focus and modus

Locus. Care should sit where neurological stability, behavioural risk and rehabilitation need can all be managed. Emergency or inpatient assessment is appropriate when there is acute neurological change, severe behavioural disturbance, inability to maintain safety, refusal of essential care or an acute confusional presentation. Medically stable patients may be followed through coordinated stroke, rehabilitation and mental health services. The setting should change when risk, support or neurological status changes.

Focus. In the acute phase, clarify the syndrome, identify urgent mimics, protect the patient and staff, and preserve participation in stroke care. In the short term, reduce distress and dangerous behaviour, explain the syndrome to caregivers, adapt rehabilitation demands and document

functional consequences. Through later recovery, reassess emerging psychosis, persistence of emotional episodes, change in deficit awareness and caregiver burden. Psychiatric, neurological and functional outcomes should be tracked on separate axes.

Modus. Management is multimodal. Use calm communication, predictable routines, correction of reversible contributors, environmental safety, rehabilitation adaptations, caregiver education and psychological support. For catastrophic reactions, grade task difficulty, stop when overload escalates and return after recovery. For anosognosia, build safety around demonstrated behaviour rather than relying on verbal agreement. For emotional incontinence, explain that expression may not represent inner mood and use the dedicated pseudobulbar affect section for mechanism and treatment. For psychosis, assess risk and impairment, coordinate with neurology and consult current stroke and prescribing guidance before patient-specific pharmacological decisions.

No verified agent or dose is available here for post-stroke psychosis, so a specific regimen should not be reconstructed from general psychosis practice. The same restraint applies to formal guideline attribution: where the evidence does not supply a named authority, use current local guidance rather than attaching a remembered label. This is not therapeutic nihilism. It is the correct separation between well-grounded syndrome recognition and patient-specific prescribing that requires a broader evidence base.

The integrated answer is concise in logic even when detailed in execution: identify which psychological operation is disturbed; describe phenomenology before inferring cause; preserve the delayed course and right-hemisphere associations of psychosis; distinguish involuntary expression from mood; recognise a brief challenge-linked catastrophic reaction and its close association with depression; and separate unawareness from unconcern and from neglect. The purpose is not merely accurate naming. It is safer care, better rehabilitation and a formulation that respects what the patient can perceive, control and understand.

> After stroke, distinguish altered reality, involuntary expression, challenge-linked overload and unawareness of deficit; the visible behaviour is not the diagnosis.

5 · Vascular cognitive impairment: spectrum, mechanisms and criteria

The marks lie in separating a vascular spectrum from the old dementia-only stereotype. **Vascular cognitive impairment** is the umbrella for cognitive impairment attributable to pathology of cerebral blood vessels; vascular dementia is its more severe form, not a synonym for the whole spectrum. The vascular injury may be ischaemic or haemorrhagic, although ischaemic disease dominates the literature because it is much more prevalent. A strong answer therefore moves from spectrum to substrate, phenotype and course, then tests whether cognitive impairment, cerebrovascular disease and their association have all been demonstrated.

IN INDIA

The achievable win is prevention: treat hypertension, diabetes and other vascular risk in primary care, and prioritise sustained risk-factor control over any expectation of structured cognitive rehabilitation.

The second source of marks is criteria discipline. Diagnostic frameworks share a causal core but set different evidentiary thresholds. A patient may fit a permissive clinical category yet fail a stricter research definition. The candidate must state each framework on its own terms, use structural imaging as evidence rather than as a label generator, and allow mixed pathology when the clinical and radiological story is not pure. The general dementia syndrome, cognitive instruments and full reversible-cause workup belong in the Dementias and neurocognitive disorders notes.

RULE **Make three links before naming vascular causation.** Establish cognitive impairment, cerebrovascular disease, and a defensible association between them. Different criteria operationalise those links differently, but none permits vascular disease on a scan to stand in for the cognitive syndrome.

5.1 The spectrum: impairment before dementia

The preferred conceptual move is from a categorical endpoint to a continuum. **Vascular cognitive impairment without dementia** names the pre-dementia stage explicitly. It allows recognition of vascular cognitive decline before the functional threshold for the severe syndrome has been crossed. At the other end lies vascular dementia. Between them are clinically important states in which cognition has declined, the vascular contribution is plausible, but the person does not have the severe form.

This terminology changes clinical reasoning. If “vascular dementia” is the only category considered, early executive slowing or attention difficulty may be dismissed until disability becomes conspicuous. The broader term asks a different question: is vascular brain disease already impairing cognition, regardless of whether the endpoint called dementia has been reached? It also makes longitudinal formulation easier because a patient can move along the spectrum as vascular burden, cognitive performance and functional independence change.

CONCEPT	WHAT IT CONTRIBUTES	WHAT IT DOES NOT ESTABLISH BY ITSELF
VCI without dementia	Recognises the pre-dementia end of the vascular cognitive spectrum.	It does not erase the need to associate cognition with vascular disease.
Vascular dementia	Names the more severe end of vascular cognitive impairment.	It should not replace VCI as the umbrella term.
Mixed vascular and Alzheimer pathology	Allows concurrent vascular and degenerative contributions.	A vascular lesion need not be the sole cause of decline.
Vascular depressive disorder	Places late-life affective and executive change beside the cognitive spectrum.	It is not automatically vascular neurocognitive disorder.

A spectrum is not an invitation to diagnose by impression. The breadth lies in severity and presentation, while causal attribution remains disciplined. The clinician still needs evidence that cognition has changed, that cerebrovascular pathology is present, and that they belong in the same formulation. General diagnostic thresholds for major or mild neurocognitive disorder should be taken from the Dementias and neurocognitive disorders notes; this section supplies the vascular lens.

5.2 Substrates, mechanisms and the shape of decline

Vascular cognitive injury is heterogeneous because the vascular lesion may be large-vessel or microvascular, and focal, multifocal or diffuse. These patterns can coexist. The anatomical substrate therefore determines which network fails, while lesion accumulation and recurrence influence the course. Strategic infarction, multi-infarct burden and small-vessel disease are named in the accompanying figure; their detailed anatomy and inherited small-vessel syndromes are covered in the dedicated strategic-infarct, small-vessel disease, post-stroke dementia and CADASIL section.

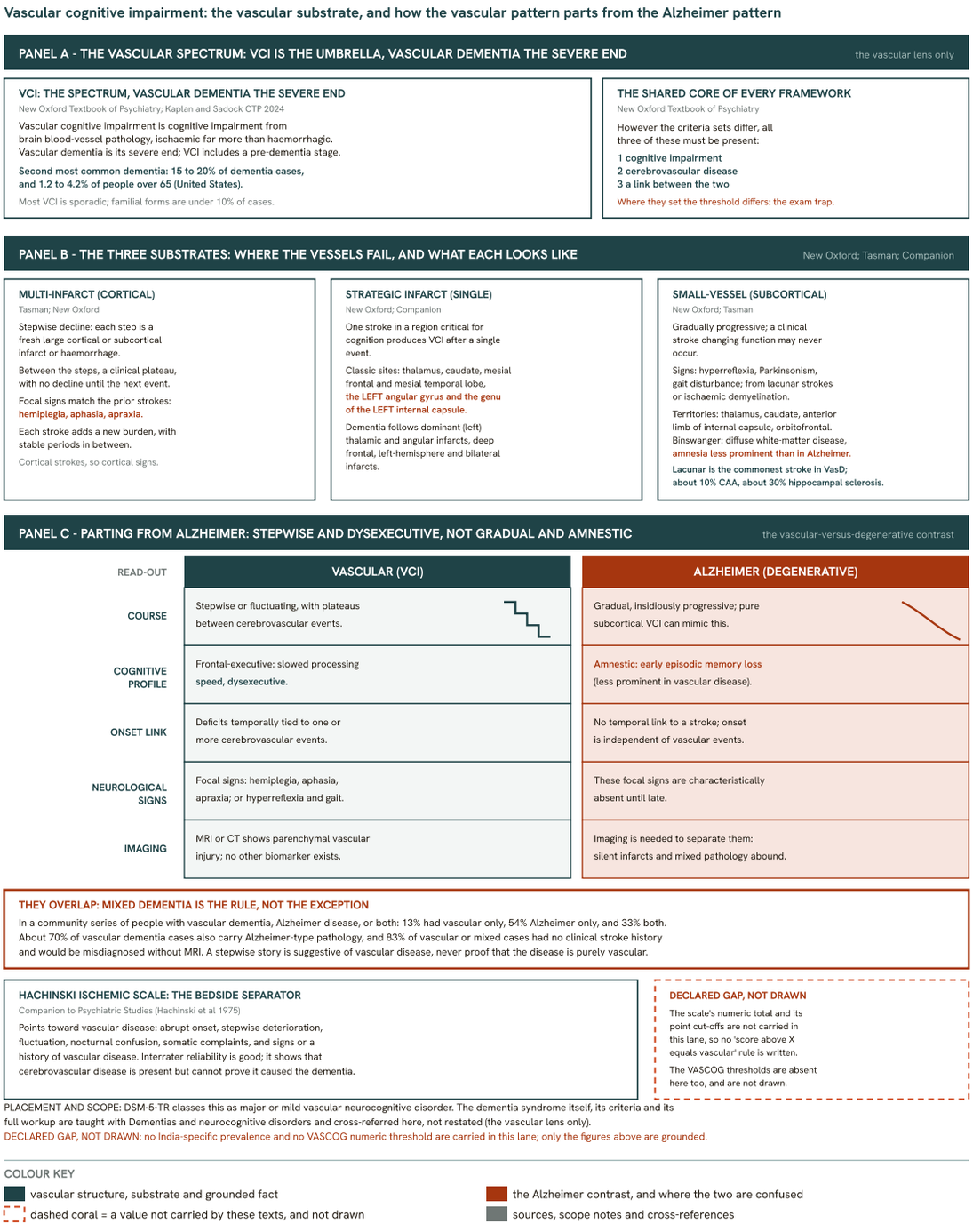


Fig 34.2 **Vascular cognitive impairment, and how it parts from Alzheimer disease.** VCI is the umbrella and vascular dementia its severe end, sitting on three substrates: multi-infarct disease deteriorates stepwise with plateaus and focal signs, a strategic single infarct in a critical site such as the left angular gyrus or the genu of the left internal capsule produces impairment after one event, and small-vessel disease creeps forward with hyperreflexia and gait change and often no clinical stroke. Against Alzheimer disease the vascular pattern reads stepwise and dysexecutive rather than gradual and amnestic, yet mixed pathology is the rule and imaging is what separates them; the Hachinski scale weighs the bedside features while its numeric cut-off is a declared gap. (New Oxford Textbook of Psychiatry; Kaplan and Sadock CTP 2024; Tasman Psychiatry; Companion to Psychiatric Studies; DSM-5-TR.)

The common pathophysiological endpoint is injury to brain parenchyma, reached through several interacting routes. **Hypoperfusion and hypoxia** reduce the delivery needed for network function and tissue survival. Oxidative stress and inflammation promote endothelial dysfunction.

Injury to the vascular control system can then impair autoregulation and neurovascular coupling, weakening the matching of blood flow to neural demand. The point is not to memorise isolated arrows but to see a feed-forward vulnerability: damaged vessels regulate perfusion poorly, and poorly supported neural networks become less resilient.

Course follows burden and distribution rather than one compulsory graph. Many patients with multiple infarctions show **stepwise or fluctuating decline**, with intervening stability and sometimes improvement. Other recognised courses include gradual onset with slow progression, rapid development followed by relative stability, and more complex patterns. Pure subcortical vascular neurocognitive disorder may progress slowly enough to simulate neurocognitive disorder due to Alzheimer disease.

MNEMONIC

V-A-S-C-U-L-A-R

Vessels establish the substrate; **A**ttention and executive function may dominate; **S**teps are classic but not compulsory; **C**ognition must be demonstrated; **U**neven profiles may occur; **L**ink the lesion to the decline; **A**llow mixed pathology; **R**equire a better explanation to be excluded.

5.3 Cognitive phenotype: executive is classic, not universal

The cognitive profile varies with the location and combination of vascular lesions. The classic pattern is **frontal-executive dysfunction**; subcortical ischaemic white-matter disease may make this especially prominent. Reduced processing efficiency, difficulty organising a sequence, poor mental flexibility and impaired goal maintenance can therefore be more revealing than a memory-led interview. This is also why a collateral description such as “he remembers but cannot manage anything” deserves domain-based analysis rather than being dismissed as inconsistency.

Classic does not mean obligatory. Other cognitive patterns occur because lesion location determines the deficit. A focal lesion can produce a sharply patterned loss, multifocal disease can yield an uneven profile, and diffuse disease can create broad inefficiency. The clinician should describe the domains actually affected and resist converting “vascular” into a fixed neuropsychological template.

At assessment, establish change from the person’s previous cognitive and functional baseline, and look specifically for complex attention, processing speed and executive organisation rather than asking only about memory. Reconcile the domain pattern with temporal course, neurological findings and the distribution of vascular injury. Finally, ask whether another brain disease or systemic disorder explains the presentation better.

The vascular-versus-degenerative contrast is therefore probabilistic, not absolute. Stepwise decline with focal neurological change strongly supports a vascular account, but gradual progression does not exclude it. Conversely, an executive profile is compatible with vascular disease but cannot prove its cause. The accompanying figure should be read as a contrast of typical patterns and substrates, not as a binary bedside algorithm.

PITFALL

Do not diagnose vascular cognitive impairment because a report mentions white-matter change. Imaging establishes vascular burden; the diagnosis still requires demonstrated cognitive impairment and a clinically credible association between cognition and vascular disease.

5.4 Epidemiology and the mixed-pathology reality

In United States data, vascular dementia is the second leading cause of dementia after Alzheimer disease. It affects **1.2-4.2% of people older than 65 years** and accounts for **15-20% of dementia cases**. Prevalence rises with age, sex differences remain unclear, and reliable prevalence statistics for VCI below the dementia threshold are lacking. These figures must retain their geographical scope; they are not Indian prevalence estimates.

13%	54%	33%	83%
VASCULAR ONLY	ALZHEIMER ONLY	BOTH PATHOLOGIES	NO STROKE HISTORY IN VASCULAR OR MIXED GROUP

Mixed pathology is not a marginal footnote. In a large community study of people with vascular dementia, Alzheimer disease or their combination, 13% had vascular disease alone, 54% Alzheimer disease alone and 33% both. Among those with vascular or mixed vascular-Alzheimer disease, **83%** had no clinical history of stroke and might have been misdiagnosed without MRI. Separately, some studies report Alzheimer-type pathology in 70% of people with vascular dementia. The exact estimates come from different studies and should not be collapsed into one denominator.

Secular data add a prevention perspective. In the Framingham Heart Study, overall dementia incidence declined over 40 years, falling by 20% every 10 years, while vascular dementia declined faster than Alzheimer disease. The excess risk of dementia after stroke fell from nine times that of people without stroke to **less than twice**. This trend supports the modifiability of population burden without implying that established vascular injury is uniformly reversible.

United States disparity data also warn against treating vascular risk as purely biological. Progression from ischaemic stroke to vascular neurocognitive disorder within 5 years was almost twice as likely among African Americans as among non-Latinx White people and occurred at younger ages. Higher rates of hypertension and diabetes, limited formal education and low socioeconomic status were proposed contributors. The finding is context-specific but illustrates how vascular exposure and social determinants can converge.

5.5 The diagnostic core and the role of imaging

Across frameworks, the shared diagnostic core is stable: **cognitive impairment**, evidence of cerebrovascular disease, and evidence that the vascular disease is associated with the cognitive syndrome. Each pillar answers a different question. Cognitive evidence establishes the clinical target. Vascular evidence establishes a plausible substrate. Association turns coexistence into an aetiological formulation.

Association should be argued, not declared. Useful reasoning includes temporal correspondence with a cerebrovascular event, concordance between lesion distribution and the affected cognitive domains, a course compatible with the observed vascular burden, and the absence of a better explanation. No single feature is universally mandatory across all systems. The weight of each feature depends on the framework being applied.

Structural neuroimaging with MRI or CT has an important diagnostic role. It can demonstrate parenchymal injury, reveal clinically silent vascular burden and help judge whether the distribution is sufficient to account for the deficits. Yet a lesion remains evidence of cerebrovascular disease, not proof of causation.

There are no other established biomarkers for major or mild vascular neurocognitive disorder. Diagnosis therefore remains an integration of history, examination, cognitive assessment and imaging rather than a laboratory confirmation. The general blood investigations, cognitive instruments and reversible-cause assessment are not repeated here; they are covered in the Dementias and neurocognitive disorders notes and the Psychotherapies, clinical assessment, MSE and nosology notes.

GOOD TO REMEMBER

A normal history for overt stroke is not a normal vascular history. Ask about abrupt functional changes and focal symptoms, examine for neurological signs, and inspect imaging before concluding that gradual decline is purely degenerative.

5.6 DSM-5-TR: major or mild vascular neurocognitive disorder

DSM-5-TR major or mild vascular neurocognitive disorder begins by requiring that the criteria for major or mild neurocognitive disorder are met. Vascular aetiology is then suggested through an either-or route: cognitive onset is temporally related to one or more cerebrovascular events, or decline is prominent in complex attention, including processing speed, and frontal-executive function. This alternative phenotype route matters because a documented stroke is not compulsory at this point in the criteria.

The remaining requirements restore causal discipline. There must be cerebrovascular disease evident from history, physical examination and/or neuroimaging that is sufficient to account for the deficits. The presentation must also not be better explained by another brain disease or systemic disorder. Thus, executive decline alone cannot establish the diagnosis, and incidental vascular lesions cannot carry the entire inference.

The probability specifier asks how firmly the vascular attribution is supported:

- Probable vascular neurocognitive disorder may be assigned when clinical criteria are supported by neuroimaging evidence of significant vascular parenchymal injury.
- It may also be probable when the syndrome is temporally related to one or more documented cerebrovascular events.

- A further probable route requires both clinical and genetic evidence of cerebrovascular disease, with CADASIL given as an example; the inherited disorder itself is covered in the dedicated substrate section.
- Possible vascular neurocognitive disorder applies when clinical criteria are met but imaging is unavailable and a temporal relationship to cerebrovascular events is not established.

The logic is deliberately more permissive than criteria designed to create homogeneous research samples. It lets a clinician preserve a vascular hypothesis when the syndrome and phenotype fit but decisive imaging or event linkage is missing. "Possible" records uncertainty; it does not authorise omission of the clinical criteria or the exclusion of better explanations.

5.7 Competing frameworks and the examination trap

FRAMEWORK	THRESHOLD OR EMPHASIS	PRACTICAL CONSEQUENCE
DSM-5-TR	Temporal relation to cerebrovascular events or prominent complex-attention and frontal-executive decline; vascular disease sufficient to explain deficits.	Possible vascular NCD remains available without imaging and without an established temporal link.
NINDS-AIREN research criteria	Clinical and neuroimaging evidence of cerebrovascular disease, plus a temporal relation to dementia.	Stricter case selection; high specificity but low sensitivity was found when clinical criteria sets were compared.
DSM-IV(R)	Dementia with focal neurological signs and symptoms, or aetiologically relevant cerebrovascular disease.	Historical either-or route.
ICD-10	Focal brain damage, aetiologically relevant cerebrovascular disease and an uneven distribution of cognitive deficits.	Adds the patchy cognitive-profile requirement.
Hachinski Ischemic Scale	Abrupt onset, stepwise deterioration, fluctuation, nocturnal confusion, somatic complaints and vascular risks or signs.	May support the presence of significant cerebrovascular disease but cannot demonstrate causation.

TRAP **Do not fuse permissive clinical criteria with strict research criteria.** DSM-5-TR permits possible vascular NCD when imaging is unavailable and no temporal link is established. NINDS-AIREN requires both clinical and imaging evidence plus a temporal relationship. A gradual executive presentation that otherwise meets the clinical criteria can therefore enter the former category yet fail the latter threshold.

The NINDS-AIREN criteria are widely used in research. Their restrictive design reduces false-positive inclusion, but the reported combination of high specificity and low sensitivity means genuine clinical cases may be missed. That trade-off is appropriate for some research questions and too restrictive for others. It is not evidence that one framework has discovered the single correct boundary.

The Hachinski Ischemic Scale is historically important and can show good interrater reliability, but it has not been well validated. Its listed clinical features suggest vascular burden; they do not prove that vascular disease caused the cognitive syndrome. Numeric decision thresholds are intentionally not reproduced because the available source does not establish them.

5.8 Clinical synthesis, differential boundaries and answer structure

A clinically useful formulation proceeds in a fixed sequence. Define the level on the vascular cognitive spectrum. Describe the affected cognitive domains and functional change. Characterise onset and course. Identify neurological and imaging evidence of cerebrovascular disease. Explain the temporal or anatomical association. Then assess competing and coexisting causes, especially mixed vascular and degenerative pathology.

The affective boundary deserves attention. The **vascular depression hypothesis** proposes that small-vessel cerebrovascular disease can damage corticostriatal circuits and create a late-onset depressive subtype. In older adults with progressive small-vessel ischaemic disease, depressive symptoms may occur with psychomotor retardation and executive dysfunction. This “vascular depressive disorder” must be differentiated from vascular neurocognitive disorder, and widely accepted diagnostic criteria remain lacking. Mood symptoms and executive inefficiency can therefore be adjacent manifestations without being interchangeable diagnoses.

The examination answer should close by naming uncertainty precisely:

- “Possible” is an evidentiary category within DSM-5-TR, not a substitute for the clinical syndrome; mixed pathology may be more credible than forcing vascular and Alzheimer disease into mutually exclusive boxes.
- Absent overt stroke does not exclude vascular injury, and gradual progression or memory complaints do not exclude VCI; concordance among phenotype, course and vascular burden remains decisive.

For a long answer, begin with the umbrella definition and pre-dementia spectrum, explain vascular mechanisms and variable course, state the classic but non-universal executive profile, and then compare criteria on shared axes. Give DSM-5-TR as the contemporary clinical cross-map, contrast it explicitly with NINDS-AIREN and historical ICD-10, and end with imaging, mixed pathology and causal restraint. This preserves bedside usefulness as well as research-framework accuracy.

> Vascular cognitive impairment is a spectrum, not a synonym for vascular dementia: prove cognition, prove cerebrovascular disease, link them, and state which criteria threshold you are applying.

6 · Strategic infarct, small-vessel disease, post-stroke dementia and CADASIL

The marks lie in pattern recognition. A candidate must distinguish cognitive decline caused by accumulated large infarcts, a single lesion in a cognitively critical site, diffuse small-vessel injury, and an inherited arteriopathy. The decisive clues are the relation to stroke, the tempo between

events, the neurological examination, the distribution of lesions and the family history. The same final label can conceal very different vascular substrates.

IN INDIA

Base the working assessment of suspected inherited small-vessel disease on the clinical picture and imaging, and refer for confirmatory genetic testing only when the result would change management.

This section develops those substrates rather than restating the general spectrum, mechanisms or diagnostic criteria of vascular cognitive impairment. It also separates post-stroke dementia as an outcome from any one pathological subtype: a patient may decline after repeated infarcts, after one strategically placed infarct, or through an apparently silent subcortical process. The full dementia syndrome and its general workup are covered in the Dementias and neurocognitive disorders notes.

RULE **Read vascular cognitive decline by event, anatomy and tempo.** Ask whether there was one event, recurrent events or no obvious clinical stroke; whether the damage is cortical, strategically focal or subcortical; and whether the course is stepwise with plateaus or gradually progressive.

6.1 A substrate-based map of vascular cognitive decline

The most useful compact classification recognises **three canonical vascular cognitive impairment subtypes**: multi-infarct, strategic-infarct and small-vessel forms. This arrangement is clinically powerful because it links history to anatomy. Multi-infarct disease reflects cumulative burdens, strategic-infarct disease reflects the disproportionate effect of one critical lesion, and small-vessel disease reflects lacunes or ischaemic white-matter injury. Small-vessel disease is also described as subcortical vascular cognitive impairment, and some authors use Binswanger disease for the white-matter form.

An expanded O'Brien classification places these canonical forms alongside hypoperfusion dementia, haemorrhagic dementia, Alzheimer disease with cerebrovascular disease, and hereditary vascular dementia represented by CADASIL. The expanded taxonomy is not a rival to the compact scheme. The compact scheme is a bedside map of common lesion patterns; the expanded scheme reminds the examiner that vascular cognitive syndromes also arise through reduced perfusion, haemorrhage, mixed pathology and inherited vessel disease.

PATTERN	EVENT RELATION	TYPICAL TEMPO	DOMINANT CLINICAL-ANATOMICAL CLUE
Multi-infarct	Repeated large cortical or subcortical infarction or haemorrhage	Stepwise decline with intervening plateaus	Focal deficits such as hemiplegia, aphasia or apraxia
Strategic-infarct	A single stroke may suffice	New impairment follows the critical event	A lesion in a region essential for cognition
Small-vessel	An obvious clinical stroke may never occur	Usually gradual progression	Hyperreflexia, parkinsonism or gait disturbance
Inherited small-vessel	Recurrent infarcts may occur without important conventional vascular risk factors	Progressive course after recurrent events	Family pattern plus characteristic small-vessel syndrome

The categories may overlap in an individual brain. A person with diffuse small-vessel injury can also sustain a strategic infarct, while repeated lacunes can generate either an apparently stepwise or a smoother decline. Classification should therefore identify the dominant mechanism and acknowledge additional burdens rather than force every patient into a pathologically pure box.

6.2 Multi-infarct disease: the step-and-plateau comparator

Multi-infarct dementia provides the classic comparator for every other vascular course. Each fresh large infarction or haemorrhage adds a new cognitive burden, producing a recognisable step down. Between events, the defining feature is relative clinical stability: there is a plateau without continuing between-step deterioration. The history must therefore describe not merely "progressive decline" but the shape of the graph. Ask what changed abruptly, which new neurological deficit appeared with it, and whether function then stabilised.

The neurological examination makes the history coherent. Prior lesions may leave hemiplegia, aphasia or apraxia, with the deficit corresponding to lesion location. Successive events can create a patchwork profile because each stroke injures a different network. The cognitive burden is cumulative, but its components need not worsen in parallel: language may fall after one event, praxis after another, and motor dependence after a later lesion.

A stepwise history should not be accepted from a vague account of "good days and bad days." Ordinary fluctuation, fatigue, intercurrent illness and environmental demands can produce variable performance without new infarction. Conversely, a patient with repeated small deep infarcts may appear to decline gradually when individual steps are clinically subtle. The clinician reconstructs dated losses, associated focal signs and plateaus from collateral history and records rather than inferring the pattern from the word "stroke."

TRAP **Do not equate all vascular cognitive decline with a stepwise course.** Step-and-plateau decline characterises the classic multi-infarct pattern, whereas small-vessel disease is often gradual and may occur without an obvious clinical stroke.

6.3 Strategic infarct: when one small lesion has a large cognitive effect

A **strategic-infarct vascular cognitive syndrome** occurs when a single stroke damages a site critical for cognitive functioning. Lesion volume alone is therefore an inadequate guide. A comparatively circumscribed infarct can disrupt a relay, hub or connecting pathway on which several cognitive operations depend. The examination answer should make the causal logic explicit: one event, one strategically placed lesion, and a cognitive change anatomically concordant with that lesion.

Classic locations include the thalamus, mesial frontal lobe, caudate and mesial temporal lobe. Dominant-hemisphere language and association systems are represented by the left angular gyrus, while a compact disconnection lesion may involve the genu of the left internal capsule. A second source broadens the high-yield pattern to dominant thalamic and angular-gyrus infarcts, bilateral infarcts, deep frontal infarcts and left-hemisphere infarcts. These are classic examples, not an exhaustive atlas; infarcts elsewhere can also be strategic.

Clinical reasoning proceeds from network to deficit. Thalamic or deep frontal injury may disturb initiation, attention, processing and memory organisation; mesial temporal injury may make memory impairment prominent; angular-gyrus injury may produce a cognitively disabling dominant-hemisphere association syndrome. The exact bedside profile depends on the damaged network and coexisting lesions. What matters diagnostically is the disproportion between a limited lesion burden and a major functional cognitive consequence.

MNEMONIC

S-T-E-P

Stroke relation: single, repeated or clinically silent; **T**empo: abrupt, stepwise or gradual; **E**xamination: focal cortical signs or subcortical motor findings; **P**attern of lesions: strategic hub, multiple territories, lacunes or diffuse white matter.

A strategic lesion should be distinguished from a merely incidental infarct. Temporal proximity helps, but anatomical concordance is the stronger argument. The clinician should describe the new cognitive domain failure, show how it altered independent function, relate it to the damaged region and check for competing diffuse or degenerative burdens. The general diagnostic thresholds for vascular cognitive impairment belong to the dedicated vascular cognitive impairment section.

6.4 Small-vessel and lacunar cognitive disease

The absence of a dramatic stroke does not exclude a vascular substrate. In **small-vessel vascular cognitive impairment**, decline is typically gradual and the patient may never report an event that caused an immediate, obvious change in neurological function. The substrate may be lacunar strokes or ischaemic demyelination. This is why an interview centred only on remembered hemiplegic or aphasic attacks misses an important vascular phenotype.

The bedside phenotype is usually subcortical. Examination may reveal hyperreflexia, parkinsonism and gait disturbance. These findings direct attention away from a purely amnestic

account and toward distributed frontal-subcortical disconnection. Cognitive slowing, reduced mental flexibility, impaired initiation and executive inefficiency may dominate functional difficulty even when the patient or family describes the problem simply as "memory loss." The clinician must translate that complaint into domains rather than assume that storage failure is primary.

Lacunar dementia has more than one tempo. It may follow a classic stepwise course accompanied by recognisable lacunar syndromes such as pure motor stroke or pure sensory stroke. Alternatively, cumulative lacunes may produce a more gradual decline. Relevant territories include the thalamus, caudate, anterior limb of the internal capsule and orbitofrontal region. Repeated disruption across these nodes can progressively degrade the circuits that organise goal-directed behaviour.

Binswanger disease refers here to widespread white-matter disease producing progressive dementia. The characteristic cognitive emphasis is slowed thinking and executive deficit, with amnestic impairment generally less prominent. This relative pattern is examinable: it does not mean memory is normal, only that executive slowing is more salient than the memory-led stereotype of dementia.

Location alone cannot always separate strategic from cumulative small-vessel disease. The thalamus and caudate appear among strategic sites, while thalamic, caudate and internal-capsule lacunes can contribute cumulatively to lacunar dementia. The distinction is causal configuration. In the strategic pattern, one lesion is sufficient and the cognitive change is closely linked to that event. In lacunar disease, several small lesions or more diffuse ischaemic injury progressively degrade the circuit. A good formulation therefore states the site and the burden: "strategic thalamic infarct" and "cumulative thalamostriatal lacunar disease" make different claims even though their anatomical vocabulary overlaps.

This distinction also disciplines radiological interpretation. A scan report listing lacunes or white-matter disease does not by itself describe the cognitive syndrome. Imaging must be reconciled with tempo, domains affected, focal signs and functional change. Equally, a small reported lesion should not be dismissed when its location plausibly explains a major new cognitive deficit.

PITFALL

Do not dismiss gait change, parkinsonism or brisk reflexes as unrelated age-associated findings when cognitive slowing is also developing. Their convergence may be the clinical signal that the cognitive syndrome is subcortical and vascular.

6.5 Post-stroke dementia: frequency, delay and determinants

Post-stroke dementia is an outcome category, not a synonym for multi-infarct dementia. Across studies, differences in population, timing and definitions produce a wide range. One source reports 15-30% at 3 months after stroke and 20-25% developing delayed dementia. Another gives a broader **6-32% developing dementia of some type after stroke**. These estimates are broadly compatible when their distinct sampling and definitions are preserved.

15-30%	20-25%	47%	48%
3-MONTH DEMENTIA	DELAYED DEMENTIA	MCI AFTER LACUNAR CVA	COGNITIVE IMPAIRMENT IN CADASIL STUDY

Risk remains elevated long after the index event. A longitudinal study found a **twofold increased risk of dementia over 10 years** after stroke. Cognitive morbidity also extends below the dementia threshold: in a study limited to lacunar ischaemic cerebrovascular accidents without large-vessel stroke, 47% had mild cognitive impairment, which was more common than physical disability. A minor motor outcome must therefore not reassure the clinician that cognition is intact.

The major post-stroke determinants are multi-infarct, recurrent and strategic strokes. Silent infarcts and cerebral white-matter lesions also increase risk. The probability is consequently shaped by cumulative tissue burden, recurrence and location, not simply by whether the presenting stroke seemed large. One pathological study identified lacunar infarcts as the most common stroke type seen in vascular dementia. Additional substrates included cerebral amyloid angiopathy in about 10% of pure vascular dementia and hippocampal sclerosis in almost 30% of vascular dementia, the latter possibly reflecting particular ischaemic vulnerability of hippocampal neurons.

These data justify longitudinal surveillance. Baseline cognitive and functional change should be reconstructed after the acute event, then reviewed when independence, adherence, rehabilitation or caregiver burden changes. Screening alone is not the diagnosis, and a delayed syndrome should not be rejected merely because cognition appeared preserved during the initial admission.

6.6 Risk architecture and prevention reasoning

Major risk factors for mild or major vascular neurocognitive disorder are shared with cerebrovascular disease and stroke. They include hypertension, diabetes, smoking, obesity, high cholesterol, high homocysteine, other atherosclerotic or arteriolosclerotic risks, atrial fibrillation and other states that increase cerebral emboli. Cerebral amyloid angiopathy, through haemorrhage, is also important. The list matters because much of the causal burden is potentially modifiable even when established infarct damage is not reversible.

Prevention reasoning should be layered rather than reduced to a generic instruction to “control vascular risk”:

- Identify the mechanism of the index event and the conditions that make recurrence likely.
- Address modifiable vascular and metabolic risks through coordinated medical care and sustained behavioural change.
- Review smoking, weight, metabolic disease and adherence without treating cognitive impairment as a moral failure.
- Look for silent cumulative burden when gait, executive function or behaviour changes despite no remembered new stroke.

- Use family history and absence of expected conventional risks to decide when an inherited arteriopathy requires consideration.

The psychiatrist's role is not to duplicate stroke medicine. It is to recognise how cognitive impairment undermines risk reduction: disorganisation affects medication use, slowed processing limits education, apathy-like behaviour can reduce activity, and caregiver strain can destabilise routines. Instructions should be simplified, collateral support enlisted with consent, and capacity assessed for the decision at hand. Current stroke guidance should direct mechanism-specific prevention.

GOOD TO REMEMBER

Ask separately about cognitive change, gait and executive function after even a physically mild lacunar event. Physical recovery and cognitive recovery are not interchangeable outcomes.

6.7 CADASIL: inherited subcortical arteriopathy

CADASIL expands to cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy. It is a subcortical small-vessel syndrome characterised by lacunar strokes, migraine and dementia. Most vascular cognitive impairment is sporadic, so the diagnosis becomes especially important when the age, recurrence pattern, migraine history, conventional risk profile and pedigree do not fit ordinary acquired small-vessel disease.

The genetic lesion involves **NOTCH3 on chromosome 19**, with linkage described at 19q12 and autosomal-dominant inheritance. The gene is expressed in vascular smooth-muscle cells and contributes to cell proliferation and differentiation. The resulting arteriopathy affects penetrating vessels: infarcts arise from thickening and fibrosis of small and medium penetrating arterial walls.

The clinical sequence is high yield. The syndrome first appears after the third decade of life, often through repeated migraine with aura. It then progresses over one decade with recurrent cerebral infarcts despite the absence of important conventional cerebrovascular risk factors, culminating in dementia, usually with pseudobulbar palsy. This is a natural-history pattern, not a rigid schedule for every affected person.

Epidemiologically, it is the most common hereditary stroke syndrome, with prevalence **up to 1 in 20,000 adults**. One study found cognitive impairment in 48% of affected individuals. Yet inherited disease remains a minority of vascular dementia overall: familial forms account for **less than 10% of vascular dementia**. Thus, a strong inherited pattern should sharpen investigation, but indiscriminate genetic attribution is poor reasoning.

6.8 Inherited vascular differential and final synthesis

Familial vascular dementia is uncommon but heterogeneous. CADASIL and hereditary cerebral haemorrhage with amyloidosis-Dutch type are among the better studied syndromes. The differential should be organised by vessel pathology, associated organ disease and inheritance rather than memorised as an undifferentiated gene list.

SYNDROME	INHERITANCE OR GENETIC BASIS	VASCULAR-SYSTEM CLUE
Hereditary cerebral haemorrhage with amyloidosis-Dutch type	Autosomal dominant; APP gene	Amyloid in meningocortical microvasculature with recurrent lobar haemorrhage
Familial British dementia with amyloid angiopathy	Autosomal dominant; BRI2, also called ITM2B, on chromosome 13	Amyloid angiopathy within a familial dementia syndrome
HERNS	Autosomal dominant	Endotheliopathy with retinopathy, nephropathy and stroke
Fabry disease	X-linked recessive alpha-galactosidase A deficiency	Lysosomal storage disease with vascular involvement
MELAS	Mitochondrial transfer-RNA mutation; maternal inheritance	Myopathy, encephalopathy, lactic acidosis and stroke-like episodes

Genetic mechanisms also caution against an absolute vascular-degenerative divide. APOE variants influence cerebrovascular risk, while presenilins interact with NOTCH3. This suggests a **mechanistic overlap between Alzheimer and vascular disease** that may contribute to their coexistence in mixed dementia. The inference is overlap, not equivalence: a vascular history does not exclude additional pathology, and a degenerative phenotype does not make vascular lesions irrelevant.

A complete answer therefore begins with substrate, not with a catch-all label. Contrast multi-infarct step-and-plateau decline with the gradual, sometimes clinically silent small-vessel course. Explain why a single infarct can be strategic, name the critical regions with correct laterality, and show that lacunar and white-matter disease favour a slowed executive-subcortical profile. Then quantify post-stroke cognitive risk, identify cumulative and modifiable determinants, and recognise the inherited pattern of migraine with aura, recurrent lacunar events, sparse conventional risk factors and autosomal-dominant transmission.

> One critical infarct, many cumulative infarcts and diffuse small-vessel injury are different routes to vascular cognitive decline; CADASIL is the inherited small-vessel prototype.

Traumatic brain injury and its psychiatric sequelae

7 · Traumatic brain injury: classification and the primary versus secondary injury model

The high-yield distinction is between grading the injury and explaining how it evolves. Traumatic brain injury is not described adequately by a scan label or by whether the patient recalls being unconscious. A defensible formulation uses converging clinical anchors to grade severity, describes the mechanical pattern of damage, and then separates damage produced at impact from processes set in motion afterward. That sequence matters because the severity label, anatomical lesion and biological phase answer different questions.

IN INDIA

Take an explicit head-injury history whenever a psychiatric presentation follows a road crash, even one that seemed minor, since road traffic injury is a common mechanism of traumatic brain injury.

The marks usually sit at the junctions: how the **Glasgow Coma Scale**, loss of consciousness and post-traumatic amnesia are integrated; why the best available score after early stabilisation is more useful than an isolated immediate score; how mild injury can coexist with a structural lesion; and why secondary injury is potentially dynamic even though the initiating trauma has ended. For psychiatrists, this framework also prevents later behavioural or cognitive change from being read as a simple linear consequence of the initial score. The accompanying figure brings the severity bands and the injury cascade together.

13-15	9-12	3-8	24 hours
MILD GCS BAND	MODERATE GCS BAND	SEVERE GCS BAND	BEST-SCORE WINDOW

7.1 Classification is multidimensional

Severity classification begins with the acute physiological disturbance, not with later symptom burden. The conventional scheme combines level of consciousness, duration of unconsciousness and duration of post-traumatic amnesia. These variables overlap but are not interchangeable. A depressed consciousness score is a sampled bedside state, while loss of consciousness and post-traumatic amnesia supply duration anchors. This fragment uses amnesia only to grade severity. Its full phenomenology, assessment and rehabilitation implications belong in the section on cognitive impairment, post-traumatic amnesia and rehabilitation after traumatic brain injury.

An anatomical axis describes the pattern of damage. Trauma may produce local damage beneath an impact, damage opposite the impact, contusions at vulnerable surfaces, or distributed white-matter injury from rotational and shearing forces. A biological-phase axis distinguishes immediate mechanical disruption from delayed physiological and cellular consequences. Thus, a complete description should avoid collapsing severity, morphology and phase into a single adjective.

RULE **Classify severity with the acute clinical anchors, then describe anatomy and phase separately.** A mild, moderate or severe label is not a substitute for naming the lesion pattern, and an anatomical lesion does not retrospectively rewrite every acute severity parameter.

This separation improves clinical reasoning. The initial classification supports communication and broad prognostic framing, whereas morphology explains which tissue was exposed to mechanical stress and the phase model explains why injury can evolve after the accident. Later psychiatric syndromes require their own assessment. Mood, anxiety, trauma-related, psychotic, personality and behavioural sequelae are taught in their dedicated traumatic-brain-injury sections rather than being inferred directly from a severity category.

A retrospective psychiatric assessment should preserve the quality of the evidence. Contemporary emergency records, serial neurological observations, imaging reports and

collateral descriptions may not agree perfectly, and later recall is often least secure around the period being classified. State which anchors were observed, which were reconstructed and which remain unknown. If the score was obtained when verbal performance could not be tested, preserve that limitation. If loss-of-consciousness duration is only estimated, do not convert it into false precision. This discipline is more informative than assigning a confident category from one ambiguous entry, and it leaves later reviewers able to distinguish evidence from inference.

7.2 Glasgow Coma Scale: structure, timing and limitations

The Kaufman's Clinical Neurology for Psychiatrists account describes the scale as measuring three readily observable neurological functions: eye opening, best verbal response and best motor response. Their combined total extends from **3 to 15**, with lower totals indicating poorer neurological function. The score is compact and reproducible enough to support handover, but it should be recorded as a clinical observation rather than treated as an explanation of the injury.

The severity bands are 13 to 15 for mild injury, 9 to 12 for moderate injury, and 3 to 8 for severe injury. Timing matters. The best score in the first **24 hours after injury** is more useful than the score obtained immediately after injury. The reason is interpretive: a single earliest observation can reflect the unstable circumstances surrounding trauma and resuscitation, while the best documented early score more usefully represents the patient's neurological capacity during that period.

The scale also has important limits. It is not readily applicable after cerebral hypoxia. Intubation prevents a verbal response, so a total that is quoted without describing this constraint may look more precise than it is. The correct response is not to discard the assessment but to record what could actually be tested, identify the reason a component is unavailable, and interpret the total in clinical context.

PITFALL

Do not copy an undocumented Glasgow Coma Scale score from a referral and let it dominate the formulation. Establish when it was obtained, whether verbal testing was possible, whether cerebral hypoxia limits interpretation, and whether a better score was documented during the early post-injury window.

7.3 The integrated mild, moderate and severe bands

The classic classification places loss of consciousness, post-traumatic amnesia and the Glasgow Coma Scale side by side. The table should be read across each row. A patient is not graded intelligently by searching for whichever isolated value produces the most dramatic label; discordant anchors should be documented, explained where possible and interpreted with the rest of the injury evidence.

SEVERITY	DURATION OF UNCONSCIOUSNESS	GLASGOW COMA SCALE	POST-TRAUMATIC AMNESIA	INTERPRETIVE POINT
Mild	Less than 30 minutes	13-15	Less than 24 hours	The label grades the acute injury; it does not mean that every later complaint will be minor
Moderate	30 minutes to 24 hours	9-12	24 hours to one week	Converging anchors strengthen the classification; disagreement requires clinical interpretation
Severe	More than 24 hours	3-8	More than one week	This is the severe row in the classic three-band scheme, not the alternative definition discussed below

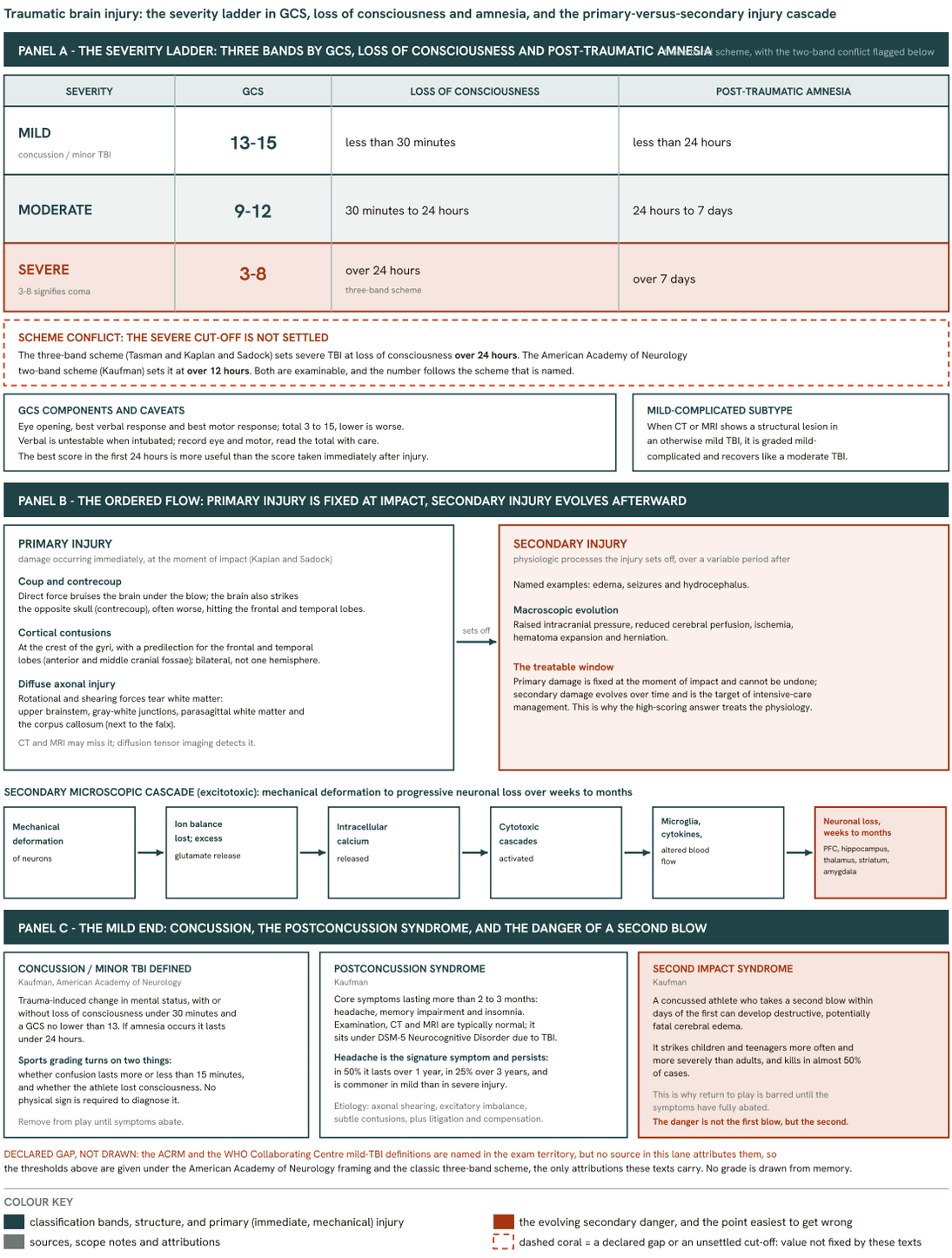


Fig 34.3 Traumatic brain injury: the severity ladder and the primary-versus-secondary cascade. The three-band scheme grades severity by GCS (13-15, 9-12, 3-8) with loss of consciousness under 30 minutes, up to 24 hours, or over 24 hours, while the American Academy of Neurology two-band scheme calls loss of consciousness over 12 hours severe, so the cut-off follows the scheme named. Primary injury (coup and contrecoup, contusions, diffuse axonal injury) is fixed at impact; secondary injury (edema, raised pressure, ischemia and the excitotoxic cascade) evolves afterward and is the treatable window. (Kaplan and Sadock, CTP 2024; Kaufman's Clinical Neurology for Psychiatrists; Tasman Psychiatry.)

Each anchor has a distinct vulnerability. The consciousness interval may be uncertain when the event was unwitnessed or documentation was delayed. Amnesia is partly reconstructed from the patient's later account and collateral history. The Glasgow Coma Scale is a sampled examination

affected by testability and timing. Using the anchors together therefore adds structure without pretending that uncertainty has disappeared.

When the anchors disagree, first check whether they refer to the same clinical period. An immediate score and a later best score are not rival measurements of an unchanging state. Next ask whether a component was untestable and whether the time intervals came from direct observation or retrospective estimation. Then report the discordance rather than manufacturing a neat answer. The classification is a disciplined summary of evidence, not a mathematical rule that makes missing or incompatible observations vanish. Imaging can add morphology, as in mild-complicated injury, but it does not erase the historical consciousness and amnesia data.

MNEMONIC

CAP

Consciousness duration, **A**mnesia duration and **P**erformance on the Glasgow Coma Scale form the severity spine. Then add anatomy and phase. CAP is a retrieval aid, not a rule for forcing discordant data into a single category.

7.4 Mild injury, concussion and mild-complicated injury

Under the American Academy of Neurology framing reported by Kaufman, **mild traumatic brain injury** is a trauma-induced alteration in mental status that may occur with or without loss of consciousness. The alteration typically consists of confusion and amnesia lasting seconds to minutes, without focal neurological signs such as hemiparesis, cranial-nerve abnormality or incoordination. Physicians may use **concussion** for mild traumatic brain injury. This conceptual definition complements the numerical mild band without making loss of consciousness compulsory.

The term mild describes initial severity. It must not be used as shorthand for no brain disturbance, no need for observation, or guaranteed absence of later symptoms. Conversely, later nonspecific symptoms do not by themselves reconstruct the acute injury as a concussion. The full post-concussion syndrome, its persistent symptom pattern and its management belong in the section on mild traumatic brain injury, concussion and post-concussion syndrome.

Imaging supplies an additional axis. Some patients who otherwise meet mild traumatic brain injury criteria have a structural lesion demonstrated by CT or MRI. This is **mild-complicated traumatic brain injury**. Its recovery trajectory resembles that of moderate injury, which leads some classifications to place the subtype with moderate traumatic brain injury. The crucial reasoning is that a mild clinical band and a positive structural study are not mutually exclusive. One describes the acute physiological severity anchors; the other demonstrates morphology.

GOOD TO REMEMBER

Write the formulation in layers: acute severity band, available Glasgow Coma Scale timing and limitations, duration anchors, and imaging status. “Mild-complicated” is precisely the situation in which reducing the case to either “mild” or “scan positive” loses useful information.

7.5 Severe injury: the threshold conflict

There is no honest way to print one loss-of-consciousness threshold for severe traumatic brain injury without naming the scheme. In the classic three-band classification, severe injury includes unconsciousness for **more than 24 hours**, post-traumatic amnesia for more than 7 days, and a Glasgow Coma Scale score of 3 to 8. These are the severe values in the integrated mild, moderate and severe table.

A different two-category neurological framing reported by Kaufman defines **severe traumatic brain injury** as prolonged post-traumatic loss of consciousness for **more than 12 hours** together with radiographic evidence of injury to the brain, skull or intracranial blood vessels. That definition changes more than the threshold. It also includes an imaging requirement and belongs to a different classificatory frame.

TRAP **Do not merge "more than 12 hours" and "more than 24 hours" into one supposedly universal severe-TBI cut-off.** The former belongs to a two-category definition that also requires radiographic injury; the latter belongs to the classic three-band loss-of-consciousness table. State the scheme, then state its threshold.

This conflict is an example of why criteria must travel with their qualifiers. If an examination asks for the mild, moderate and severe table, give the integrated three-band values. If discussing the alternative neurological definition, identify its paired radiographic requirement. Do not average the thresholds, silently choose one, or imply that the sources describe the same construct with casual wording differences.

7.6 Primary injury: impact, coup, contrecoup and contusion

Primary brain injury is the tissue damage occurring immediately at the time of trauma. It is the direct mechanical event. The pattern depends on how the head and brain move, where force is transmitted and which tissue interfaces bear deformation. This category includes local impact damage as well as distributed injury from rotational and tensile-shearing forces. Calling it primary is temporal and mechanistic; it does not mean clinically unimportant or necessarily focal.

A direct blow can disrupt brain tissue beneath the site of impact, producing a **coup injury**. The same trauma can propel the brain against the opposite internal surface of the skull, producing a **contrecoup injury**. Contrecoup damage frequently exceeds coup damage. The frontal and temporal lobes are especially vulnerable because their anterior surfaces meet the sharp contours of the anterior and middle cranial fossae.

Traumatic cerebral contusions may occur at the crests of gyri and show a predilection for frontal and temporal regions housed in the anterior and middle cranial fossae. This anatomical pattern helps explain why apparently remote impact can coexist with damage at the brain's basal and anterior surfaces. It also cautions against assuming that the site of the external blow identifies the only injured region.

- **At impact:** ask where force entered, but also consider movement of the brain within the skull.

- **Across the skull:** distinguish tissue beneath the blow from damage at the opposite internal surface.
- **At vulnerable surfaces:** remember the frontal-temporal predilection of contusions.

7.7 Traumatic axonal injury: distributed mechanical damage

Traumatic axonal injury, also called diffuse axonal injury, consists of multifocal white-matter damage produced by rotational and tensile-shearing forces. “Diffuse” should not be read as uniform damage to every part of the brain. The defining idea is distributed, multifocal axonal injury created by mechanical deformation, often involving bilateral or midline structures rather than a single cortical impact site.

Commonly injured regions include the upper brainstem and diencephalic structures, grey-white matter junctions, parasagittal cerebral white matter and the corpus callosum. The corpus callosum is particularly sensitive because it lies near the falx. This distribution follows the physics of tissues moving differently at interfaces and around relatively fixed structures. It is therefore conceptually distinct from a coup contusion, even though the mechanisms can coexist in the same traumatic event.

The distinction between focal impact injury and distributed axonal injury is useful to psychiatrists because neither the external wound nor a single focal lesion necessarily captures the functional network disturbance. It does not license a retrospective microscopic diagnosis from symptoms alone. The mechanism must remain an anatomically plausible component of the injury formulation, supported by the available neurological assessment and investigations.

A concise mechanical classification can therefore be retained as follows:

- **Local impact pattern:** coup injury, contrecoup injury and surface contusion.
- **Distributed shearing pattern:** multifocal axonal injury at characteristic white-matter and midline regions.

7.8 Secondary injury: physiological and cellular amplification

The accident ends; the biology does not necessarily stop. Secondary brain injury refers to physiological processes initiated by trauma that unfold over a variable period afterward. Examples include oedema, seizures and hydrocephalus. The wider cascade includes raised intracranial pressure, reduced cerebral perfusion, ischaemia, expansion of a haematoma and herniation. These are consequences of the original insult, but they are not identical to the instantaneous mechanical damage.

At cellular level, mechanical deformation disrupts ion homeostasis, drives excessive release of glutamate and other neurotransmitters, releases intracellular calcium and activates cytotoxic cascades. Delayed processes also include microglial activation, inflammatory cytokine release and altered cerebral blood flow. These mechanisms link an immediate physical event to continuing metabolic stress, inflammation, impaired perfusion and further neuronal injury.

Damage can continue over weeks to months in vulnerable regions including prefrontal cortex, hippocampus, thalamus, striatum, amygdala and forebrain nuclei. This prolonged biological

course does not mean that every later symptom proves ongoing tissue destruction. It means that a purely static model of trauma is incomplete. Clinical change after injury requires reassessment of neurological state, complications, medication and substance effects, sleep, pain, psychiatric syndromes and environmental demands rather than automatic attribution to either the original impact or the secondary cascade.

The primary-secondary distinction also prevents a common conceptual error: treating secondary injury as a second accident. It is an evolving consequence of the first insult. Primary damage is mechanically delivered at impact; secondary damage is mediated through later physiological and cellular processes. Raised intracranial pressure, hydrocephalus and post-injury seizures are named here as parts of that cascade, while their detailed neuropsychiatric assessment belongs in the dedicated section on those complications. Rehabilitation and pharmacological management likewise belong in their respective traumatic-brain-injury sections.

For examination writing, the causal chain should be explicit. Begin with deformation at impact, identify the focal or distributed mechanical pattern, and then show how disturbed perfusion, pressure, excitatory signalling, calcium handling and inflammation can amplify injury afterward. Do not list these as unrelated complications. Their teaching value lies in the sequence from mechanical force to physiological instability and cellular toxicity. Equally, do not imply that every secondary process occurs in every patient. The model supplies a framework for surveillance and interpretation; the individual formulation depends on observed clinical and investigative evidence.

> Grade traumatic brain injury with Glasgow Coma Scale, loss of consciousness and post-traumatic amnesia, then separate immediate mechanical primary injury from the evolving physiological and cellular processes of secondary injury.

8 · Mild traumatic brain injury, concussion and the post-concussion syndrome

Mild injury does not mean trivial injury, and a normal scan does not mean an imaginary syndrome. **Mild traumatic brain injury**, often discussed clinically as concussion, is defined by a trauma-related change in mental status within specified severity limits. The examination marks lie in separating what qualifies as mild injury, what makes persistent symptoms clinically coherent, and why symptom burden may not track conventional injury-severity markers.

> **IN INDIA**
>
> Give the patient and family clear written advice on rest, staged return and the danger of a second blow, and do not assume that trained sideline supervision is in place.

The psychiatrist commonly enters after the emergency narrative has faded. The patient may now be worried by headache, poor memory or disturbed sleep; the family may be uncertain whether recovery is occurring; and routine examination or imaging may be unrevealing. A sound answer neither dismisses symptoms nor converts every complaint into proof of structural damage. It

reconstructs the injury, defines the time course, recognises the characteristic symptom pattern, searches for competing explanations, and plans review according to function and risk.

50%	25%	Usually normal	Almost 50%
HEADACHE BEYOND 1 YEAR	HEADACHE BEYOND 3 YEARS	EXAMINATION AND IMAGING	SECOND-IMPACT MORTALITY

8.1 Operational definition of mild traumatic brain injury

The operational definition begins with **trauma-induced alteration in mental status**. Loss of consciousness may occur, but it is not mandatory. When consciousness is impaired, the duration remains **less than 30 minutes**. The **Glasgow Coma Scale** score is **no lower than 13**. If amnesia occurs, it lasts **less than 24 hours**. These limits identify the mild end of traumatic brain injury; they do not predict that every later symptom will be mild.

This definition is easy to distort in an examination answer. Concussion is not synonymous with being knocked unconscious. The positive requirement is an injury-related alteration in mental status; impaired consciousness is an optional feature constrained by duration. Likewise, the amnesia limit is part of severity placement, not an invitation to teach the broader construct of post-traumatic amnesia here. The full severity classification and the primary versus secondary injury model belong in the section on traumatic brain injury classification and injury mechanisms; the full post-traumatic amnesia construct belongs with cognitive impairment and rehabilitation after traumatic brain injury.

RULE **Define concussion by altered mental status after trauma, not by mandatory loss of consciousness.** Then state the consciousness, Glasgow Coma Scale and amnesia limits without turning a mild-severity label into a prognosis.

The operational band performs a classificatory job. It gives clinicians a common language for the initial injury and helps organise acute communication. It cannot, by itself, settle whether a later headache is genuine, whether cognitive inefficiency is functionally important, or how long recovery will take. That distinction between classification and outcome is the conceptual hinge of this topic.

8.2 Clinical assessment after the injury

Assessment should begin with a chronology rather than a symptom inventory. Establish the injury event, the immediate alteration in mental status, any impairment of consciousness, any amnesia, and the evolution of complaints since then. The clinician is trying to connect a present syndrome to a plausible index injury while remaining open to complications and alternative causes. A vague history of “head injury sometime earlier” is insufficient; an equally vague declaration that the scan was normal is not a rebuttal.

A focused assessment can be organised around a short clinical sequence:

- **Reconstruct the index event:** clarify the mental-status change and document the available severity anchors without inferring details that were never observed.

- **Describe the present complaints:** ask about headache, memory difficulty and insomnia, then translate each complaint into its effect on work, study, self-care, relationships and ordinary routines.
- **Establish the trajectory:** determine what improved, what persisted and what newly appeared, because a changing pattern deserves fresh clinical explanation rather than automatic attribution to concussion.
- **Seek corroboration:** use records and collateral history where available, especially when the patient cannot confidently reconstruct the immediate post-injury period.

The neurological and mental-state examinations answer different questions. The neurological examination searches for evidence that would redirect the case beyond an uncomplicated mild-injury formulation. The mental-state examination characterises distress, attention during the interview, confidence in memory, sleep-related preoccupation, mood and the meaning the patient assigns to symptoms. Neither examination should be used as a credibility test. Observable performance and subjective difficulty may diverge without proving deception or absence of impairment.

GOOD TO REMEMBER

Document function alongside symptoms. “Memory is poor” is diagnostically weak; examples of lost task efficiency, repeated errors, abandoned routines or reduced tolerance for ordinary cognitive load make the complaint assessable over time without pretending that bedside observation alone measures its cause.

If the course is atypical, worsening or clinically unstable, do not protect the original label. Reassess the patient and widen the medical differential through the appropriate emergency or neurological pathway. Detailed imaging decision rules and red-flag lists should be applied from current head-injury guidance and the clinical setting rather than reconstructed from memory.

8.3 Post-concussion syndrome: the persistent clinical pattern

Kaufman's Clinical Neurology for Psychiatrists notes that **post-concussion syndrome** lacks a strict definition. Neurologists base the diagnosis on persistence of one or more core symptoms, especially **headache, memory impairment and insomnia**, for **more than 2 to 3 months**. The formulation therefore combines a preceding mild traumatic brain injury, a recognisable symptom pattern and persistence beyond the expected early period. It is not established by duration alone.

The term is useful when it organises follow-up, but it can mislead if treated as a unitary lesion with a single biomarker. The symptoms are subjective and nonspecific, and routine assessment often supplies no positive structural marker. This is a clinical diagnosis built from history, symptom pattern, course and exclusion of better explanations, not a radiological diagnosis waiting for a visible lesion. The typical examination and imaging profile is set out in the comparison below.

CLINICAL AXIS	MILD TBI OR CONCUSSION	PERSISTENT POST-CONCUSSION PRESENTATION	INTERPRETIVE CAUTION
Anchor	Trauma-related alteration in mental status within mild-injury limits	A prior concussion followed by continuing complaints	Do not diagnose concussion from later nonspecific symptoms alone
Consciousness	Impairment may be present or absent	Historical feature, not a requirement for current symptom validity	Do not demand a blackout
Core symptom anchor	Immediate mental-status alteration	Headache, memory impairment or insomnia	The symptoms remain nonspecific and require clinical formulation
Examination and imaging	Used to assess the injury and competing pathology	Physical examination, neurological examination, CT and MRI are typically normal	Normal findings neither prove nor disprove the subjective burden
Severity relation	Classifies the initial injury	Symptoms do not correlate with Glasgow Coma Scale score or amnesia duration	Initial severity is not a symptom meter

TRAP **Do not write "normal CT or MRI excludes post-concussion syndrome."** Routine structural studies and examination are typically normal; their principal value is assessing other pathology, not validating or invalidating every persistent complaint.

Diagnostic discipline requires a balanced stance. Accept the patient's report as clinically relevant, define its functional consequences, and still examine for other neurological, psychiatric, sleep-related and contextual explanations. This is not scepticism. It is the ordinary causal work required whenever a common, nonspecific symptom follows a memorable event.

8.4 Post-concussion headache

Post-concussion headache is the signature and most common post-concussion symptom in the clinical account. Its persistence is clinically important, as shown in the accompanying statistics strip. The same account reports that post-concussion headache occurs more often after mild injury than after moderate or severe injury. This counterintuitive pattern is an examination favourite because it blocks the lazy assumption that symptom frequency must rise in a straight line with injury severity.

Headache should be described, not merely named. Establish its relation to the injury, subsequent course, functional effect and associated concerns. Then examine the patient and decide whether the present pattern remains compatible with the working post-concussion formulation or demands renewed investigation. The label "post-concussion" is an aetiological hypothesis. It must not stop the clinician from reconsidering causation when the presentation changes.

The persistence figures also change communication. A clinician who promises rapid disappearance may unintentionally intensify alarm when symptoms continue. Equally, presenting persistence as inevitable encourages passivity and catastrophising. The better message is conditional: prolonged headache is recognised, its duration does not map neatly onto initial severity, and management should remain active, symptom-focused and function-oriented while alternative explanations are reviewed when appropriate.

PITFALL

Do not use injury severity to decide whether headache is believable. The clinical pattern is paradoxical: headache is reported more frequently after mild injury than after more severe injury, and persistent symptoms do not correlate neatly with the usual initial severity parameters.

Specific headache phenotyping, acute investigation and treatment should follow current headache and head-injury guidance and the patient's medical context. In an examination answer, it is safer and more accurate to state the management principles than to invent a familiar dose.

8.5 Why symptoms persist: a biopsychosocial formulation

Proposed neurological explanations include **diffuse axonal shearing**, excitatory neurotransmitter imbalance and subtle cerebral contusions. These mechanisms explain why a conventional structural study may be unrevealing despite a biologically plausible injury. They remain proposed explanations, not routine bedside measurements, and should not be presented as if a normal scan has demonstrated microscopic damage in an individual patient.

Prolonged symptoms are also associated with psychiatric and socioeconomic factors, including litigation, compensation, premorbid intellectual characteristics and premorbid personality abnormalities. The correct frame is **biopsychosocial formulation**: neurological injury, symptom interpretation, emotional response, prior vulnerabilities, environmental demands and social contingencies can interact. This formulation places psychiatric and socioeconomic associations alongside neurological injury rather than beneath it.

This requires careful language. Compensation or litigation is not a synonym for fabrication. Premorbid personality is not a moral defect. Psychiatric contribution does not make a symptom unreal. Each factor is a potential modifier of persistence, distress, disability or help-seeking and must be assessed on its own evidence. A formulation should state what is observed, what is inferred and what remains uncertain.

MNEMONIC

MIND

Mental-status alteration defines the injury; **I**njury mechanisms may be subtle; **N**ormal examination or imaging is common in the persistent syndrome; **D**uration and disability require a biopsychosocial formulation. The mnemonic preserves the logic without claiming a single cause.

The absence of correlation with estimated impact force, Glasgow Coma Scale score or amnesia duration is especially important. It means that conventional severity anchors cannot adjudicate the later symptom experience. Their job was to classify the acute injury. The later task is to explain persistence and functional impact. Confusing these jobs produces either overmedicalisation or dismissal.

8.6 Sports concussion and second-impact risk

Sports concussion grading in the clinical account uses the duration of confusion and the presence or absence of loss of consciousness. Confusion is separated by a 15-minute threshold, while loss of consciousness is recorded as present or absent. Physical symptoms or signs are not required to diagnose concussion in the injured athlete. This again reinforces the central principle that concussion is a disturbance of brain function, not a diagnosis that waits for a visible external sign.

AAN guidance recommends removing a concussed athlete from play immediately; the athlete should not return merely because they insist they feel able to continue. The athlete remains out until symptoms have abated and a licensed professional has evaluated recovery. The purpose is not bureaucratic caution. It is prevention of another injury while the brain remains vulnerable.

Second impact syndrome describes a further blow received within days of the original concussion, followed by destructive and potentially fatal cerebral oedema. Children and teenagers are affected more frequently and more severely than adults. Reported mortality is strikingly high, as shown in the accompanying statistics strip. This is the high-stakes reason why apparent determination, competitive pressure or absence of obvious physical signs must never be allowed to substitute for recovery and professional clearance.

The older grading framework is worth knowing because it appears in textbook and examination language, but bedside action should follow current sport-specific guidance. Take any graduated return-to-play protocol, stage intervals and exercise thresholds directly from that guidance rather than inventing them. The non-negotiable principle is to remove the athlete from play, allow symptoms to resolve, obtain professional assessment and prevent repeat injury during vulnerability.

8.7 Diagnostic formulation and communication

A defensible formulation has layers. Begin with whether the index event meets the mild-TBI definition. Then describe the present symptom pattern and its duration. Record examination and imaging findings without treating normality as a verdict on credibility. Identify functional impairment and contextual modifiers. Finally, state competing explanations and the plan for review. This structure keeps diagnosis provisional enough to remain safe and specific enough to guide care.

The clinician should avoid polarised explanations. “It is all brain damage” overstates what routine assessment can prove. “It is only stress” erases the injury and usually damages trust. A more accurate explanation is that concussion is a genuine functional disturbance after trauma, persistent symptoms can occur despite normal routine investigations, and biological,

psychological and social factors may all influence recovery. This allows uncertainty without abandonment.

Separate symptom, impairment and disability in ordinary language. A symptom is what the patient experiences; impairment is the difficulty demonstrated in a particular function; disability is the restriction that emerges when those difficulties meet the person's real-world demands. The distinctions prevent a single complaint from carrying the entire causal argument. They also make follow-up meaningful because improvement may occur in function before complete symptom disappearance, or symptoms may remain while participation expands.

The broader psychiatric sequelae of traumatic brain injury, including mood, anxiety, trauma-related and psychotic presentations, are taught in the dedicated psychiatric-sequelae section. Personality change, aggression and disinhibition have their own section. Cognitive rehabilitation and chronic traumatic encephalopathy also belong elsewhere, as does pharmacological management in TBI psychiatry. Naming these possibilities is necessary; reproducing their criteria or treatments here would blur ownership and weaken the concussion answer.

A clinical letter should therefore communicate the injury basis, current symptoms, objective findings, functional consequences, uncertainty and safety plan. It should avoid implying malingering from normal imaging, avoid promising a fixed recovery date, and avoid using the mild label to minimise present disability. Precise neutral documentation is particularly important when occupational, educational, sport or compensation decisions depend on it.

8.8 Management principles: LOCUS, FOCUS and MODUS

Management is organised by current risk and function, not by the reassuring adjective "mild".

LOCUS: emergency or inpatient reassessment is appropriate when the patient is unstable or the course raises concern for pathology beyond an uncomplicated concussion. A stable patient with persistent symptoms can usually be followed in an outpatient pathway with access to medical, neurological, psychiatric and rehabilitation expertise as the formulation requires. Sports settings add a firm removal-from-play boundary and professional clearance before return.

FOCUS: in the acute phase, protect the patient from repeat injury, reassess evolving symptoms and communicate uncertainty clearly. In the short term, track headache, memory difficulty, insomnia and functional tolerance rather than relying on a global statement that the patient is "better". In the middle phase, the target becomes restoration of ordinary activity without interpreting every fluctuation as fresh damage. In the long term, persistent disability requires renewed formulation, attention to psychiatric and socioeconomic modifiers, and review for alternative explanations.

MODUS: treatment is multimodal. Education should validate the injury while preventing catastrophic interpretations. Psychological work can address fear, symptom monitoring, loss of confidence and avoidance when these maintain disability. Social intervention may include coordinated communication with family, educational or occupational systems and sport personnel. Rehabilitation input should be selected according to demonstrated functional need. Medicines, when considered for individual symptoms, belong to the pharmacological-

management section and must follow current guidance, comorbidity, adverse-effect and interaction review.

Follow-up should compare the patient with their own earlier state. Review the symptom pattern, daily participation, sleep, confidence, distress and any new clinical concern. If the working formulation stops explaining the course, reopen it. Persistent post-concussion symptoms are not a licence for endless passive observation; neither are they a licence for escalating unproven interventions. The goal is safe recovery of function with proportionate investigation and treatment.

> Concussion is defined by trauma-related altered mental status, not obligatory loss of consciousness; persistent symptoms can be real despite normal routine examination and imaging, and severity markers do not measure later symptom burden.

9 · Psychiatric sequelae of traumatic brain injury: depression, anxiety, PTSD and psychosis

After traumatic brain injury, the psychiatric diagnosis must explain a change over time, not merely attach a label to distress after trauma. Depression, anxiety, post-traumatic stress disorder, psychosis and secondary mania can each follow traumatic brain injury, may coexist, and can interfere with recovery in different ways. The marks lie in showing disciplined attribution: establish the pre-injury baseline, reconstruct the injury and subsequent course, define the current syndrome, and test whether another neurological, psychiatric, substance-related or treatment-related explanation fits better.

The apparent contradiction in the literature is itself examinable. Reported frequencies vary with case selection, injury severity, timing and diagnostic method, while some syndromes emerge after a clinically quiet interval. A strong answer therefore distinguishes frequency from individual causation and separates symptom resemblance from syndromal diagnosis. It also recognises that psychiatric assessment continues beyond the early recovery period rather than closing when the acute injury has settled.

11%	12% TO 30%	RR 1.65	29.4%
POOLED GAD ESTIMATE	PTSD IN CIVILIAN COHORTS	SUBSEQUENT SCHIZOPHRENIA	MDD AT 12 MONTHS

9.1 Diagnostic frame: syndrome, chronology and attribution

Begin with linked narratives: what the person was like before injury, what happened around the injury, and how the present psychiatric state developed. Premorbid mood, anxiety, psychotic and substance-related illness may recur after trauma; new symptoms may also be an acquired consequence of brain injury or the psychological meaning of the event and its losses. The task is not to force a false choice between “organic” and “psychological.” It is to formulate how cerebral injury, trauma exposure, disability, disrupted roles and premorbid vulnerability converge in the present syndrome.

Bidirectional vulnerability matters when reading the history. People with premorbid psychiatric disorders have a 70% higher risk of sustaining traumatic brain injury. Consequently, an association between injury and later symptoms does not prove that every disorder began with the injury. Conversely, a premorbid diagnosis does not justify dismissing a genuine post-injury change. Compare baseline phenomenology, severity, functional effect and temporal pattern with the current presentation.

Attribution becomes stronger when the syndrome has a coherent onset after injury, represents a clear change from baseline, fits the observed neurological and psychosocial context, and remains after reasonable mimics have been considered. Collateral history is especially valuable because impaired recall, reduced insight or family reinterpretation can distort the chronology. Records may clarify the injury and early behaviour, while relatives can describe change in ordinary function. Neither source should replace direct examination.

RULE **Diagnose the psychiatric syndrome first, then argue its relation to the traumatic brain injury.** Temporal association supports attribution, but chronology, baseline change, phenomenological coherence and exclusion of better explanations make the causal formulation defensible.

9.2 Depression: frequency, timing and persistence

Post-TBI depressive disorder is common but its reported frequency is strikingly heterogeneous. Across the broad literature, estimates range from **6% to 77%**, reflecting differences in diagnostic criteria, sampling time and injury severity. A narrower source estimate places post-traumatic depression at 25% to 50%. These ranges overlap and should be presented as differently framed estimates, not averaged into a new figure.

Risk appears highest during the first year after injury, and the disorder may persist; one study found that two-thirds of affected patients remained symptomatic for a year or longer. Yet surveillance must not end after that early high-risk period. Among those without depression during the first year, about 25% developed it during the second year. The temporal lesson is practical: assess mood repeatedly during rehabilitation and later functional transitions, including return to work, loss of role, persistent disability and changing family expectations.

The more granular diagnostic estimates make the burden easier to compare. At 12 months postinjury, approximately **29.4% met DSM-IV criteria for major depressive disorder, compared with an annual major-depression rate of 6.7% in the general population**; depressive disorder not otherwise specified and dysthymic disorder were estimated at 19.6% and 1%, respectively. These historical diagnostic categories should not be silently converted into current manual criteria. They show the scale and distribution observed in the cited cohort, while contemporary diagnosis still requires the current classification framework.

Controlled comparison supports an injury-related excess without eliminating the contribution of trauma itself. In a longitudinal cohort of 158 patients with traumatic brain injury and 27 orthopaedic controls, 54% of the brain-injured group developed a mood disorder at some point during the first year, compared with 22% of patients with multiple traumatic injuries without

central nervous system involvement. The comparator is important: each group experienced major trauma, but only the brain-injured group had central nervous system involvement.

9.3 Depression: clinical meaning and anatomical model

Depression after traumatic brain injury is not merely sadness about disability, although loss and demoralisation may contribute. Diagnose a depressive syndrome by integrating mood, loss of interest, biological change, negative cognition, risk, function and course, while interpreting cognitive and somatic complaints in the context of brain injury. Fatigue, slowed thinking, sleep disturbance and reduced activity may arise from several post-injury processes. Their presence should prompt careful phenomenology rather than automatic inclusion or exclusion.

The syndrome has consequences beyond emotional suffering. Once present, post-traumatic depression predicts poorer quality of life, interferes with rehabilitation and adherence, reduces the chance of complete recovery, and increases the risk of comorbid post-traumatic stress disorder and aggression. Thus mood assessment belongs inside the rehabilitation formulation. Reduced participation may be a depressive consequence, a cognitive limitation, apathy, fear-based avoidance or a mixture. The behavioural observation is the beginning of analysis, not the diagnosis.

Left lateral prefrontal involvement provides a useful anatomical correlate without becoming a lesion rule. In one series, post-TBI major depression was associated with reduced grey-matter volume in the lateral aspect of the left prefrontal cortex. A proposed systems account links depression with deactivation of more lateral and dorsal frontal cortex and increased activation of ventral limbic and paralimbic structures. This model explains how disturbed regulation between frontal control systems and affect-generating networks could contribute to depressive experience.

Anatomy must be used proportionately. A left prefrontal finding can support biological plausibility, but absence of that finding does not exclude depression and its presence does not diagnose it. The clinical syndrome remains primary. Professional sport offers another association rather than an individual diagnostic test: professional football players who sustain concussions are 1.5 to 3 times more likely to develop depression than teammates without head injury.

> **GOOD TO REMEMBER**
>
> A patient who disengages from rehabilitation needs a mood formulation, not a character judgement. Ask whether the dominant process is depressive distress, fear-based avoidance, cognitive overload, reduced initiation or treatment toxicity before attributing “poor motivation.”

9.4 Anxiety disorders after traumatic brain injury

Post-TBI anxiety disorders form a spectrum rather than a single undifferentiated complaint. Generalised anxiety disorder may be the most common anxiety disorder after traumatic brain injury. A meta-analysis of 22 studies including 1,145 participants found estimates from 2% to 28%, with a pooled prevalence of **11%**. The range again warns against treating a single figure as universal across settings and injury severities.

Other anxiety presentations show different patterns. Panic disorder has been reported in 6% to 14%, with traumatic brain injury doubling risk; agoraphobia occurred in 7%, also at twice the expected risk. Social anxiety disorder occurred in 5%, twice the rate after other injuries. By contrast, specific phobias were reported at 1% to 10%, similar to the general population, while obsessive-compulsive disorder at 1% to 5% was not significantly elevated. The examination point is discrimination: not every anxiety diagnosis is increased to the same extent.

PRESENTATION	SUPPORTED EPIDEMIOLOGICAL SIGNAL	CLINICAL QUESTION	INTERPRETIVE CAUTION
Depressive disorder	Very wide reported frequency, with greatest risk early and possible persistence	Is there a depressive syndrome rather than isolated fatigue or disengagement?	Somatic and cognitive symptoms need contextual interpretation
Generalised anxiety	Most common anxiety candidate, with a pooled estimate from mixed-severity studies	Is worry pervasive across domains and difficult to disengage from?	Do not collapse all post-injury fear into generalised anxiety
Post-traumatic stress	Higher likelihood after TBI than after other traumatic injuries	Does the presentation organise around traumatic threat and its reminders?	Amnesia for the event is not reliably protective
Psychotic disorder	Reported frequency and timing vary greatly across samples	Are hallucinations or delusions prominent and attributable to injury?	Exclude symptoms occurring only during delirium

Assessment should specify the feared outcome, triggers, mental and bodily response, avoidance, safety behaviours and functional cost. Anxiety may focus on recurrence of injury, bodily sensations, cognitive failure, public embarrassment or traumatic reminders. These themes can coexist, but naming the dominant fear system leads to a clearer diagnosis than recording “anxious after TBI.” Drug choices and cautions belong to the dedicated section on pharmacological management in traumatic brain injury psychiatry; psychological care should follow current syndrome-specific guidance.

9.5 Post-traumatic stress disorder and the amnesia trap

Post-traumatic stress disorder after TBI is neither paradoxical nor rare enough to ignore. Veterans with traumatic brain injury show a threefold greater rate of PTSD than veterans without traumatic brain injury, while civilians with traumatic brain injury have almost twice the likelihood seen after other traumatic injuries. Reported comorbidity spans 12% to 30% in civilians and 12% to 89% in veterans. Population, exposure and ascertainment therefore need to accompany any quoted range.

The classic error is to assume that impaired explicit recall blocks trauma-related illness. Earlier accounts proposed that amnesia for the event would protect against PTSD, but later studies did not support that conclusion. **Implicit trauma memory** offers the bridge: even after moderate or

severe injury, aspects of the traumatic experience may be encoded implicitly and may continue to shape emotion and behaviour. A patient need not provide a coherent autobiographical narrative before trauma cues can provoke distress, arousal or avoidance.

TRAP **Do not write that post-traumatic amnesia protects against PTSD.** Explicit recollection may be incomplete while implicit trauma memory still influences emotional and behavioural responses; moderate or severe TBI does not make PTSD impossible.

Clinically, explore what is remembered, what is reconstructed from others, what remains fragmentary, and what sensory or situational cues trigger a response. Avoid leading the patient toward a narrative that is not genuinely recalled. At the same time, do not demand a detailed narrative as proof of trauma-related pathology. The formulation may rest on cue-linked distress, avoidance, altered threat perception and behavioural change even when episodic recall is limited.

The combination of traumatic brain injury and PTSD appears to produce worse outcomes than either condition alone. This makes dual recognition important: cognitive or behavioural problems should not be attributed exclusively to brain injury when a trauma syndrome is active, and trauma-related symptoms should not obscure neurological limitations. Their combination can shape rehabilitation engagement, family interpretation and functional recovery.

9.6 Psychosis after traumatic brain injury

Psychotic disorder due to TBI is characterised by prominent hallucinations or delusions judged to be a direct physiological consequence of traumatic brain injury, with symptoms occurring exclusively during delirium excluded. This definition demands more than discovering that injury occurred before psychosis. Establish the psychotic phenomena, their chronology, the neurological context, premorbid and family history, substance exposure, current medical state and whether fluctuating confusion better explains the experience.

Reported occurrence varies dramatically by study design. Retrospective review of World War II records found a rate of 7%, whereas a prospective inpatient rehabilitation study found hallucinations and/or delusions at some point after injury in 64% of people with moderate or severe TBI. These are not interchangeable populations or methods. The broad spread should provoke methodological caution, not a midpoint estimate.

Phenomenology is more consistent than the headline rates. Among 71 published schizophrenia-like cases, almost all patients had auditory hallucinations, one in five also had visual hallucinations, 85% had delusions, most often persecutory, and 43% had negative symptoms. The predominance of delusions, paranoia and auditory hallucinations is also described in an alternate clinical account. Visual hallucinations can occur, but their presence should widen assessment rather than automatically disprove the post-traumatic formulation.

Latency is central. The mean onset in the schizophrenia-like case series was **3.3 years after injury**. Another source describes a bimodal distribution, with onset within the first 2 years or after 5 years. A mean can coexist with a bimodal distribution, so the accounts are not formally

contradictory. Together they warn that psychosis may not begin in the immediate recovery period.

Risk evidence further supports vigilance without determinism. A meta-analysis of nine studies involving 180,859 people found subsequent schizophrenia risk elevated after traumatic brain injury, with relative risk 1.65 and a 95% confidence interval from 1.17 to 2.32. Family history of schizophrenia confers particularly heightened risk. An alternate account adds family history of psychosis and prolonged unconsciousness as risk factors, reports equal occurrence after mild and more severe injury, notes that most cases were male, and estimates psychosis in about 20% of severe TBI survivors.

PITFALL

Do not attribute hallucinations to a chronic post-traumatic psychosis while attention, awareness and cognition are fluctuating. Psychotic symptoms occurring only during delirium belong to the delirium formulation; its diagnostic criteria and subtypes are taught in the dedicated section on delirium.

9.7 Secondary mania and the seizure interface

Secondary mania after TBI is less frequent than post-traumatic depression. Estimated bipolar-type disorder rates during the first postinjury year range from 2% to 9%. The syndrome should be distinguished from isolated irritability, impulsivity, sleep disruption, emotional lability or frontal disinhibition. An acquired mood syndrome requires an organising change in mood, with associated activation interpreted as part of that syndrome rather than counted from a behavioural checklist.

In one cohort, manic episodes lasted about 2 months, while elevated, expansive or irritable mood persisted for a mean of 5.7 months. Manic syndromes were significantly associated with hyperactivity, disinhibition, aggression and hypersexuality, but were not related to injury type or severity or to personal or family psychiatric history. The apparently longer mood disturbance than episode duration illustrates why the clinician should describe the syndromal episode as well as the residual affective state.

Secondary mania is associated with post-traumatic seizures, particularly focal-onset seizures with impaired awareness and temporal-lobe epilepsy. Post-traumatic psychosis is likewise associated with seizure disorder in approximately one-third of cases. These associations justify integrating seizure history into psychiatric assessment, but they do not transfer ownership of seizure classification or anticonvulsant choice to this fragment. The psychiatric implications of post-injury seizures are covered in the dedicated section on raised intracranial pressure, hydrocephalus and post-injury seizures; classification and pharmacology belong in the Epilepsy and psychiatry notes.

9.8 Integrated assessment, communication and care boundary

A useful formulation ends in a map of what must be observed, treated and reviewed. The interview should move from chronology to syndrome, from syndrome to attribution, and from

attribution to functional consequences. The following sequence prevents the assessment from becoming a list of post-injury complaints:

- **Baseline:** document premorbid psychiatric illness, personality, function and relevant family history.
- **Course:** reconstruct injury, early neurobehavioural change, symptom onset, remissions and delayed emergence.
- **Phenomenology:** separate depressive, anxiety, trauma-related, manic and psychotic experiences instead of using "behaviour change" as a diagnosis.
- **Mimics and modifiers:** consider fluctuating cognitive states, substances, treatment effects, pain, sleep disturbance and the psychological impact of disability.
- **Function and risk:** assess rehabilitation participation, self-care, relationships, work, self-harm, aggression, vulnerability and the family's capacity to support care.
- **Review:** define what change would confirm improvement, what deterioration requires reassessment, and who will provide longitudinal observation.

MNEMONIC

MAPS

Mood syndromes, including depression and secondary mania; **A**nxiety syndromes; **P**ost-traumatic stress; **S**chizophrenia-like psychosis. MAPS is a recall spine for psychiatric sequelae, not a diagnostic instrument.

Communicate uncertainty honestly. "After TBI" describes chronology; "due to TBI" is a causal formulation that requires support. Explain to families that brain injury can alter vulnerability and expression without making every later emotion neurological or every harmful act inevitable. Repeated review is often more accurate than premature certainty, especially when syndromes overlap or emerge late.

Keep the care boundary explicit. Personality change, aggression and disinhibition are taught in their dedicated section. Cognitive impairment, post-traumatic amnesia, rehabilitation and chronic traumatic encephalopathy are taught separately. Pseudobulbar affect is cross-referred to the dedicated section on its phenomenology and treatment. Drug choices, doses, cautions and seizure-threshold considerations belong to the dedicated section on pharmacological management in traumatic brain injury psychiatry, with general antidepressant pharmacology in the Mood disorders: pharmacotherapy notes.

After traumatic brain injury, diagnose the syndrome, reconstruct its chronology, test causal attribution, and keep depression, anxiety, PTSD, psychosis and secondary mania distinct even when they coexist.

10 · Personality change, aggression and disinhibition after traumatic brain injury

After traumatic brain injury, a changed person may be the presenting complaint even when the family cannot name a psychiatric syndrome. The clinically important change may involve social judgement, impulse control, emotional expression, motivation or aggressive behaviour. The psychiatrist must convert a moralised account such as "he has become rude" into an operational description of what changed, when it changed, what triggers it and which control function is failing.

IN INDIA

Lead with behavioural management, family psychoeducation and environmental structure; where medication is used for aggression, choose a familiar agent at the lowest effective dose and review the need regularly.

This topic earns marks through distinctions. Personality change is broader than aggression; disinhibition is a failure of restraint; agitation is not synonymous with aggression; and apathy is a low-output disorder that may be mistaken for depression. A strong answer links phenomenology to prefrontal circuitry, uses collateral history to establish change from baseline, assesses risk without equating all irritability with violence, and keeps pharmacological detail within the dedicated section on pharmacological management in traumatic brain injury psychiatry.

COMPORTMENT	DISINHIBITION	AGGRESSION	APATHY
SOCIAL DECISION-MAKING	FAILED RESTRAINT	THREAT OR INJURY	FAILED INITIATION

10.1 The core construct: acquired change in personality and comportment

Post-traumatic personality change is an acquired alteration in the patient's characteristic manner of relating, deciding and regulating behaviour after brain injury. It is best established as a difference from the premorbid person, not as a free-standing adjective applied during a difficult interview. The family may describe a newly abrupt, suspicious or argumentative manner. These descriptions become clinically useful only after the examiner asks for concrete episodes, context, consequences and comparison with the previous baseline.

Comportment refers to the regulation of behaviour in its social and emotional setting. The relevant prefrontal circuitry modulates decisions according to reward and punishment, helps generate and express emotion, and supports insight into one's own conduct. Injury can therefore leave basic language or motor capacity available while degrading the ability to choose what is appropriate, anticipate interpersonal consequences or recognise that one's conduct has changed.

This explains the apparent paradox often seen in consultation. The patient may understand the words of a rule, recall that relatives objected, and still repeat the behaviour when an immediate cue or frustration appears. Knowledge of the rule and online use of the rule are different capacities. The examiner should therefore document whether the failure concerns understanding, memory, initiation, inhibition, emotional modulation or insight rather than compressing all of them into "personality disorder."

RULE **Describe acquired behaviour in operational terms before assigning motive or diagnosis.** Establish the premorbid baseline, identify the failed control function, and show how the change affects safety, relationships and ordinary roles.

The word acquired matters. A longstanding interpersonal style may shape the post-injury presentation, but it is not itself evidence of injury-induced change. Conversely, a dramatic departure from baseline may be missed if the clinician relies only on the patient, because impaired insight is part of the relevant circuitry. The formulation must hold premorbid traits and new neurological change together without allowing either to erase the other.

10.2 Neuroanatomical logic of disinhibition

Kaufman's Clinical Neurology for Psychiatrists links personality change after traumatic brain injury with frontal and temporal damage. When frontal inhibitory systems are impaired, behaviour that would ordinarily be checked can reach expression. The resulting **disinhibition** may appear as unbridled aggressiveness, excessive talk, impulsivity, hyperactivity or a more generally unrestrained interpersonal manner.

Disinhibition is therefore not simply "too much behaviour." It is behaviour insufficiently filtered by context, future consequence and social meaning. A patient may speak at length despite cues to stop, act on an immediate urge before considering risk, or escalate rapidly after a minor frustration. The shared mechanism is weak restraint, although the surface behaviours differ. This functional description is more useful than assuming that every activated presentation is a primary mood episode or that every offensive act is deliberate.

The anatomical bridge is sharpened by the well-known case of **Phineas Gage**. Modern imaging of the injury demonstrated damage involving orbitofrontal and medial prefrontal regions, areas contributing to reward-punishment decisions, emotional processing and insight. The case is memorable because it illustrates how disruption of control circuitry can alter social conduct without reducing the person to a simple motor or language deficit.

Localisation should still remain proportionate. A behaviour is not a scan, and a colourful symptom does not establish a precise lesion. Frontal and temporal injury may be distributed, and several behavioural functions may fail together. Use the anatomical account to explain the pattern, not to claim a focal site from one impulsive incident. The dorsolateral, orbitofrontal and medial frontal syndromes in full belong in the dedicated section on frontal lobe syndromes and their subtypes.

MNEMONIC

BRAKE

Baseline personality; **R**eward and punishment decisions; **A**ffect generation and expression; **K**eeping impulses in check; **E**valuating one's own conduct through insight. BRAKE is a clinical reading frame for comportment, not a diagnostic instrument.

10.3 Phenomenology: separate the behavioural syndromes

The phrase "behavioural disturbance" is too coarse for either an examination answer or a clinical formulation. The same ward report may contain pacing, shouting, threats, impulsive touching, repetitive demands, emotional indifference and failure to begin self-care. These observations do not all name the same construct. The table separates them by the dominant failure and by what must be demonstrated before using the label.

CONSTRUCT	CORE CLINICAL MEANING	TYPICAL DESCRIPTION AFTER TBI	QUESTION THAT SEPARATES IT
Personality change	Acquired alteration in characteristic manner, potentially abrupt, suspicious or argumentative	A sustained departure from premorbid interpersonal style	What is genuinely new compared with baseline?
Comportment change	Impaired modulation of reward-punishment decisions, emotional expression and insight	Poor social judgement despite apparently intact basic abilities	Can the patient use context and consequence to guide conduct?
Disinhibition	Loss of inhibitory control with aggressiveness, loquaciousness, impulsivity or hyperactivity	Behaviour escapes restraint when an urge or cue appears	Did the person understand the boundary but fail to inhibit the response?
Agitation	Excessive, usually nonproductive motor activity associated with inner tension	Restless motor output that need not threaten anyone	Is there excessive motor activity, threat, injury, or a combination?
Aggression	Overtly threatening or injurious conduct toward a person or object	Usually reactive and impulsive in the setting of TBI-related cognitive impairment	What was threatened or harmed, and what immediately preceded it?
Apathy	Reduced motivation, initiation, interest, activity, emotional responsiveness or spontaneity	Low self-generated behaviour, sometimes without subjective distress	Is the main failure distress, desire, initiation, or motor capacity?

Several constructs may coexist. A patient can be apathetic for much of the day yet become impulsively aggressive when pressed to perform a task. Another may pace from inner tension without threatening anyone. A third may make offensive comments because inhibitory control is poor but never become physically aggressive. The formulation should preserve these distinctions rather than choosing the most dramatic label as the whole diagnosis.

Descriptions should also separate frequency from severity and intent from effect. A brief threat can be clinically serious; repeated restless movement may be disruptive without being aggressive; an impulsive act can cause major injury without having been planned. Neutral behavioural

language protects accuracy and dignity. It also gives the team something observable to track rather than inviting arguments about whether the patient is "really difficult."

10.4 Agitation is not aggression

Agitation is excessive, usually nonproductive motor activity accompanied by inner tension. Its centre of gravity is motor overactivity. **Aggression** is overtly threatening or injurious behaviour directed toward another person or an object. Its centre of gravity is threat or harm. The patient may have either construct alone or the constructs may occur together.

This distinction changes observation. For agitation, record what the body is doing, whether the movement serves a purpose, the apparent tension and the environmental setting. For aggression, document the target, the threatening or injurious act, the immediate antecedent, the consequence and how the episode ended. "Agitated and aggressive" without this detail hides the very information needed for formulation and prevention.

In traumatic brain injury with cognitive impairment, aggressive behaviour tends to be **reactive and impulsive aggression** rather than proactive aggression. The episode commonly reads as a rapid response to frustration, demand, misunderstanding or immediate provocation rather than as planned instrumental harm. This does not make the behaviour harmless or remove responsibility for safety. It changes the causal question from "What long-term goal did the aggression serve?" to "What antecedent met an impaired regulatory system?"

TRAP **Do not use agitation and aggression as interchangeable words.** Pacing with tension is not automatically violence, while a threat or injurious act may occur without sustained motor overactivity. Define the observed construct before discussing cause.

Overt Aggression Scale may be used to track response. Its value here is conceptual as well as practical: repeated observation should be organised around overt behaviour rather than global impressions. Detailed instrument administration and scoring belong to the Psychotherapies, clinical assessment, MSE and nosology notes. In this section, the essential point is to use consistent behavioural anchors across observers and across time.

10.5 Why aggression occurs: a layered risk formulation

Post-traumatic aggression does not arise from lesion location alone. The supported risk formulation combines premorbid factors, the location of injury and the sequelae produced by the injury. Premorbid poor social functioning is relevant, and substance misuse has been associated in some studies. Frontal-lobe injury carries greater risk than injury to other brain regions. The most powerful risk factor in the clinical account is **TBI-induced depression**.

The depression association is not a decorative comorbidity. During the first year after traumatic brain injury, significant aggressive behaviour was found in **17 of 30 patients with major depression, or 57%**, compared with **10 of 44 patients without a mood disorder; p = .004**. The comparison explains why mood assessment belongs inside an aggression formulation rather than after it.

The risk factors answer different questions. Premorbid functioning describes the regulatory and social context brought into the injury. Lesion location indicates which control systems may have been disrupted. Post-injury sequelae describe new states that can amplify irritability, distress or behavioural dyscontrol. A useful formulation shows how these layers converge in this patient instead of presenting them as a memorised list.

- **Baseline:** establish premorbid social functioning, usual conflict style and any substance-related context without assuming that history determines the present episode.
- **Brain injury:** identify whether frontal involvement and impaired inhibition plausibly fit the observed reactive pattern.
- **Current sequelae:** assess depression and other post-injury problems that may alter tolerance, judgement or emotional regulation.
- **Antecedents:** reconstruct what happened immediately before the behaviour, including demands, frustration, misunderstanding and environmental overstimulation.
- **Consequences:** document harm, near-harm, family burden, occupational disruption and what responses appear to escalate or settle the episode.

The risk formulation must remain dynamic. A historical vulnerability is not a permanent prediction, and an absence of previous violence is not proof of current safety. Likewise, frontal injury is a risk factor, not a behavioural destiny. The clinician's job is to integrate enduring background with present state, immediate triggers and observed control, then revise the formulation when the pattern changes.

GOOD TO REMEMBER

When aggression appears after traumatic brain injury, assess mood early. Depression may be clinically less dramatic than the behavioural episode yet more important to the risk formulation than a long catalogue of remote vulnerabilities.

10.6 Apathy: the low-output counterpoint

Apathy after traumatic brain injury involves impairment of motivation, initiation, interest, activity, emotional responsiveness or spontaneity. The patient may not begin tasks, may contribute little without prompting, or may show reduced emotional engagement. The central observation is diminished self-generated behaviour. It should not be confused with inability to understand a task or inability to perform the required movement.

Apathy is especially easy to mislabel as depression. Patients with apathy are often not distressed by their reduced activity, whereas the clinician may infer sadness simply from sparse speech, inactivity or blunted responsiveness. Depression and apathy can coexist, but they are not synonyms. Ask whether the patient wants to act, feels distressed by the loss, initiates when structure is removed, responds to prompting and shows broader depressive experience. The distinction matters because an apparent low-output syndrome and an affectively painful syndrome require different formulations.

Imaging evidence links post-traumatic apathy with damage in the left hemisphere, particularly the frontal lobe, anterior cingulate, insula, corpus callosum and corona radiata. The distributed list fits the clinical idea that motivation and initiation depend on connected systems rather than a single isolated point. Laterality must be retained accurately: the reported association is left-sided.

Apathy also clarifies why "personality change" should not be treated as synonymous with disinhibition. Traumatic brain injury can produce a high-output failure of restraint, a low-output failure of initiation, or a mixed picture. In a mixed presentation, behaviour may be sparse until an external demand appears, after which the patient reacts impulsively. That is not inconsistency. It indicates that initiation and inhibition are separable control functions.

PITFALL

Do not diagnose depression solely because the patient is inactive, emotionally unresponsive or dependent on prompts. Establish subjective distress and the broader mood syndrome, while separately describing motivation, initiation and spontaneity.

10.7 Bedside assessment and documentation

The decisive evidence is usually a triangulation of patient interview, direct observation and collateral history. Begin with chronology: the premorbid interpersonal style, the injury, the earliest observed change, the subsequent course and the current pattern. Ask relatives for episodes rather than labels. "Argumentative" should become a description of what was said, what preceded it, whether correction altered the behaviour and whether the patient later understood its effect.

Direct observation should be equally operational. Note initiation of conversation, ability to wait, response to limits, modulation of voice, interruption, persistence after feedback and recognition of interpersonal cues. An apparently calm structured interview does not exclude dyscontrol in a noisy home or demanding ward. Conversely, conflict during one interview does not by itself establish acquired personality change. Context is part of the phenomenon.

Risk assessment should distinguish current intent from impaired control. Ask directly about recent threats or injury, targets, access to means, substance use around episodes, escalating frequency, warning signs and the family's ability to maintain safety. Then examine the reactive sequence: antecedent, interpretation, impulse, act and consequence. This sequence identifies where prevention may be possible without pretending that a behavioural formulation can guarantee prediction.

Documentation should use neutral verbs. Record "paced continuously," "struck the door after a limit was set," or "continued speaking despite repeated cues" rather than "was impossible" or "behaved badly." State what came from collateral history and what was observed directly. Describe insight as specific to the event: the patient may recognise that an act occurred yet fail to appreciate why it was dangerous or how it affected others.

Track patterns consistently. Where aggression is the target, the Overt Aggression Scale can support repeated measurement. Use the score alongside the narrative of antecedents, targets and

consequences. Broader cognitive testing may clarify associated impairment, yet the instruments and their scoring are taught in the Psychotherapies, clinical assessment, MSE and nosology notes. The behavioural formulation remains grounded in change from baseline and conduct in context.

10.8 Synthesis, communication and treatment boundary

A concise diagnostic synthesis should state the acquired behavioural change, dominant control failure, anatomical coherence, relevant risk factors and degree of insight. For example, the formulation may describe a new reactive pattern with poor inhibition after frontal injury, amplified by a current depressive syndrome, while acknowledging premorbid social vulnerability. This says more than "aggression due to TBI" because it identifies the mechanism that needs to be tracked.

Communication with relatives should validate paired realities: the behaviour may arise from injured control systems, and its consequences still require firm safety boundaries. Neurological explanation is not moral condemnation, but neither is it permission to ignore harm. Families often need help separating the person from the behaviour while continuing to record antecedents, recognise escalation and seek urgent help when safety cannot be maintained.

Do not let anatomy become fatalism. Risk factors describe probability and mechanism, not inevitability. The patient retains capacities that can be supported, environments can change the load placed on inhibitory systems, and mood or other sequelae may be clinically modifiable. The present fragment establishes the target syndrome and the reasoning needed to distinguish its components. Detailed medication selection, doses, cautions and the lowered seizure-threshold problem belong to the dedicated section on pharmacological management in traumatic brain injury psychiatry.

For an examination answer, end where the evidence ends. Define personality and comportment change, explain disinhibition through frontal control failure, distinguish agitation from aggression, characterise reactive impulsive aggression, present the layered risk formulation with depression prominent, and contrast apathy with depression. Then add assessment through collateral history, operational observation and repeated behavioural tracking. This sequence is complete without borrowing treatment details or reproducing the full frontal-lobe syndrome classification.

> After traumatic brain injury, describe whether the dominant failure is social judgement, inhibition, threat control or initiation; do not collapse personality change, disinhibition, agitation, aggression and apathy into one label.

11 · Cognitive impairment, post-traumatic amnesia, rehabilitation and chronic traumatic encephalopathy

The marks lie in following cognition across time, not in treating every post-injury memory complaint as the same disorder. **Post-traumatic amnesia** is an evolving recovery period in which new learning is prominently impaired while memory for the trauma and the immediately

surrounding past is also disturbed. It must be distinguished from the confusional state that can precede it and the executive retrieval problem that can follow it, and from the much later question of neurodegeneration after repeated injury.

This distinction has practical force. The duration of amnesia carries unusual prognostic weight, rehabilitation targets change as the dominant cognitive problem changes, and apparent recovery of conversation does not prove restoration of memory or judgement. At the chronic end, a history of traumatic brain injury can increase later cognitive risk without establishing chronic traumatic encephalopathy. A strong answer therefore moves from definition and bedside interpretation to prognosis, rehabilitation, later dementia risk and the strict pathological boundary around CTE.

Strongest	Within 6 months	Until 18 months	Autopsy only
PTA DURATION AS OUTCOME PREDICTOR	MOTOR AND LANGUAGE MAXIMUM	INTELLECTUAL RECOVERY MAY NOT PEAK	DEFINITIVE CTE DIAGNOSIS

11.1 What post-traumatic amnesia means

PTA begins to make clinical sense when arousal and simple attention have relatively recovered, yet the patient remains unable to lay down a stable record of ongoing experience. Its core is impaired formation of new memories after injury, accompanied by loss of memory immediately before or during the event. The apparent alertness can deceive: a patient may answer, converse and engage briefly while later retaining little of what occurred. This is why ordinary social responsiveness cannot be used as proof that amnesia has ended.

The mnemonic disturbance reflects injury to hippocampal systems that support memory function. This is a functional explanation, not permission to infer a focal structural lesion in every patient. The clinician should identify whether information is being consistently retained across encounters, whether orientation is becoming stable, and whether the account of the event is contracting or changing during recovery. Collateral observation is particularly valuable because the patient cannot reliably report a period that was not successfully encoded.

The **Galveston Orientation and Amnesia Test** can assess the duration and severity of PTA. It belongs here as the named instrument for this construct, but its item content, administration and scoring should be learned from the authorised instrument source and are not reproduced here. General teaching on standardised cognitive instruments belongs in the Psychotherapies, clinical assessment, MSE and nosology notes.

RULE **Do not equate wakefulness with recovery from post-traumatic amnesia.** Relative return of arousal and simple attention may coexist with a continuing inability to form new memories, so repeated observation of retention matters more than conversational fluency.

11.2 Retrograde loss, anterograde failure and the bedside question

Retrograde amnesia covers memory loss for the trauma and immediately preceding events. This retrograde gap tends to diminish during recovery, so the patient may progressively recover portions of the lead-up to the injury. The clinical question is therefore not simply whether a gap

exists, but whether its boundary is changing and whether the reconstructed account comes from genuine recall, collateral information or later inference.

Anterograde amnesia concerns newly presented information. It is uncommon in mild traumatic brain injury but very common after moderate-to-severe traumatic brain injury. The essential mechanism is failed encoding: information never entered a durable memory trace. Consequently, the anterograde period itself is never subsequently recovered. A patient may later learn what others report happened, but this acquired narrative is not recovery of the original experience.

A compact assessment keeps the following questions separate:

- **Past boundary:** What is missing from the trauma and the immediately preceding period, and is that boundary shrinking?
- **New retention:** Does information discussed now remain available after a delay and across subsequent encounters?
- **Source:** Is the later account recalled, learned from others or reconstructed from context?

This separation prevents a common interpretive error. Improvement in retrograde recall does not prove recovery of new learning, and an orderly narrative supplied after the event does not show that the person encoded the original period. Assessment is longitudinal because PTA is a recovery state, not a single interview finding.

11.3 The cognitive recovery sequence

Acute traumatic encephalopathy can be understood as a changing hierarchy. After emergence from coma, a persistent vegetative state or a minimally conscious state, the patient may enter a **post-traumatic confusional state**. This is delirium-like, with acute and fluctuating impairment of attention, perceptual disturbance, delusional thought, psychomotor agitation or retardation, and affective lability. The full delirium syndrome and its diagnostic criteria are taught in the dedicated delirium section; here the point is its position in post-injury recovery.

RECOVERY PHASE	DOMINANT DISTURBANCE	MEMORY INTERPRETATION	CLINICAL IMPLICATION
Disorder of consciousness	Impaired level of consciousness	Memory cannot be interpreted independently of arousal	Establish the level and trajectory of consciousness first
Post-traumatic confusional state	Fluctuating attention, perception, thought, psychomotor activity and affect	Inconsistent registration occurs within a broader confusional state	Do not reduce the presentation to isolated amnesia
Post-traumatic amnesia	Failure to form new memories despite relative recovery of arousal and simple attention	Encoding failure dominates	Track retention and the changing amnestic boundary
Post-PTA dysexecutive phase	Executive dysfunction associated with frontal-subcortical injury	Retrieval failure becomes more important than encoding failure	Shift rehabilitation toward executive control and compensation

After PTA resolves, **post-traumatic dysexecutive syndrome** tends to predominate because closed head injury has a predilection for frontal-subcortical circuitry. The patient may still describe "poor memory," but the mechanism has changed. During PTA, the central problem is failure to encode; later, information may have been stored but cannot be efficiently organised, searched for or retrieved. This distinction explains why a single complaint can require different assessment and rehabilitation strategies at different points in recovery.

GOOD TO REMEMBER

Ask what kind of memory failure is occurring now. Repetition without later retention suggests continuing encoding failure; knowledge that is inconsistently accessed after PTA points toward executive retrieval difficulty. The label "memory problem" is too broad to plan rehabilitation.

11.4 Cognitive pattern, localisation and awareness

The location of trauma correlates inconsistently with the resulting cognitive impairment. Traumatic injury often does not respect the tidy localisation expected from a single focal lesion, so a scan location should not be made to explain every deficit. The important grounded exception is left temporal lobe injury, which routinely produces vocabulary difficulty resembling anomic aphasia. This is a useful localising clue, not a template for converting all post-TBI cognitive findings into focal lobe syndromes.

Awareness is equally important. Patients after TBI, especially those with right hemisphere involvement, may show **anosognosia** or denial of their deficits. The problem is not mere disagreement with staff. Unawareness obstructs realistic goal setting, interferes with rehabilitation and may expose the patient to further traumatic brain injury. A person who does not recognise impaired judgement or memory cannot reliably calibrate risk, assistance or readiness to resume demanding roles.

Assessment should therefore triangulate the patient's account, observed performance and collateral information. Discrepancy is clinically informative, but it must not be used as a moral verdict. Some patients underestimate deficits because awareness systems are impaired; others accurately describe failures not obvious in a short interview. The psychiatrist's task is to define the discrepancy, test its functional consequences and build goals that preserve dignity while acknowledging risk.

PITFALL

Do not interpret confident self-report as evidence of intact capacity for rehabilitation decisions. Post-TBI unawareness can be part of the cognitive syndrome, particularly with right hemisphere involvement, and may make the most certain patient the least reliable judge of current limitations.

11.5 Prognosis and the shape of recovery

The duration of PTA is a more reliable predictor of overall neuropsychological outcome than either the depth or duration of coma. It predicts the broad cognitive and functional burden because it samples the period during which organised new learning remains disrupted. This does

not turn duration into destiny. It gives the clinician a stronger prognostic anchor than the dramatic appearance of the earliest coma alone.

Recovery is domain-specific rather than synchronous. Motor and language abilities usually reach their maximum earlier, whereas intellectual recovery may peak substantially later, as summarised in the statistics strip. This lag matters when families assume that improved walking or fluent speech means cognition has also plateaued. It also argues against declaring the final intellectual outcome too early merely because visible neurological recovery has slowed. Older patients generally recover more slowly and less completely than younger patients.

Prognosis is modified by more than intracranial pathology. Adverse associations include older age, lower premorbid cognitive reserve, poorer socioeconomic status, limited social support, involvement in legal or work-compensation proceedings, and neurological or psychiatric conditions arising before or after injury. The APOE-epsilon4 allele has also been associated with poorer clinical outcome. These are modifiers, not automatic explanations for an individual's disability and not grounds for dismissing symptoms.

The practical formulation should state the injury-related anchor, the present cognitive phase, domain-specific strengths and weaknesses, awareness, psychiatric comorbidity, social supports and real-world participation. Prognosis is then expressed as a trajectory with uncertainty. This is more defensible than a fixed promise and more useful than the vague statement that “recovery varies.”

TRAP **Do not use coma duration as the best cognitive prognostic marker when PTA duration is available.** Coma is visually dramatic, but the duration of post-traumatic amnesia is the more reliable predictor of overall neuropsychological outcome.

11.6 Rehabilitation: locus, focus and modus

Cognitive rehabilitation after traumatic brain injury is primarily multidisciplinary and nonpharmacological. The overall purpose is not simply to improve a test score. It is to restore intellectual functioning where possible, strengthen remaining abilities, build compensatory mechanisms and increase safe participation. Treatment must follow the changing cognitive phase: an approach suited to confusion or failed encoding will not be sufficient when the dominant barrier is later executive retrieval.

LOCUS. Early care belongs in a setting that can manage impaired consciousness, confusion, agitation and safety while repeatedly reassessing recovery. As medical stability and participation improve, rehabilitation can move through structured inpatient or outpatient work into the patient's ordinary environment. Locus is chosen by supervision needs, functional dependence, behavioural stability, caregiver capacity and access to the relevant disciplines, not by diagnosis alone.

FOCUS. During the confusional and amnestic phases, the immediate targets are safe engagement and recognition of what information is not being retained. After PTA, focus shifts toward executive organisation, retrieval, judgement, awareness and the barriers that prevent therapy

participation. Across recovery, depression, anxiety and insomnia require active identification and treatment because they can worsen distress, efficiency and engagement. Long-term goals should be framed in observable function and participation rather than in the disappearance of every subjective complaint.

MODUS. The grounded rehabilitation package includes:

- **Restorative disciplines:** cognitive, behavioural, physical, occupational and speech rehabilitation, coordinated around shared functional goals.
- **Psychiatric and sleep care:** identification and treatment of depression, anxiety and insomnia, integrated with rather than separated from rehabilitation.
- **Social and compensatory work:** peer interaction, enhancement of remaining functions and development of compensatory mechanisms for deficits that persist.

Medication is adjunctive and the evidence base is limited. Methylphenidate and other dopamine-enhancing medicines may improve attention and thereby directly or indirectly support memory; anticholinesterases may improve memory in patients with severe deficits. These statements support cautious target-based consideration, not a dose, hierarchy or routine prescription. Detailed choice, adverse-effect cautions and monitoring belong in the dedicated section on pharmacological management in traumatic brain injury psychiatry.

Current head-injury and neurorehabilitation guidance should determine transfer criteria, service intensity and local prescribing safeguards. The examination-quality principle is stable: select the setting by need, select the target by phase, and combine cognitive, behavioural, physical, occupational, speech, psychiatric and social modes rather than waiting for a drug to restore cognition.

MNEMONIC

TRACE

Track PTA duration; **R**ecognise retrieval failure after encoding failure; **A**ssess awareness of deficit; **C**oordinate multidisciplinary compensation and restoration; **E**nforce the postmortem boundary for definitive CTE diagnosis.

11.7 Traumatic brain injury and later dementia risk

Long-term decline after TBI must be handled probabilistically. In survivors of moderate TBI who carry two ApoE4 alleles, the risk of Alzheimer disease may be **double**; after severe TBI in the same genetic context, it may be **four times** the risk. Studies of veterans found a **60% increase** in dementia risk among those with a TBI history compared with veterans without such a history.

These associations do not mean that every later cognitive complaint is degenerative, that genotype fixes an individual's outcome, or that dementia after TBI is synonymous with CTE. They mean that previous injury belongs in the risk formulation. A patient with progressive decline still requires the ordinary diagnostic approach rather than a shortcut from history to

label. The dementia syndrome and its full diagnostic workup belong in the Dementias and neurocognitive disorders notes.

Clinically, separate the following questions. What residual deficit has remained relatively stable since the injury? What function is changing now? What alternative neurological, psychiatric, sleep-related, medical or medication-related explanation could account for that change? This temporal analysis protects against opposite errors: overlooking a progressive disorder because "the patient always had TBI," and diagnosing neurodegeneration from a static acquired deficit.

11.8 Chronic traumatic encephalopathy: phenotype, pathology and diagnostic boundary

Chronic traumatic encephalopathy is a neuropathological diagnosis. Definitive diagnosis is currently possible only at autopsy. The defining lesion is irregular phosphorylated tau aggregated in neurons and astrocytes around small vessels at the depths of cortical sulci. Every component matters: phosphorylated tau, neuronal and astrocytic involvement, a perivascular distribution, and concentration at sulcal depths. Generic "tau deposition" is too imprecise for the defining pathology.

The clinical language has changed across contexts. **Dementia pugilistica**, the classic form described in professional boxers, emphasises parkinsonism and nonprogressive cognitive deficits. The modern CTE phenotype places greater emphasis on prominent psychiatric symptoms and progressive cognitive deficit, while parkinsonism can occur in both.

AXIS	CLASSIC ACCOUNT	MODERN ACCOUNT	INTERPRETIVE LIMIT
Historical setting	Professional boxers	Broader progressive neurodegeneration related to repeated TBI	Exposure history supports suspicion but is not diagnostic
Cognitive course	Primarily nonprogressive deficits	Deficits tend to progress	No distinguishing cognitive pattern has been established
Clinical emphasis	Parkinsonism with cognitive deficit	Prominent psychiatric symptoms	Psychiatric symptoms are not a neuropathological diagnosis
Motor syndrome	Parkinsonism occurs	Parkinsonism also occurs	Its presence does not separate the forms

The epidemiological signals explain concern but do not create an in-life diagnostic test. Depending on career length, boxers have an approximate **20% risk of dementia**. Among professional National Football League players, mortality from neurodegenerative disease is **three times higher** than in the general population of the United States. Before death, affected players may develop memory loss, depression, aggressive behaviour and executive dysfunction; autopsy studies describe excess cerebral tau with plaques and tangles.

The diagnostic trap is overreach. No distinctive pattern of cognitive deficit has been validated for CTE, and a history of TBI is not specific because TBI also increases the risk of conventional dementia. Therefore, a living patient with repeated injury, psychiatric symptoms and decline may

warrant careful assessment, longitudinal observation and investigation for established causes, but cannot be given a definitive neuropathological diagnosis from that constellation. Current evidence does not supply an operational in-life clinical pattern that can replace the postmortem standard.

PTA is primarily an encoding failure and the later dysexecutive phase a retrieval problem; definitive CTE remains a postmortem diagnosis.

12 · Pharmacological management in traumatic brain injury psychiatry

After traumatic brain injury, the safest prescription is the one tied to a defined target, chosen for cognitive tolerability, and reviewed often enough to be stopped. Pharmacological management after brain injury is not a list of preferred drugs. It is a method of matching a symptom target to the phase and setting of care while protecting attention, memory, arousal and seizure safety. The examiner therefore expects more than an agent name: state the target syndrome or behaviour, distinguish acute control from chronic treatment, explain the evidence limit, and specify how iatrogenic worsening will be detected.

IN INDIA

SSRIs are a sensible first choice for mood and anxiety after traumatic brain injury; prefer agents that do not lower the seizure threshold and avoid a heavy anticholinergic load, and start any dopaminergic agent for apathy under specialist advice.

Nonpharmacological care should be prioritised, with medication used as an adjunct rather than a substitute. This principle keeps rehabilitation, psychological treatment, environmental modification and family work visible even when the question asks specifically about drugs. The psychiatric syndromes and behavioural phenotypes themselves are described elsewhere in the traumatic brain injury sections; the present task is their TBI-specific pharmacological management.

SSRIs	Beta-blockers	Prodopaminergic	Adjunctive
FIRST-LINE FOR DEPRESSION	MORE RELIABLE FOR AGGRESSION	TRIAL OPTION FOR APATHY	ROLE OF MEDICATION

12.1 The TBI-sensitive prescribing frame

TBI-sensitive prescribing begins by locating the patient. In emergency and inpatient care, the immediate focus is dangerous agitation, severe distress and behaviour that prevents essential assessment or treatment. In rehabilitation, the focus shifts toward participation, irritability, disinhibition, mood and cognitive efficiency. In outpatient care, longer-term depression, anxiety, trauma-related symptoms, psychosis, secondary mania or apathy may become the treatment target. The locus changes what can be observed, how rapidly deterioration can be detected, and which adverse effects are acceptable.

LOCUS	FOCUS	MODUS	PRESCRIBING QUESTION
Emergency setting	Acute agitation, distress or immediate risk	De-escalation, correction of drivers, environmental control; medication only when needed	Will the drug obscure neurological or cognitive reassessment?
Inpatient unit	Stabilisation and safe participation in care	Nursing structure, family input, rehabilitation measures and a target-specific drug trial	Is the apparent response therapeutic benefit or merely sedation?
Rehabilitation setting	Engagement, behavioural control and functional recovery	Cognitive and behavioural rehabilitation with adjunctive medication	Does the medicine improve the target while preserving learning?
Outpatient setting	Persistent affective, anxiety, behavioural or motivational symptoms	Psychotherapy, social and vocational rehabilitation, family work and rational pharmacotherapy	Can benefit be demonstrated in ordinary function?
Refractory illness	Severe symptoms despite adequate care	Reformulation, specialist review and an appropriate procedural option	Has treatment resistance been established without avoidable polypharmacy?

The practical sequence is simple. Define an observable target, record its functional consequence, remove or reduce medicines that may be producing the same problem, and select a single intervention whose risks fit the injured brain. Begin cautiously and increase slowly, but still allow an adequate dose and duration before declaring failure, tapering or adding an adjunct. “Start low and go slow” is not permission to leave the patient indefinitely on an ineffective token dose.

RULE **Treat a target, not the history of head injury.** Name the symptom or behaviour, choose the least cognition-disrupting reasonable option, and judge benefit against function rather than quietness alone.

12.2 Before the prescription: target, burden and safety

The pre-prescribing assessment asks whether medicine is necessary now, whether a current medicine is contributing, and what observation will count as improvement. A target such as “less aggression during personal care” is more useful than “better behaviour.” Baseline arousal, attention, memory efficiency, sleep, motor restlessness and day-to-day function should be described in clinically meaningful terms. This makes later deterioration visible and prevents sedation from being mistaken for recovery.

Brain-injured patients require frequent reassessment for adverse effects and drug interactions, with particular restraint toward polypharmacy and medicines that interfere with attention or memory. Anticonvulsants, antipsychotics and minor tranquillisers may themselves impair cognition; this does not make every use wrong, but it raises the threshold for adding them

without a defined indication. Their general pharmacology belongs in the Epilepsy and psychiatry notes and the Schizophrenia: management, antipsychotics and adverse effects notes.

MNEMONIC

TARGET

Target one symptom or behaviour; **A**ssess baseline cognition and function; **R**educe contributory medicines; **G**ive one rational trial; **E**valuate benefit and harm repeatedly; **T**aper what has no continuing indication.

A defensible monitoring plan therefore includes the following elements:

- **Target:** the syndrome, behaviour or functional barrier being treated.
- **Benefit:** the change expected in distress, participation, safety or ordinary performance.
- **Harm:** cognitive dulling, excessive sedation, neurological adverse effects, behavioural activation or treatment-emergent restlessness.
- **Decision:** continue, adjust, taper or reformulate at a planned review rather than accumulating indefinite adjuncts.

Current institutional and national prescribing guidance should be checked for ordinary contraindications, interaction screening and agent-specific monitoring. No named guideline or TBI-specific monitoring schedule is supplied by the permitted evidence, so neither should be reconstructed from memory.

12.3 Post-TBI depression: first-line treatment and the evidence paradox

Post-TBI depression pharmacotherapy usually begins with an SSRI. Sertraline is the most studied SSRI in this population, yet the major sertraline trials did not establish efficacy. This is the central evidence paradox: clinical first-line status reflects overall safety and tolerability as well as efficacy evidence, while the trial record remains mixed. A good answer preserves this tension and does not convert “most studied” into “proven best.”

The prevention evidence illustrates why dose figures require context. A subacute-recovery trial of post-TBI depression prevention used **sertraline 100 mg/day** in 94 patients. The placebo group had four times the hazard of developing depression, and the **number needed to treat was 5.9**. A separate subacute-recovery trial of post-TBI depression prevention using sertraline 50 mg/day for 3 months found no significant difference from placebo. A post-TBI depression treatment vignette also began sertraline at 50 mg/day. These are trial and vignette doses for post-TBI depression, not a recommended target range.

Selection among antidepressants should favour minimal anticholinergic burden, minimal sedation and minimal lowering of the seizure threshold. Tricyclic antidepressants are not preferred after TBI because their anticholinergic effects and seizure-threshold lowering are particularly disadvantageous. Serotonin-norepinephrine reuptake inhibitors can also lower the seizure threshold and should be used at the lowest effective dose. The general comparative

pharmacology and routine selection of antidepressants belong in the Mood disorders: pharmacotherapy notes.

Small randomised studies suggest that methylphenidate may improve depression, cognition and fatigue. That broader possible benefit may be relevant when the clinical target spans affective and cognitive complaints, but small-study signals should not be presented as equivalent to an established first-line antidepressant strategy. The choice still requires a defined target and repeated assessment of function.

TRAP **Do not quote the sertraline trial doses as a TBI therapeutic range.** The evidence supplies doses used in prevention trials and a treatment vignette, but it does not supply a recommended titration schedule or target range for post-TBI depression.

12.4 Refractory depression and neurostimulation

Electroconvulsive therapy after TBI is not contraindicated merely because traumatic brain injury has occurred. It may be considered for refractory post-TBI depression, provided technique is adapted to reduce cognitive and seizure-related burden. The recommended approach in the cited account is the lowest effective energy, brief-pulse stimulation, a nondominant unilateral current, with treatments spaced **2 to 5 days apart**.

The clinical reasoning is not "TBI excludes ECT," nor is it "ECT is routine." First confirm that the depressive target is severe and genuinely refractory, reconsider whether cognitive symptoms, apathy or medication adverse effects are being mislabelled as persistent depression, and ensure that the procedural plan permits close cognitive observation. The wider interval and conservative technique make the cognitive-safety principle explicit. Procedural consent, anaesthetic assessment and ordinary medical safeguards remain part of local practice, but no unsupported protocol is supplied here.

Repetitive transcranial magnetic stimulation requires caution after TBI because it may increase seizure risk. This is a warning against casual extrapolation from ordinary depression practice. It does not establish that the procedure can never be used, and it does not justify inventing a stimulation protocol. Where neurostimulation is considered, specialist assessment should integrate the injury history, current cognitive status, seizure-related risk and the strength of the indication.

GOOD TO REMEMBER

Previous traumatic brain injury is not, by itself, a prohibition against electroconvulsive therapy. The examination-quality answer couples that statement with conservative technique, wider spacing, cognitive observation and caution with repetitive transcranial magnetic stimulation.

12.5 Acute agitation versus chronic aggression

Acute post-TBI agitation requires a cognitive-protection strategy. Avoid anticholinergic medicines and benzodiazepines because they can worsen cognition and are deliriogenic, and be cautious with typical antipsychotics because cognitive recovery may be adversely affected. Before

adding a sedative drug, reassess whether pain, fear, overstimulation, an unfamiliar environment or an iatrogenic adverse effect is sustaining the behaviour. Medication that suppresses expression without correcting the driver may complicate neurological and psychiatric reassessment.

The evidence behind antipsychotic caution must be stated at the correct altitude. Animal work suggests that haloperidol and risperidone may impair cognitive recovery; in one rat study haloperidol, but not olanzapine, impaired cognitive performance after TBI. This is a safety signal, not a human comparative efficacy trial and not proof that every atypical antipsychotic is cognitively harmless. Also examine for akathisia, because antipsychotic-induced motor restlessness may be misread as worsening aggression and treated with further antipsychotic exposure.

Chronic post-TBI aggression has a different pharmacological frame. Options include amantadine, beta-blockers such as propranolol or pindolol, and SSRIs such as sertraline; anticonvulsants may be considered despite limited data. Antidepressant treatment alone may be insufficient. Beta-blockers more reliably suppress aggressive behaviour, while valproate and carbamazepine have been reported to suppress violent outbursts. Agent choice should follow the dominant target and the patient's medical and cognitive tolerability, not a reflex hierarchy detached from context.

The controlled evidence tempers enthusiasm. Trials using **amantadine 200 mg/day** and **carbamazepine up to 400 mg/day** for post-TBI irritability, aggression and anger found no significant active-placebo difference on most outcome measures. These are doses from negative trials, not target doses. The result does not prove that the named agents never help an individual patient; it means the clinician must be modest about expected benefit and explicit about the stopping rule.

PITFALL

Escalating antipsychotics for apparent “aggression” can worsen the very picture being treated when the behaviour is actually akathisia, cognitive toxicity or delirium. Re-examine the phenotype before increasing exposure.

12.6 Disinhibition, PTSD and anxiety

Post-TBI disinhibition may be approached with SSRIs or anticonvulsants used along the same broad lines as in mania. SSRIs may be useful when reduced sexual drive would also address hypersexual behaviour. In a comportment vignette, sertraline reduced irritability, outbursts and hypersexuality. The goal is behavioural control with preserved participation, not global emotional blunting. Treatment of coexisting cognitive impairment may itself improve behavioural control, reinforcing the need to combine medication with rehabilitation rather than treating disinhibition as an isolated chemical problem.

For trauma-related and anxiety presentations after TBI, SSRIs are a reasonable first-line pharmacological strategy because of their safety and tolerability. Prolonged exposure, cognitive processing therapy and cognitive behavioural therapy are favoured treatment modes, so the

prescription should sit inside a psychological formulation. Anticholinergic medicines and benzodiazepines should be avoided because their adverse cognitive effects are especially problematic after brain injury.

The largest placebo-controlled trial of prazosin for trauma-related nightmares was negative. The lesson is not that nightmares are unimportant, but that a familiar indication outside TBI should not be imported as settled evidence without qualification. Describe the target, prioritise the supported psychotherapeutic mode, and review whether a medication produces meaningful sleep and daytime benefit without cognitive cost.

Disinhibition, anxiety and agitation can look superficially similar when the history is compressed into "restless and difficult." Their pharmacological implications differ. Disinhibition is an impulse-control and comportment target; anxiety requires a fear-based formulation; acute agitation demands an immediate search for drivers and cognitive toxicity. The prescription follows that distinction.

12.7 Psychosis and secondary mania

For psychosis due to TBI, atypical antipsychotics are likely to remain the main pharmacological treatment by extrapolation from idiopathic psychosis, because direct clinical trials in TBI are absent. The phrase "by extrapolation" matters. It declares the evidence gap and prevents ordinary antipsychotic practice from being presented as TBI-specific proof. Choose and monitor treatment with particular attention to neurological and cognitive tolerability. Receptor pharmacology and general comparative drug selection belong in the Schizophrenia: management, antipsychotics and adverse effects notes.

Secondary mania after TBI may reasonably be managed along the broad lines of idiopathic bipolar disorder. Lithium and valproate are options, while case reports describe atypical antipsychotics such as quetiapine or olanzapine. Persistent cognitive impairment increases susceptibility to neurological adverse effects from lithium and anticonvulsants. This shifts the balance toward cautious initiation, close observation and a low threshold to reconsider treatment when neurological or functional decline emerges, without supplying unsupported thresholds or serum targets.

The general pharmacokinetics, therapeutic range and non-TBI adverse-effect teaching for lithium belong in the Mood disorders: pharmacotherapy notes; anticonvulsant pharmacology belongs in the Epilepsy and psychiatry notes. In this section the examinable point is the acquired-brain-injury modification: usual syndrome-based treatments remain available, but evidence is often extrapolated and neurological tolerability may be poorer.

When psychosis, mania and aggression coexist, avoid building a drug for every symptom. Decide which syndrome best organises the presentation and whether a single agent can address the dominant target. Polypharmacy makes attribution difficult: improvement cannot be assigned confidently, and cognitive or neurological worsening may be hidden among overlapping adverse effects.

12.8 Apathy is not simply untreated depression

Post-TBI apathy calls for a different pharmacological hypothesis from depression. Case reports and case series support trials of prodopaminergic agents such as methylphenidate, amantadine or bromocriptine, while bupropion is generally avoided because it lowers the seizure threshold in a population already at raised seizure risk. The evidence level is modest, so treatment should be framed as an individual trial with a behavioural and functional endpoint, not as a guaranteed restorative treatment.

The key examination distinction is direction of effect. SSRIs are first-line pharmacotherapy for post-TBI depression, but studies in the general population suggest that SSRIs may worsen apathy. Therefore reduced initiation should not automatically trigger antidepressant escalation. Reassess whether the patient has sadness, distress and depressive cognitions, or instead a primary reduction in self-generated, goal-directed behaviour. The full phenomenology belongs with the psychiatric sequelae of traumatic brain injury; the prescribing consequence belongs here.

A useful endpoint is not that the patient appears more animated during a brief interview. Look for initiation of ordinary activity, participation in rehabilitation, completion of routines and reduced need for prompting. Family observations can help, but the target should be concrete enough that expectancy and general activation are not mistaken for meaningful recovery. Cognitive treatment may also improve behavioural control and engagement, so a medication trial must remain embedded in rehabilitation.

Some agents appear in more than one indication in this topic. Methylphenidate may have relevance to depression, cognition, fatigue and apathy; amantadine appears among options for apathy and chronic aggression. This overlap is not a licence for nonspecific prescribing. It is a reason to state the principal target before treatment and to judge the outcome against that target.

12.9 Review, adequacy and rational stopping

An adequate therapeutic trial balances caution with sufficiency. Begin at a tolerable intensity, progress carefully, and allow adequate exposure before concluding that a treatment has failed. At the same time, each addition should carry a review point and a reason to stop. This prevents “go slow” from becoming passive under-treatment and prevents partial response from becoming permanent polypharmacy.

At review, ask linked questions. Did the target improve in a way that matters? Was cognition, arousal, neurological function or rehabilitation participation worsened? Is the medicine still necessary in the present phase and locus of care? A drug that was defensible during inpatient containment may no longer be appropriate after the environment settles. Conversely, a long-term affective or behavioural syndrome may require a sustained plan rather than repeated short, poorly evaluated trials.

Apparent non-response should trigger reformulation before augmentation. Check that the original target was correctly identified, that the patient received an adequate trial, that adverse effects are not mimicking the disorder, and that psychosocial or environmental drivers are being

treated. When benefit is absent or outweighed by cognitive cost, taper according to current agent-specific guidance rather than leaving the medicine in place "because of TBI."

> After TBI, prescribe for one explicit target, protect cognition and seizure safety, test benefit against function, and stop medicines that cannot justify their place.

The mature examination answer is therefore organised, not encyclopaedic. Start with locus, focus and modus; state nonpharmacological priority; distinguish acute agitation from chronic aggression; give syndrome-specific choices with their evidence limits; and close with monitoring and deprescribing. Doses should be printed only when TBI-specific evidence supplies them and should retain their trial or vignette context. That discipline is clinically safer than a remembered formulary and academically more honest than false precision.

Delirium and the amnestic syndromes

13 · Delirium: definition, diagnostic criteria and clinical subtypes

The marks lie in recognising a syndrome, not in calling every confused patient delirious.

Delirium is an acutely developing, fluctuating disturbance centred on attention and awareness, accompanied by disturbance in another cognitive domain and attributable to a physiological cause. DSM-5-TR classifies it as a neurocognitive disorder, but the bedside task is broader than attaching a label: demonstrate change from baseline, identify fluctuation, establish the cognitive pattern, respect exclusions and connect the syndrome to a medical, toxic, medication-related or withdrawal process.

Several distinctions prevent a vague answer. Attention is not the same as orientation, although each may be impaired. The syndrome is also not identical to the pathological process producing it: **acute encephalopathy** refers to the rapidly developing underlying brain process, whereas delirium names its clinical syndrome. The major diagnostic systems overlap in clinical description but organise the diagnosis differently. A disciplined answer therefore defines the syndrome, states each framework on its own terms, and then classifies psychomotor activity and course.

0.4%	6%-56%	UP TO 70%	UP TO 80%
COMMUNITY ADULTS	INCIDENCE IN HOSPITAL	MECHANICAL VENTILATION	TERMINAL ILLNESS NEAR DEATH

13.1 The clinical definition: a pattern of change

The defining disturbance is in **attention**: the capacity to direct, focus, sustain and shift mental engagement is reduced. This explains why a patient may answer an opening question yet lose the thread, become captured by irrelevant stimuli, or fail to follow a brief exchange. Attention must be distinguished from the amount of information remembered. Poor registration may follow poor attention, but an isolated memory complaint does not by itself establish delirium.

Awareness concerns orientation to and engagement with the environment. Its disturbance makes the patient less accurately situated in the immediate context. The diagnostic emphasis is on a departure from the person's usual state. A low cognitive baseline does not prevent delirium; it makes collateral comparison more important. The clinician asks what changed, when it changed, and whether the degree of engagement varies across observations.

The temporal signature is acute development with fluctuation. Under DSM-5-TR, the change usually emerges over **hours to a few days** and tends to vary in severity during the course of a day. A lucid interview therefore cannot erase convincing evidence of impairment earlier in the same illness. Conversely, a single disorganised interaction is insufficient unless the full pattern and physiological attribution are demonstrated.

Another cognitive disturbance completes the clinical picture. The affected domain may involve memory, orientation, language, visuospatial function or perception. Abnormal perceptions are common, especially visual or tactile hallucinations, but they are accompanying phenomena rather than the diagnostic centre. Behavioural or emotional disturbance may be prominent; neither substitutes for the required disturbance of attention and awareness.

RULE **Diagnose the pattern of acute change, not the loudest symptom.** Impaired attention and awareness, fluctuation, additional cognitive disturbance and a physiological basis carry more diagnostic weight than agitation, hallucinations or disorientation considered alone.

13.2 DSM diagnostic criteria: retain the full sequence

DSM-5-TR presents the diagnosis as an ordered criteria set. The order is educationally useful: define the core disturbance, establish its time course, add another cognitive domain, apply the neurocognitive and arousal exclusions, and require evidence of physiological causation. Omitting the final steps turns a syndrome definition into a symptom list.

CRITERION	REQUIRED CONTENT	DIAGNOSTIC WORK PERFORMED
A	Disturbance of attention accompanied by reduced awareness of the environment.	Identifies the core cognitive state rather than an isolated behavioural symptom.
B	Development over a short period, change from baseline, and fluctuation in severity during the course of a day.	Establishes onset, comparison state and variability.
C	An additional disturbance involving memory, disorientation, language, visuospatial ability or perception.	Shows that the syndrome extends beyond attention and awareness.
D	The disturbances are not better explained by a pre-existing, established or evolving neurocognitive disorder, and do not occur in severely reduced arousal such as coma.	Prevents misclassification of another neurocognitive state or coma.
E	History, examination or laboratory evidence supports direct physiological causation by a medical condition, intoxication, withdrawal, medication, toxin or multiple causes.	Links phenomenology to a physiological aetiology.

Criterion B requires the whole temporal sequence to remain visible: brief development, change from baseline, and fluctuation. “Acute confusion” is too imprecise because it does not show what changed or whether the course varies. Criterion C should also be stated as an additional cognitive disturbance, not as mandatory disorientation. A patient need not display every listed cognitive manifestation.

Physiological attribution is not an optional afterthought. The evidence may come from the history, physical examination or laboratory findings and may support one cause or several. The diagnostic answer should therefore pair syndrome recognition with a causal formulation, while the detailed aetiological model and pathophysiology remain separate topics.

MNEMONIC

A-B-C-D-E

Attention and awareness; **B**rief development, baseline change and fluctuation; **C**ognition additionally disturbed; **D**ifferential and severely reduced arousal exclusions; **E**tiological evidence. This preserves the diagnostic sequence without replacing the formal wording.

13.3 The highest-yield exclusion: another neurocognitive disorder or coma

The most commonly truncated part of the DSM-5-TR answer is Criterion D. The disturbance must not be better explained by another pre-existing, established or evolving neurocognitive disorder. This does not mean that a person with an established neurocognitive disorder cannot

also develop delirium. It means that the new attentional and awareness disturbance, its time course and its fluctuation must require an explanation beyond the prior condition.

Baseline is therefore a clinical comparator, not a screening score. Collateral history should establish the person's usual attention, awareness, communication, cognition and function, then describe the new departure. If previous impairment was already present, the clinician must demonstrate an acute superimposed change rather than simply relabel chronic cognitive difficulty. The full dementia syndrome and its workup belong in the Dementias and neurocognitive disorders notes.

The same criterion states that the disturbances do not occur in the context of a severely reduced level of arousal such as coma. This boundary matters because assessment of attention and awareness requires sufficient arousal for meaningful engagement. A patient who cannot be aroused enough to participate is not brought within the DSM-5-TR delirium criteria merely because a severe physiological brain disturbance is present.

GOOD TO REMEMBER

Write the baseline and arousal clauses explicitly. “Acute onset, fluctuating course and inattention” is recognisable shorthand, but it leaves the most discriminating exclusion unstated. In a vignette, ask whether the observed change exceeds the previous cognitive state and whether arousal permits attention to be assessed.

Disorientation, hallucinations, sleep-wake disturbance, emotional change and motor behaviour may strengthen the phenomenological description, but none repairs a missing Criterion D analysis. Similarly, evidence of infection, metabolic disturbance or drug exposure does not prove delirium unless the clinical syndrome is present. The diagnosis requires the appropriate phenomenology together with physiological attribution.

13.4 ICD characterization and etiological coding

ICD-11 characterises delirium through disturbed attention and awareness that develops over a short period and tends to fluctuate during the course of a day, accompanied by other cognitive impairment. The additional impairment may involve memory, orientation, language, visuospatial ability or perception. Behavioural and emotional disturbances are often present, and intoxication or withdrawal may cause the syndrome.

This characterization is clinically close to the shared syndrome core, but its classification spine is etiological. ICD-11 begins with **6D70** Delirium and then records whether the cause is a disease classified elsewhere, a psychoactive substance including medication, multiple etiological factors, another specified cause, or an unknown or unspecified cause.

ICD CATEGORY	ETIOLOGICAL MEANING	HOW TO USE IT CONCEPTUALLY
6D70.0	Delirium due to disease classified elsewhere	Name the syndrome and link it to the responsible disease.
6D70.1	Delirium due to psychoactive substances, including medications	Keep exposure, intoxication, withdrawal and medication context explicit.
6D70.2	Delirium due to multiple etiological factors	Avoid forcing a single-cause label when several factors contribute.
6D70.Y	Other specified delirium	Use when the cause is specified but not represented by the preceding categories.
6D70.Z	Delirium of unknown or unspecified cause	Preserve diagnostic uncertainty rather than inventing attribution.

Substance-class coding can become more specific, including alcohol-induced and sedative, hypnotic or anxiolytic-induced delirium. Those code branches establish aetiological placement; they do not replace a full withdrawal assessment. Withdrawal timelines, severity instruments and treatment regimens belong in the Substance use disorders notes.

13.5 The diagnostic systems must not be fused

The safe comparison begins by stating the overlap. Each framework centres disturbed attention and awareness, short development, fluctuation and additional cognitive impairment. Each permits physiological causes that include medical illness and substance-related states. This common clinical core supports recognition, but it does not authorise the candidate to build a hybrid list and attribute it to either manual.

TRAP **Do not present one harmonised "DSM and ICD criteria" list.** DSM-5-TR explicitly places the "not better explained" and severely reduced arousal or coma exclusion in Criterion D, whereas ICD-11 supplies the verified clinical characterization and organises the classification primarily by aetiology. State the frameworks separately, then compare them.

The distinction is more than examination etiquette. A formal exclusion determines whether a patient belongs inside a diagnostic set; an aetiological branch determines how an established syndrome is classified by cause. Treating these as interchangeable erases the work each system is doing. In a structured answer, lead with ICD-11, cross-map to DSM-5-TR, and identify the coma or severely reduced arousal clause as specific to the latter criteria presented here.

- For DSM-5-TR, preserve the complete A-to-E diagnostic logic and make Criterion D visible.
- For ICD-11, state the verified characterization without reconstructing an unverified enumerated essential-features list.
- For ICD-11 coding, place aetiology at the centre and retain an unspecified category when causation remains uncertain.

- In either system, do not let agitation, hallucinations or disorientation displace attention, awareness and temporal change.

This method also prevents false certainty. A patient can satisfy the clinical syndrome while the exact cause remains under investigation. Conversely, a plausible physiological insult does not establish delirium without the characteristic cognitive and temporal pattern. Syndrome recognition and causal attribution are linked tasks, but they are not the same inference.

13.6 Psychomotor subtypes: hyperactive, hypoactive and mixed

Psychomotor subtyping describes the activity pattern within established delirium. It must not become a substitute for the diagnostic criteria. The activity level can guide recognition and communication, but attention and awareness remain disturbed across subtypes. A quiet presentation is therefore fully compatible with delirium.

Hyperactive delirium has increased psychomotor activity. Agitation, mood lability and refusal to cooperate with medical care may accompany it; hallucinations and inappropriate behaviour may also be evident. It is more frequently recognised and is often associated with medication side effects and drug withdrawal. Its visibility explains why clinicians may mistake motor activation for the syndrome itself.

Hypoactive delirium has reduced psychomotor activity, with sluggishness and lethargy that may approach stupor. It is more frequent in older adults and is often unrecognised in emergency departments and hospitals. The Maudsley account associates this subtype with poorer prognosis. The central clinical danger is omission: reduced movement may be read as sleepiness, fatigue, low mood or cooperative calm while the attentional disturbance passes unnoticed.

Mixed level of activity includes patients whose activity rapidly fluctuates and also those with an apparently normal psychomotor level despite disturbed attention and awareness. The Maudsley description expresses the mixed pattern as features of increased and reduced motor activity. These descriptions are complementary reminders that activity can alternate, and that normal-looking motor behaviour does not exclude the cognitive syndrome.

> **PITFALL**
>
> Do not screen only the restless patient. Hyperactivity announces itself; hypoactivity can disappear into the ward routine. When behaviour becomes unusually quiet, slow or disengaged, assess attention, awareness, baseline change and fluctuation rather than assuming that absence of agitation means absence of delirium.

13.7 Course specifiers and the meaning of persistence

DSM-5-TR separates course from psychomotor activity. **Acute course** lasts **a few hours or days**, whereas **persistent course** lasts **weeks or months**. In hospital settings, delirium usually lasts about one week, although some symptoms often continue after discharge.

Course specifiers answer a different question from onset. The syndrome may begin over a short period yet continue beyond the immediate precipitating event. Persistence therefore does not by

itself convert delirium into a chronic neurocognitive disorder, nor does prolonged cognitive difficulty permit the clinician to abandon review of baseline, fluctuation, arousal and physiological attribution.

Activity subtype and duration should be documented independently. A patient may be predominantly quiet during a brief episode, activated during a prolonged episode, or alternate motor states while the syndrome continues. Collapsing these axes into labels such as “acute hyperactive delirium” without separately observing cognition, course and cause makes later reassessment difficult.

Documentation should keep the axes separate. Describe onset as the interval over which attention and awareness changed from baseline, and fluctuation as variation in severity across observation, collateral accounts and repeated examination. Record duration using the appropriate manual specifier. Record activity as hyperactive, hypoactive or mixed rather than inferring a stable subtype from a single encounter. This format lets another clinician revise one axis without discarding the entire formulation.

Persistent symptoms after discharge also make handover language important. The receiving clinician needs the previous baseline, the observed syndrome, the suspected cause, the pattern of fluctuation and the residual deficits. A bare statement that the patient “remains confused” loses the diagnostic architecture and encourages chronicity to be mistaken for a different syndrome without reassessment.

13.8 Bedside synthesis and examination answer

The clinical synthesis moves from observation to formulation. Establish that arousal permits meaningful assessment. Demonstrate impaired attention and reduced environmental awareness. Obtain collateral evidence of acute change and fluctuation. Identify another cognitive disturbance. Decide whether a pre-existing or evolving neurocognitive disorder better explains the presentation. Then seek evidence for a direct physiological cause and classify activity and course.

Bedside screening instruments can operationalise parts of this assessment, but they do not replace the diagnostic formulation; their administration and interpretation are covered in the dedicated delirium-screening section. Standard cognitive instruments are similarly adjuncts, not substitutes for collateral baseline and repeated observation, and their content and scoring belong in the Psychotherapies, clinical assessment, MSE and nosology notes.

The epidemiological gradient explains why case finding matters. Delirium is uncommon among community adults in the population estimate presented here, but it becomes much more frequent among medically vulnerable groups and in high-acuity settings. About **one-third** of patients older than 70 years admitted to hospital have delirium. Prevalence reaches up to 60% among nursing-home residents aged 75 years and older. These figures should sharpen vigilance without becoming a shortcut: setting changes prior probability, not the defining criteria.

A compact long answer begins by defining delirium through attention, awareness, acute baseline change, fluctuation, additional cognition and physiological attribution. It then states the ICD-11 characterization and etiological structure before cross-mapping the complete DSM-5-TR criteria and highlighting Criterion D. Psychomotor activity and duration are classified on separate axes. The answer closes by distinguishing delirium from acute encephalopathy, another neurocognitive disorder and severely reduced arousal. This sequence is concise without sacrificing the framework-specific distinction.

The answer should not drift into the separate territories of screening algorithms, aetiological mechanisms, investigation, management, prevention or withdrawal treatment. Name those tasks only when they clarify the boundary of the diagnosis. The present item is complete when the reader can recognise the syndrome, state the systems without conflation, apply the exclusion correctly and subtype the observed activity and course.

Delirium is an acute, fluctuating disturbance of attention and awareness with additional cognitive impairment and physiological attribution; preserve the DSM-specific coma exclusion and the ICD etiological spine.

14 · The Confusion Assessment Method and delirium screening at the bedside

Bedside delirium screening converts a vague impression of "confusion" into an observable clinical argument. The marks lie in showing how change from baseline, fluctuation, attention, thought organisation and arousal are assembled, rather than merely expanding an acronym. A strong answer also separates detection from the search for cause: a screening result identifies a syndrome that needs clinical attention, but does not name the precipitating illness, replace physical assessment or prescribe management.

IN INDIA

Use the Confusion Assessment Method or another brief bedside screen, and train ward nurses and residents to apply it, because delirium is otherwise easily missed.

The **Confusion Assessment Method** is a brief, validated diagnostic algorithm. Its value is practical: it gives the examiner a repeatable structure while preserving the central role of history, collateral information, observation and mental status examination. The diagnostic criteria and clinical subtypes of delirium are considered separately in this chapter. Here the task is narrower and highly examinable: perform the screen correctly, apply its logical rule, document the evidence and recognise the limits of the result.

BASELINE	OBSERVE	TEST	INTEGRATE
ESTABLISH CHANGE	SEEK FLUCTUATION	ATTENTION AND AROUSAL	APPLY THE ALGORITHM

14.1 What screening is meant to accomplish

Screening should answer a focused question: does the present bedside pattern justify identifying delirium and pursuing the clinical consequences of that finding? It is not a generic cognitive

examination and it is not a substitute for formulation. Begin by defining the patient's usual cognitive and functional state, then establish what has changed. A patient who cannot supply a coherent history may still be assessed because the evidence comes from several sources: the patient's performance, observed behaviour, nursing observations, records and a reliable informant.

The screen must remain connected to clinical context. Reduced participation may arise from impaired arousal, language difficulty, sensory limitation, motor impairment, severe distress or unfamiliarity with the task. These possibilities do not make screening useless; they determine which observations are interpretable. Record adaptations and state when a feature cannot be assessed confidently. A forced binary answer conceals uncertainty and can be less useful than a transparent account of what was observed.

Before testing, make the encounter examinable. Introduce yourself, obtain the patient's attention, reduce avoidable distraction and use language the patient can understand. Check whether a response can be expressed by speech, gesture or another reliable mode. The screen should challenge cognition, not accidentally challenge hearing, vision, literacy or motor output. When a barrier persists, name it beside the affected feature. This prevents later readers from mistaking "not demonstrated" for "demonstrated absent."

- Establish the usual baseline and the nature of the recent change.
- Use collateral and ward observations to reconstruct variation across the clinical course.
- Test attention directly rather than inferring it from social fluency.
- Describe the evidence for each algorithmic feature before recording the overall result.

RULE **A screen is an organised bedside inference, not a score detached from its observations.** Preserve the chain from baseline and behaviour to feature-level findings, algorithm and clinical interpretation.

14.2 The clinical feature set of the CAM

The instrument primarily concentrates on **four** major clinical features. **Acute onset** asks whether the present state represents a recent departure from the patient's usual condition. **Fluctuation** asks whether the manifestations vary during the course rather than remaining uniform. These are temporal observations, so the bedside interview alone is often insufficient. The examiner must compare the current encounter with earlier observations and with the patient's baseline.

Inattention concerns failure to direct, sustain or manipulate attention adequately for the task. It should be tested and also observed throughout the interaction. **Disorganised thinking** is reflected in a failure to maintain a coherent, relevant or logically connected line of thought. **Altered level of consciousness** concerns arousal rather than the content of thought. Thought disorder and altered arousal are therefore alternative downstream features in the diagnostic rule, not synonyms for poor attention.

The full instrument also looks for disorientation, memory impairment, psychomotor change, disturbance of the sleep-wake cycle and perceptual disturbance. These observations enrich the

clinical description but should not be substituted for the defining algorithm. This distinction matters in written answers: describing many compatible symptoms is not equivalent to demonstrating that the required logical combination is present.

ASSESSMENT AXIS	BEDSIDE QUESTION	BEST SOURCE OF EVIDENCE
Onset	Is this a recent change from the usual state?	Collateral history, records and prior observation
Course	Has the presentation varied across the clinical course?	Serial examination and the ward narrative
Attention	Can the patient engage, sustain and manipulate a simple mental set?	Direct task performance plus behaviour across the interview
Thinking	Are answers relevant, coherent and logically connected?	Conversation and responses to structured questions
Consciousness	Is the level of arousal altered?	Direct observation before and during testing

14.3 Applying the diagnostic algorithm

The CAM diagnostic rule has a conjunctive core and an alternative final limb. The patient must have evidence of acute onset, a fluctuating course and inattention. In addition, the examiner must identify either disorganised thinking or an altered level of consciousness. The word “either” is important: both final-limb features may be present, but the algorithm does not require both. Conversely, a final-limb feature cannot compensate for absence of the temporal and attentional core.

This logical architecture prevents two common shortcuts. The first is calling any disorientation delirium without establishing change, fluctuation and attention. The second is excluding delirium because the patient is not visibly agitated or grossly incoherent. Neither shortcut applies the algorithm. The examiner should instead move feature by feature, decide whether the evidence is present, absent or not interpretable, and only then integrate the result.

MNEMONIC

AFA + D/C

Acute onset, **F**luctuating course and **A**ttention failure form the required core; add either **D**isorganised thinking or altered **C**onsciousness. The letters preserve the AND-plus-OR structure rather than creating a simple symptom list.

The result should be documented as a reasoned conclusion. A useful note states the baseline source, the observed change, evidence for variability, the attention task and behaviour, the organisation of thought, the level of arousal, and the resulting algorithmic interpretation. If collateral information is unavailable, say so. If language or motor limitation prevents a task, describe the limitation and use other interpretable evidence without pretending that an unperformed test was normal.

TRAP **Do not reduce the CAM to "any feature is positive."** The temporal change and fluctuation, inattention, and the final either-or limb have distinct logical roles; a list of compatible symptoms does not reproduce the algorithm.

14.4 Establishing onset and fluctuation at the bedside

Acute onset is relational: it describes change from the patient's own baseline, not simply poor performance compared with an ideal norm. Ask an informant what the patient could usually do, communicate and understand before the present illness. Establish when the difference was first recognised and what made it noticeable. Records and nursing notes may show that the patient's engagement, speech or arousal differs from an earlier encounter even when the exact beginning cannot be reconstructed.

Fluctuation is similarly longitudinal. A calm, coherent interview does not erase a convincing history of marked variation, and a difficult encounter should not be treated as the whole course. Seek concrete contrasts: periods of better and poorer engagement, varying ability to follow conversation, or changes in arousal noted by staff or family. Avoid vague collateral such as "sometimes confused" when the informant can describe what the patient actually did and how that differed from usual functioning.

Operationally, ask for the last clearly usual state and the first clearly changed state without inventing precision that the history cannot support. Compare observations made in different care contexts and under different levels of fatigue or stimulation. Separate fluctuation in cognition or arousal from ordinary variation in cooperation, frustration or preference. When the bedside picture and the longitudinal account disagree, repeat the screen and preserve both observations for comparison.

GOOD TO REMEMBER

Before asking the patient to perform a cognitive task, ask the ward team what changed and how the state has varied. The temporal features may already be visible in the clinical narrative, while a single polished interview can conceal them.

14.5 Testing attention and observing arousal

Attention testing should be brief, comprehensible and matched to the patient's ability to hear, speak and respond. Common bedside operations include digit span, with repetition of **five digits forward** and **three digits backward**, and asking the patient to recite the days of the week or months of the year backward. These are not interchangeable with casual conversation. Familiar social responses can remain superficially fluent even when the patient cannot hold a simple mental set.

Observe the process, not merely completion. Does the patient register the instruction, lose the sequence, become captured by environmental stimuli, need repeated redirection or abandon the task? A failure may support inattention, but interpretation still requires checking comprehension and response capacity. Simplify the instruction when language is uncertain, ensure that hearing

and vision are adequate for the selected task, and document why a result is unreliable when these conditions cannot be met.

Arousal should be assessed before cognitive demand is increased. Note whether the patient can be engaged and maintain wakeful contact long enough for meaningful testing. Altered consciousness may itself satisfy the alternative final limb of the algorithm, but it also affects how much confidence can be placed in other responses. The examiner should not manufacture a detailed cognitive profile from a patient whose arousal prevents valid participation.

The Mini-Mental State Examination, Mini-Cog and Montreal Cognitive Assessment are commonly used bedside cognitive tests in delirium screening, but a tool does not replace the mental status examination. Their item content, scoring and standardised interpretation belong to the Psychotherapies, clinical assessment, MSE and nosology notes. In this context they may contribute cognitive observations; they do not replace the CAM logic or the temporal history.

14.6 CAM-ICU: validity with the population kept attached

The **CAM-ICU** is the critical-care application of the approach. In mechanically ventilated older patients, it showed **95% sensitivity** and **88% specificity** when compared with expert clinical diagnosis. Administration usually takes about 2 minutes. These figures make the instrument easy to remember, but their population label is part of the fact, not a footnote.

Sensitivity describes how effectively the instrument identifies patients who have the target condition against the chosen reference assessment; specificity describes how effectively it excludes those who do not. Neither measure turns a screen into an etiological diagnosis. The result must still be read with the bedside circumstances, the adequacy of testing and the clinical course. A technically completed screen cannot repair an incorrect baseline history or an uninterpretable response.

> **PITFALL**
>
> Do not quote the critical-care validity figures as though they were universal performance characteristics for every ward patient. They belong to the mechanically ventilated older population in which that application was assessed.

The same caution applies when communicating results. State the instrument and setting, the features found, the response limitations and the action required from the clinical team. “Screen positive” is less useful than a feature-level account showing which observations drove the result. If the state later changes, repeat assessment and preserve the comparison rather than overwriting the earlier description.

Serial use is clinically useful only when the conditions of assessment remain visible. A different result may reflect genuine change, a better interval, altered arousal, improved communication or removal of a testing barrier. Therefore compare feature-level findings, not merely the final label. Handover should identify which observation changed and which remained stable. This makes repeated screening a record of the clinical course instead of a pile of disconnected results.

14.7 Choosing among bedside instruments

Instrument choice depends on the clinical setting, the purpose of assessment, the patient's capacity to participate and the training available to the examiner. The aim is not to collect overlapping scores. Choose a tool that answers the immediate detection question, then use the clinical examination to understand the result and its limitations.

INSTRUMENT	ESTABLISHED USE IN THE AVAILABLE EVIDENCE	BOUNDARY FOR BEDSIDE USE
Confusion Assessment Method	Validated in inpatient units, emergency rooms and intensive-care settings	Apply its feature logic; do not treat it as a cause-finding workup.
4A's Test (4AT)	A quick delirium screening tool that does not require special training to administer	Use the authorised instrument; its scored items and thresholds are not reproduced here.
CAM-ICU	Validated for critically ill patients in the intensive-care setting	Keep setting-specific evidence attached to any interpretation.
Intensive Care Delirium Screening Checklist	Validated for critically ill patients in the intensive-care setting	Do not import an unverified scoring rule from memory.
Delirium Rating Scale-Revised-98	Validated in general medical and geriatric populations	Use according to its authorised administration and interpretation.
Mini-Mental State Examination, Mini-Cog and Montreal Cognitive Assessment	Common bedside cognitive tests used during delirium screening	Cognitive screening supports assessment but does not replace the mental status examination.

The 4AT is attractive where a rapid tool without special training is needed, but its worksheet must not be reconstructed from recollection. The Intensive Care Delirium Screening Checklist and CAM-ICU belong to critical-care practice, while the Delirium Rating Scale-Revised-98 has validation in general medical and geriatric populations. Naming these settings is more informative than producing an ungrounded league table of scores.

14.8 Interpretation, documentation and examination synthesis

The final product is a clinical statement that another doctor can verify. Record the informant and baseline, the evidence for recent change and variation, the attention task used, the observed organisation of thought, the level of arousal, any barriers to assessment and the algorithmic conclusion. This format makes disagreement productive: a later examiner can identify whether the difference lies in the history, the observed feature or the rule's application.

A positive result should trigger the clinical response appropriate to suspected delirium, including investigation of the underlying cause and attention to immediate safety, but those management details belong in the dedicated investigation and management section. A negative result should not silence a strong longitudinal concern when the assessment occurred during a better interval

or when the patient could not be tested adequately. Re-examination is part of honest interpretation because the target phenomena can vary.

Common documentation failures are avoidable. Do not write “confused” without describing the change. Do not equate disorientation with the complete algorithm. Do not report an attention task as passed when the patient never understood the instruction. Do not quote a validity estimate without its population. Do not let a cognitive screening score replace observation of arousal, attention and course. Each error breaks a different link in the chain from bedside evidence to inference.

The wording of uncertainty matters. “Feature absent” means the available observations argue against it. “Feature not established” means the history or examination did not supply enough evidence. “Feature not assessable” means a barrier prevented a valid judgement. These statements lead to different next steps: accept the observation, obtain better collateral, adapt the examination or repeat it later. Collapsing them into a negative result creates false reassurance and weakens continuity between teams.

The concise examination answer therefore has a recognisable spine. Define the Confusion Assessment Method as a brief validated diagnostic algorithm. State and explain the core feature set, distinguishing temporal change, attention, thinking and consciousness. Apply the required AND-plus-OR rule rather than listing symptoms. Describe bedside attention testing and the need for collateral and serial observation. Name setting-appropriate alternatives without reproducing unsupported scoring systems. Finish with validity kept population-specific and with the screen’s clinical limits.

> CAM requires acute onset, fluctuation and inattention, plus either disorganised thinking or altered consciousness; document the evidence for every limb before declaring the result.

15 · Delirium: aetiology, predisposing and precipitating factors, and pathophysiology

The examiner is asking for a causal formulation, not a catalogue of diseases. A strong answer explains why the same medical insult produces delirium in one patient but not another, then connects that vulnerability model to disturbances of arousal and attention and cerebral regulation. The central argument is that delirium arises from an interaction between the patient’s baseline reserve and the burden of new insults. Aetiological categories identify what can supply those insults; pathophysiological hypotheses explain how very different causes can produce a common syndrome.

This section therefore moves from bedside causation to brain mechanism. It does not restate the diagnostic criteria, clinical subtypes, screening instruments, investigation, management, prevention, or outcomes, which are addressed in their respective sections. Substance-withdrawal states are included only as causes and as mechanistic contrasts; their timelines, severity assessment and treatment belong in the Substance use disorders notes.

BASELINE	ACUTE	NETWORK	EEG
VULNERABILITY	PRECIPITANT	DYSREGULATION	PHYSIOLOGY

15.1 The multifactorial vulnerability model

The **multifactorial vulnerability model** separates background susceptibility from the event that brings the syndrome into expression. Predisposing factors are characteristics already present before the acute episode; precipitating factors initiate or lead to delirium. The distinction is conceptual rather than merely chronological. Baseline vulnerability lowers the amount of additional physiological or environmental stress required, while a robust patient generally needs a larger or more cumulative burden of stressors.

This is often called a **two-hit** model, but the label should not be misread as a literal event count. It describes the interaction of vulnerability and insult. Either side may itself be cumulative: frailty, sensory impairment and chronic disease may coexist before admission, while infection, medication changes, sleep loss and immobilisation may accumulate afterwards. The explanatory value lies in the balance between the sides, not in counting isolated causes.

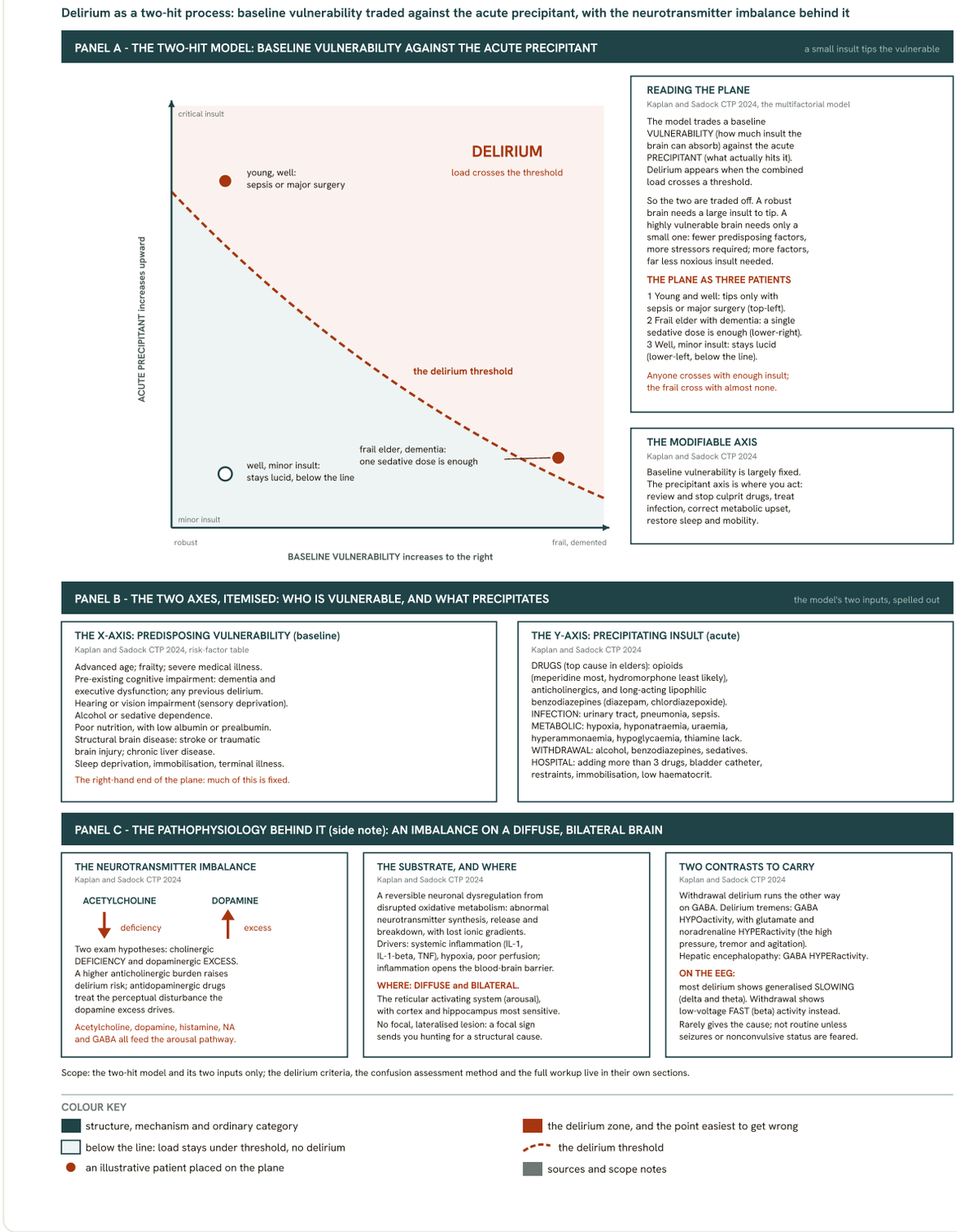


Fig 34.4 **Delirium as a two-hit process.** The multifactorial model plots baseline predisposing vulnerability against the acute precipitant: a robust brain crosses into delirium only with a large insult, while a highly vulnerable brain (advanced age, dementia, sensory impairment, frailty) needs only a small one, so the three example patients sit on either side of one threshold. Panel B itemises the two axes, and the side note gives the pathophysiology carried by these texts, a cholinergic deficiency and dopaminergic excess on a diffuse, bilateral brain, with the delirium tremens and hepatic encephalopathy GABA contrasts. (Kaplan and Sadock CTP 2024.)

The accompanying figure should be read across that balance. A highly vulnerable patient may cross the clinical threshold after a modest additional insult; a patient with little baseline vulnerability requires a greater acute burden. This explains why an apparently minor ward event

can be causally important in one person without being sufficient in another. It also explains why identifying one plausible precipitant should not end the causal search.

The model is probabilistic, not deterministic. A predisposing factor tells the clinician that the threshold may be lower; it does not prove that delirium must occur. A precipitant supplies causal pressure, but its significance depends on the host in whom it acts. This prevents symmetrical errors: dismissing a modest insult because it appears too small, or assuming that a large-looking insult explains the entire episode without considering the patient's prior vulnerability.

RULE **The smaller the baseline cerebral reserve, the smaller the insult needed to produce delirium.** Conversely, low baseline vulnerability generally requires a larger or cumulative precipitating burden.

15.2 Predisposing factors: the vulnerable host

Predisposing factors describe reduced reserve before the acute insult. The strongest clinical idea is not that each factor independently "causes" delirium, but that several factors can make cerebral function easier to destabilise. Pre-existing cognitive impairment, including dementia or executive dysfunction, and a previous history of delirium indicate an already vulnerable cognitive system. Advanced age, frailty and severe medical illness similarly signal limited capacity to absorb a new physiological disturbance.

Other vulnerabilities operate by reducing the reliability of input, physiological reserve or adaptation to the hospital environment. Hearing or visual impairment makes accurate interpretation of surroundings more difficult. Poor nutritional status, reflected by low albumin or prealbumin, chronic liver disease, terminal illness, sleep deprivation and immobilisation marks a host in whom metabolic and environmental stress may be less well tolerated. Alcohol or sedative dependence adds vulnerability because abrupt changes in exposure can become clinically important.

Structural brain disease, including stroke or traumatic brain injury, belongs on the predisposing side when it is established background pathology. The same diagnostic family may appear on the precipitating side when an acute brain event initiates the episode. Thus, classification depends on the temporal and causal role of the condition in the particular patient, not merely on its name.

Predisposition is also clinically dynamic. Sleep loss and immobilisation may already be present before an acute deterioration, then deepen during admission and function as ongoing precipitants. The useful question is therefore not "Which list owns this factor?" but "What role is it playing now?" Keeping baseline state and recent change in separate columns preserves the logic of the model even when the same exposure spans the transition into delirium.

- Cognitive reserve: pre-existing cognitive impairment and previous delirium.
- General reserve: advanced age, frailty, severe medical illness and terminal illness.
- Brain substrate: established stroke, traumatic brain injury or other structural brain disease.
- Sensory and nutritional reserve: hearing or visual impairment and poor nutritional status.

- Dependence and environment: alcohol or sedative dependence, sleep deprivation and immobilisation.

15.3 Precipitating factors: the acute burden

Precipitating factors are new insults that initiate delirium in a susceptible brain. Some are direct consequences of illness, while others are created or amplified by care. Bed rest or immobilisation, physical restraints, sleep deprivation and low haematocrit are recognised precipitants. Their importance is easily underestimated because none looks like a dramatic neurological event in isolation. Within the multifactorial model, however, several modest stresses may be sufficient when baseline vulnerability is high.

Medication exposure is particularly important. Opioids, anticholinergic medicines and benzodiazepines are prominent medication precipitants. In hospital, risk also rises with **more than three newly added medicines**. The count is not a diagnostic rule; it is a warning that rapid polypharmacy increases the chance of central effects, interaction, accumulation and attribution error. A medication list should therefore be read as a time sequence: what was introduced, stopped or escalated around the change in mental state?

Hospital processes may become part of the causal chain. Bladder catheters, malnutrition and iatrogenic events such as hospital-acquired infection or electrolyte abnormality are additional precipitants. A catheter, immobility, restraints, sleep loss and new medicines may accumulate during the same admission. Delirium may therefore emerge from a network of interacting insults rather than a single neat lesion.

A precipitating-factor formulation should preserve sequence and burden. It asks which exposure preceded the change, which persisted as the state evolved, and which appeared only after delirium was already established. This temporal discipline distinguishes plausible initiating factors from later consequences. It also keeps causal confidence proportional to the evidence: several contributors may be ranked as likely or possible without pretending that bedside chronology can always isolate a single sufficient cause.

QUESTION	PREDISPOSING SIDE	PRECIPITATING SIDE
When is it present?	Before the acute episode	At or near the onset
What does it do?	Sets baseline vulnerability	Initiates or leads to delirium
Typical examples	Cognitive impairment, frailty, sensory impairment, structural brain disease	New medicines, restraints, sleep deprivation, catheter use, iatrogenic events
Clinical reasoning	High vulnerability lowers the required insult	Low vulnerability requires a larger burden

PITFALL

Do not promote the first abnormality found into "the cause" without testing its timing and explanatory power. The multifactorial model permits several simultaneous precipitants, especially in a highly vulnerable inpatient.

15.4 Aetiological map: think beyond the ward chart

The **aetiological map** has broad families: systemic illness, medication effects, withdrawal states, primary brain disease, and surgery or trauma. These categories are not rival diagnoses. A single patient may occupy several columns, and the same process can affect the brain through more than one mechanism. The map prevents premature closure by forcing the answer to include systemic, toxic, withdrawal-related, neurological and procedural possibilities.

AETIOLOGICAL FAMILY	EXAMPLES WITHIN THE PERMITTED EVIDENCE	PATHOPHYSIOLOGICAL ROUTE TO CONSIDER
Systemic illness	Infection; dehydration, hypoxia, hypoglycaemia, hyperammonaemia, uraemia, hyponatraemia, thiamine deficiency; cardiovascular conditions	Inflammation, impaired oxygenation, perfusion or metabolism
Medicines	Anticholinergics, benzodiazepines and other sedative-hypnotics, opioids, antiarrhythmics, fluoroquinolones, clarithromycin, digoxin and interferons	Altered neurotransmission within arousal and attention systems
Withdrawal states	Alcohol, benzodiazepine or other sedative-hypnotic withdrawal	Loss of inhibitory tone with excitatory and noradrenergic overactivity in alcohol withdrawal
Primary brain disease	Stroke or transient ischaemic attack, trauma, meningitis, encephalitis, vasculitis, nonconvulsive status epilepticus and postictal states	Disruption of diffuse bilateral cortical and arousal networks
Surgery or trauma	Hip-fracture repair and coronary artery bypass grafting	Procedural stress superimposed on baseline vulnerability

MNEMONIC

System, Medicines, Withdrawal, Brain, Surgery

Use this sequence as a broad causal sweep: **S**ystemic illness, **M**edicines, **W**ithdrawal, primary **B**rain disease, and **S**urgery or trauma. It is a search scaffold, not a claim that the categories are mutually exclusive.

The category list also clarifies an important boundary. Nonconvulsive status epilepticus and postictal states can enter the delirium differential as primary brain causes, but seizure classification and anticonvulsant pharmacology belong in the Epilepsy and psychiatry notes.

Likewise, the presence of a withdrawal category does not authorise importing the full withdrawal syndrome into this causal section.

The categories converge rather than compete. Systemic illness may alter inflammation and perfusion; a medicine may alter neurotransmission; withdrawal may shift inhibitory and excitatory balance; and primary brain disease may directly disrupt distributed networks. Once several pathways converge on the same vulnerable arousal-attention system, the bedside phenotype may look similar despite very different starting points. That is why aetiology must be framed broadly while the mechanistic explanation remains integrated.

15.5 Older inpatients: infection and medication dominate

Among hospitalised older adults, infection and medication are the most important causes, and **medication is the single most common cause in older patients**. This emphasis follows directly from the vulnerability model. Older inpatients commonly bring baseline vulnerabilities into an environment where acute illness, procedures and medication changes accumulate. The aetiological answer should therefore give medication exposure the same seriousness as infection rather than treating it as an afterthought.

The important infectious causes in this setting include urinary tract infection, pneumonia and sepsis. The frequent medication causes are opioids, anticholinergic medicines and benzodiazepines. These groups also appear among general precipitants, but the older-inpatient emphasis is sharper: they are common enough that chronology and actual exposure deserve explicit reconstruction whenever mental state changes after admission.

Within opioids, the comparative signal is specific: meperidine is most likely and hydromorphone least likely to induce delirium. Within benzodiazepines, the most lipophilic agents with the longest elimination half-lives, including chlordiazepoxide, flurazepam and diazepam, are most likely to cause delirium. These comparisons should not be converted into a general prescribing algorithm here. Their purpose is aetiological: they refine suspicion when a delirium begins after exposure.

> **GOOD TO REMEMBER**
>
> In an older inpatient, reconstruct medication exposure as carefully as infection. Review new additions, cumulative sedative and anticholinergic burden, and whether several small hospital precipitants appeared together.

15.6 Neurotransmitter hypotheses: arousal and attention lose balance

The definitive pathophysiology remains incompletely defined, but neurotransmitter hypotheses provide a useful bridge from cause to phenotype. The central pairing is **cholinergic deficiency** with **dopaminergic excess**. Acetylcholine supports the distributed processing required for arousal and attention; reduced cholinergic function makes these systems less stable. Consistent with this model, greater anticholinergic burden increases delirium risk.

Increased dopaminergic neurotransmission is believed to contribute to the perceptual disturbances seen in delirium. The clinical observation that antidopaminergic antipsychotic

drugs can reduce such disturbances supports the hypothesis, but it does not establish dopamine excess as the sole cause of the syndrome. Drug selection, dosing and monitoring belong in the management section.

The arousal-attention pathway is chemically plural. Acetylcholine, dopamine, histamine, norepinephrine and GABA all influence it. Delirium should therefore not be described as a simple deficiency disease of one transmitter. Different aetiologies may perturb different parts of the system, while impaired metabolism, inflammation and altered perfusion can disturb several transmitters at once. The paired cholinergic and dopaminergic hypotheses are high-yield organising principles within a wider network model.

It helps to distinguish level of explanation. Neurotransmitter change is a downstream functional description, while infection, hypoxia, impaired perfusion or medication exposure may be upstream drivers. The same upstream insult may disturb several transmitter systems, and different upstream insults may converge on a similar transmitter imbalance. This layered account is more coherent than assigning every aetiology its own isolated pathway.

TRAP **Do not write "delirium is caused by acetylcholine deficiency."** Cholinergic deficiency and dopaminergic excess are implicated hypotheses within a broader disturbance involving multiple transmitters, metabolism, inflammation and distributed arousal networks.

15.7 Inflammation, oxidative metabolism and diffuse brain dysfunction

A second major account begins outside the neuron. **Systemic inflammation** is associated with increased inflammatory cytokines, including **IL-1 and IL-1-beta** and TNF. Inflammation can increase blood-brain-barrier permeability and affect microglia and astrocytes. The implication is not that every case is an inflammatory encephalitis, but that systemic illness can alter the cerebral milieu and destabilise neuronal regulation without requiring a focal lesion.

Other routes converge on energy failure. Hypoxia, impaired blood flow, reduced tissue perfusion and impaired metabolism can disrupt oxidative metabolism. Delirium is accordingly conceptualised as a reversible syndrome of neuronal dysregulation: energy-dependent ionic gradients become disturbed, and the synthesis, release or metabolism of neurotransmitters becomes abnormal. This framework links systemic infection, cardiopulmonary compromise and metabolic derangement to a common failure of neuronal organisation.

The neuroanatomical expression is **diffuse bilateral cortical dysfunction**, not a focal or lateralised process. The **reticular activating system** is assumed to be affected because it regulates alertness, while neocortical and limbic inputs to that system contribute to attention. The cerebral cortex and hippocampus are relatively more sensitive to metabolic disruption than other brain regions. Arousal, attention and memory can therefore fail together even when no single cortical territory accounts for the presentation.

This anatomical model has a practical interpretive consequence. A global change in mental state is compatible with diffuse metabolic or inflammatory dysfunction, whereas a focal neurological finding should prompt a search for a structural cause rather than being absorbed uncritically into

the label of delirium. Primary brain disease can cause delirium, but the clinical syndrome itself is not represented as a unilateral lesion.

The pathway can be summarised as a cascade without claiming a single final mechanism: systemic disturbance alters inflammation, oxygen delivery, perfusion or metabolism; the cerebral environment and cellular regulation become unstable; ionic gradients and transmitter handling are disrupted; and diffuse cortical plus arousal networks lose coordinated function. Reversibility is possible because the model concerns dysregulation rather than necessarily permanent neuronal destruction, although the underlying illness may still be serious.

15.8 State-specific mechanisms and the EEG correlate

Some aetiologies create recognisable transmitter contrasts. Delirium tremens is associated with GABA hypoactivity and hyperactivity of glutamate and norepinephrine. The increased noradrenergic drive of alcohol withdrawal helps account for high blood pressure, tremor and agitation. This is a mechanistic statement only; the withdrawal timeline, severity instruments and benzodiazepine regimens are taught in the Substance use disorders notes.

Hepatic encephalopathy provides the opposite GABA-direction contrast: GABA hyperactivity is implicated. Benzodiazepines show why transmitter labels must be applied in context. By enhancing GABA tone in corticothalamic networks, benzodiazepines can themselves produce cognitive impairment implicated in delirium, even though loss of inhibitory GABA activity characterises the withdrawal state. “More GABA” or “less GABA” is therefore not a universal delirium formula; the direction depends on the aetiological state and network involved.

The **electroencephalographic signature** of most delirium is generalised slow-wave activity in the delta and theta range, matching the concept of diffuse cerebral dysfunction. In hyperadrenergic alcohol or sedative withdrawal, the contrast is increased low-voltage fast beta activity. Thus, slowing is the usual exam answer, while fast activity points toward a withdrawal-related physiological state.

Electroencephalography rarely identifies the underlying cause and is not routinely performed solely because delirium is present. It becomes relevant when seizure activity or nonconvulsive status epilepticus is suspected. This preserves the distinction between a physiological correlate and an aetiological test: the tracing may support diffuse dysfunction or reveal a seizure-related alternative, but it does not replace the clinical causal formulation.

> Delirium is best understood as a vulnerable brain exposed to sufficient acute stress, producing reversible dysregulation of metabolism and neurotransmission across diffuse arousal and attention networks.

16 · Investigation and management of delirium

Delirium is a medical emergency with a psychiatric phenotype. The high-scoring answer therefore begins with a search for the precipitating illness or physiological derangement, not with a sedative prescription. Diagnosis remains clinical, but investigation explains why the brain has

become acutely dysfunctional and directs definitive treatment. The prescribing question comes later: whether dangerous agitation, severe distress or disruptive psychotic symptoms persist despite correction of causes and supportive care.

IN INDIA

Treat the underlying cause and use non-drug measures first; reserve haloperidol or olanzapine for dangerous agitation at the lowest effective dose, and keep dexmedetomidine for the intensive-care setting.

The practical hierarchy is **cause-directed treatment**, environmental and nursing support, then narrowly targeted symptomatic medication when the risk-benefit balance justifies it. Antipsychotics and benzodiazepines do not remove the cause. Formal diagnostic criteria, subtypes and bedside screening belong in their dedicated delirium sections; prevention bundles and longer-term outcomes are also addressed separately.

FIND	FIX	SUPPORT	RESERVE
THE PRECIPITANT	THE DERANGEMENT	THE PATIENT	SYMPTOM DRUGS

16.1 Management architecture: LOCUS, FOCUS and MODUS

LOCUS is determined by medical urgency and the resources needed for assessment, observation and treatment. A patient with delirium generally requires an emergency or inpatient medical setting, because the syndrome may signal an unstable underlying disorder and because cognition, cooperation and risk can change rapidly. Psychiatry contributes phenomenological assessment, behavioural containment and medication advice, but the patient remains under active medical evaluation rather than being diverted into a purely psychiatric pathway.

FOCUS changes across the episode. Acutely, priorities are physiological stability, identification of the precipitant, immediate safety and relief of severe distress. Once the cause is being corrected, focus shifts to restoring orientation, sleep-wake organisation, hydration, mobility and ordinary communication. As the state settles, the team reviews whether supportive measures can be simplified and whether any symptom-control medicine can be withdrawn. The diagnostic and treatment plan should be revisited whenever the course does not fit the presumed cause.

MODUS is deliberately multimodal. It combines investigation, correction of medical and medication-related contributors, nursing and environmental measures, family participation, mobilisation, sensory support and judicious pharmacotherapy. Psychological work in the acute state is supportive rather than insight-oriented: brief reassurance, repeated explanation and reduction of frightening misinterpretation. Social work may be needed to establish baseline function, identify available caregivers and make the discharge environment workable.

RULE **Treat the cause before treating the behaviour.** Symptom control may make care possible, but it is an adjunct to investigation and definitive medical treatment, never a substitute for them.

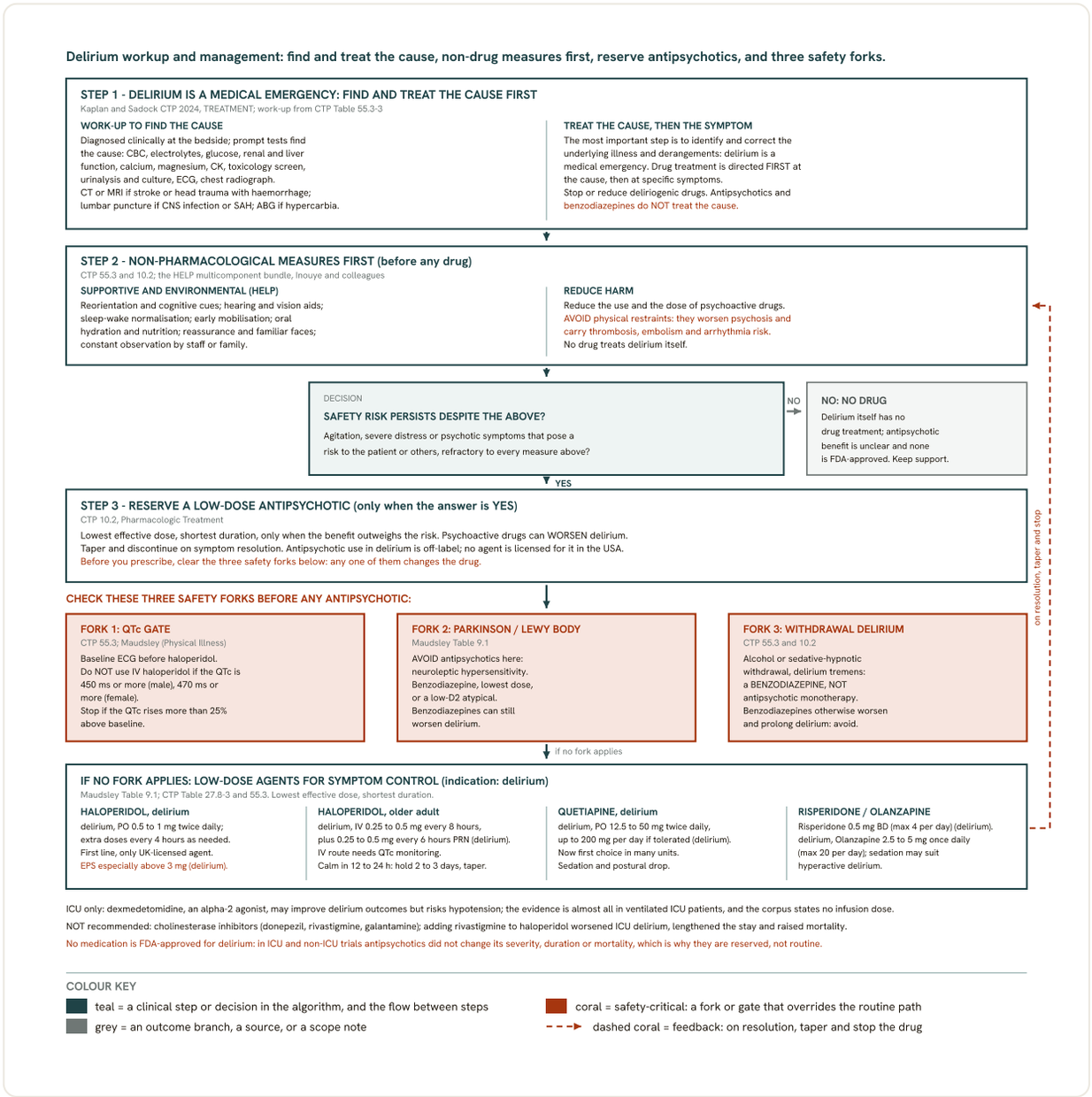


Fig 34.5 **Delirium: the workup-and-management algorithm.** Because delirium is a medical emergency, the path starts with finding and treating the cause and with non-pharmacological measures, not with a prescription; an antipsychotic is reserved for agitation, severe distress or psychosis that poses a safety risk and is refractory to those measures, at the lowest effective dose with a baseline ECG and QTc limits, and tapered on resolution. Three safety forks override the routine path: a baseline QTc gate before intravenous haloperidol; in Parkinson's disease and Lewy body dementia antipsychotics are avoided, and if a drug is essential a cautious lowest-dose benzodiazepine or a low-dopamine-blockade atypical such as quetiapine or clozapine is used under specialist guidance, recognising that benzodiazepines can themselves worsen delirium; and withdrawal delirium including delirium tremens is treated with a benzodiazepine rather than antipsychotic monotherapy. (Kaplan and Sadock 2024; Maudsley Prescribing Guidelines.)

The accompanying figure should be read as a recurrent loop rather than a single pass: stabilise, investigate, intervene, observe response and reopen the differential if the patient worsens or fails to improve. This protects against the seductive error of stopping the workup once a plausible contributor has been found.

16.2 Bedside investigation begins before the laboratory form

Investigation starts with verification of the syndrome and reconstruction of change from baseline. Establish what the patient was like before the acute illness, when the change was first

noticed, how alertness and attention have varied, and whether the presentation is compatible with delirium rather than a stable psychiatric syndrome. Obtain collateral history because the patient's account may be incomplete or internally inconsistent. The predisposing-versus-precipitating model is discussed in the dedicated aetiology section; here its purpose is to keep the search broad and prioritised.

The medication history is part of the examination, not an administrative appendix. Reconcile prescribed drugs, recent additions or withdrawals, non-prescription preparations, substances and possible access to another person's medication. Ask the ward team or family about actual exposure rather than relying only on the chart. Link each possible contributor to timing, physiological plausibility and change after correction. Avoid the opposite errors of ignoring medication effects and blaming every medicine without evidence.

Physical examination and observation guide test selection. Look for instability, dehydration, pain, infection, focal neurological findings, respiratory compromise, trauma and evidence of intoxication or withdrawal. Observe swallowing, mobility, continence, sensory impairment and the patient's ability to cooperate safely with essential care. A fluctuating behavioural presentation still requires an ordinary medical examination. Agitation is not evidence that examination can be deferred, while quietness is not evidence that the state is benign.

- Define baseline cognition, function and usual behaviour from a reliable informant.
- Reconstruct the temporal relationship between illness, procedures, medication changes and altered mental state.
- Repeat focused examination when the state changes rather than treating the first assessment as permanent.
- Document what remains unexplained, so diagnostic uncertainty stays visible to the next team.

PITFALL

Finding a urinary abnormality, sedating medicine or recent procedure does not prove that it is the sole precipitant. Delirium is often clinically multifactorial. Continue the search when severity, timing or response is not adequately explained.

16.3 Core laboratory and physiological workup

The **core delirium workup** is broad because reversible systemic disturbances can converge on a similar bedside syndrome. Tests should be interpreted in the clinical context, not ordered as an unexamined panel. A complete blood count may support a search for infection, anaemia or systemic illness. Electrolytes, glucose, renal function, liver function, calcium and magnesium identify metabolic and organ-function disturbances that can impair cerebral function or alter drug handling.

Creatine kinase and inflammatory markers may be useful when examination suggests muscle injury, systemic inflammation or a severe behavioural state. Syphilis serology, medication levels and toxicology testing are selected when the history, risk context or unexplained course makes

them relevant. Urinalysis with culture can identify urinary pathology, but the result must still be related to symptoms and the whole clinical picture. An electrocardiogram forms part of medical assessment and is a safety requirement before some symptom-control choices. Chest radiography is included when respiratory or thoracic pathology is plausible.

INVESTIGATION DOMAIN	INCLUDED TESTS OR SAMPLES	CLINICAL QUESTION
Haematological and inflammatory	Complete blood count, inflammatory markers	Is there evidence of systemic illness, infection or tissue stress?
Metabolic and organ function	Electrolytes, glucose, renal and liver function, calcium, magnesium	Is a correctable physiological derangement present?
Muscle and medication-related	Creatine kinase, indicated medication levels, toxicology screen	Is there muscle injury, accumulation, intoxication or an exposure not captured by history?
Infective sampling	Urinalysis with culture, selected serology	Does the presentation warrant targeted investigation for infection?
Cardiorespiratory	Electrocardiogram, chest radiograph	Is there a medical contributor or a treatment-related cardiac constraint?

A normal result does not clear the patient of delirium, because delirium is diagnosed at the bedside and the relevant cause may be clinical, medication-related, evolving or outside the initial panel. Conversely, an abnormal result does not automatically establish causation. Rank abnormalities by their ability to explain the onset, severity and course, correct what is actionable, and observe whether the mental state changes as expected.

16.4 Conditional investigations: image or sample for a reason

Escalate beyond the core workup when history or examination points toward a neurological, respiratory or inflammatory cause. Lumbar puncture is indicated when central nervous system infection, an autoimmune disorder or subarachnoid haemorrhage is suspected. It is not a routine ritual for every confused patient. The decision follows assessment of whether the suspected condition is plausible and whether the procedure can be performed safely.

CT or MRI is selected when stroke is suspected or head trauma raises concern for haemorrhage. Imaging should answer a focused structural question. A psychiatric history must never lower the threshold for recognising focal findings or trauma, while a normal scan does not negate a clinically established delirium arising from systemic illness. Where immediate access differs, the available modality and urgency determine the practical sequence, but the clinical question remains the same.

Arterial blood gas analysis is appropriate when hypercarbia is a concern in chronic obstructive pulmonary disease. This is an example of hypothesis-driven testing: bedside respiratory assessment creates the question, and the test evaluates a physiological disturbance that routine

chemistry may not answer. Similar reasoning should govern every added investigation. Order a test because its result can revise the causal formulation or immediate management.

Detailed neuropsychological testing is usually deferred because impaired attention makes higher-order results difficult to interpret. This is not therapeutic neglect. Repeated bedside assessment is better suited to a fluctuating acute state; formal cognitive evaluation becomes meaningful after the patient can engage consistently. Standardised cognitive instruments and their scoring belong in the Psychotherapies, clinical assessment, MSE and nosology notes.

GOOD TO REMEMBER

Write the indication beside every conditional investigation. “CT because of focal findings after an acute change” is clinically stronger than “CT brain to rule out organicity,” which neither prioritises a diagnosis nor explains how the result will change care.

16.5 Definitive treatment and the non-pharmacological foundation

The decisive intervention is correction of the underlying medical illness, toxic exposure, medication effect or physiological derangement. This may require antimicrobial, respiratory, metabolic, surgical or medication-related treatment directed by the responsible medical team. Psychiatry should keep the causal plan visible in its note. Writing only “manage agitation” accidentally reframes an emergency as a behaviour problem.

Non-pharmacological support begins immediately and runs alongside definitive treatment. Reorient the patient calmly and repeatedly without arguing about every mistaken belief. Ensure access to appropriate sensory aids. Use familiar people and consistent explanations where possible. Support hydration and mobilisation according to medical safety, normalise the sleep-wake pattern, and provide reassurance. These measures reduce avoidable cognitive load and fear while preserving function.

The environment should make the correct behaviour easier. Keep communication brief, concrete and respectful. Introduce staff and explain procedures before touching the patient. Reduce unnecessary transfers, conflicting instructions and avoidable night-time disruption. Family can supply baseline information, familiar reassurance and observation, but should not be made solely responsible for containment. Nursing care remains active treatment: attention to comfort, elimination, nutrition, mobility, skin integrity and safe use of sensory aids prevents secondary burdens from perpetuating distress.

MNEMONIC

CAUSE first

Correct the precipitant; **A**id reorientation; **U**se sensory aids; **S**upport sleep, hydration and reassurance; **E**ncourage safe mobilisation. The mnemonic describes active treatment, not a prevention bundle.

Physical restraints should be avoided as far as possible. They can worsen psychotic symptoms and are associated with deep vein thrombosis, pulmonary embolism and cardiac dysrhythmias in

delirious patients. Continuous observation by staff or family may reduce the need for restraint. If immediate containment becomes unavoidable under local policy, the team should treat it as a temporary safety intervention, continue cause-directed care and reassess the need repeatedly.

16.6 The pharmacological threshold: rescue, not routine treatment

There is **no U.S. FDA-approved medicine for delirium or its behavioural disturbance**. Antipsychotic use is off-label, and studies in general medical and intensive-care settings have not shown reliable improvement in the outcomes that matter most, including severity, resolution, mortality or delirium duration. This evidence should stop routine prescribing, but it does not remove the need for proportionate rescue treatment when behaviour creates immediate danger or intolerable distress.

The indication is narrow: use a low-dose antipsychotic only when severe agitation or psychotic symptoms remain refractory to non-pharmacological care and create a safety risk. Choose the lowest effective dose, prescribe against a clearly documented target, and continue only while benefit outweighs risk. Taper and discontinue after symptom resolution. A calmer patient is not proof that the cause has been treated; sedation can make examination and fluctuation harder to observe.

Within the acute **LOCUS**, the **FOCUS** is a specific behaviour that prevents safe assessment or essential care, threatens the patient or others, or causes severe distress. The **MODUS** remains combined: staff presence, de-escalation, environmental support and cause-directed treatment continue while medicine is used. The prescription should state the delirium indication so it is not mistaken for treatment of a primary psychotic disorder during transfer or discharge.

TRAP **Do not write "haloperidol is the treatment of delirium."** It may control dangerous agitation or psychotic symptoms; it does not treat the precipitating illness, and routine antipsychotic use has not shown dependable delirium outcome benefit.

Antipsychotic receptor pharmacology and broader drug selection belong in the Schizophrenia: management, antipsychotics and adverse effects notes. Here the comparison is deliberately limited to delirium-scoped use, low dosing, route, tolerability and cardiac or neurological constraints.

16.7 Delirium-scoped antipsychotic dosing

Doses used for symptomatic control in delirium are low and indication-specific. Do not import a schizophrenia regimen. Oral treatment is preferable when the patient can take it safely and the clinical situation permits; intramuscular administration is an option when oral administration is not feasible and urgent behavioural control is necessary. Route choice also depends on monitoring capacity and the need to avoid coercion.

AGENT AND DELIRIUM INDICATION	DELIRIUM-SCOPED SCHEDULE	PRACTICAL CAUTION
Haloperidol, oral, for severe agitation or psychotic symptoms in delirium	**0.5-1 mg twice daily, with additional doses every 4 hours as needed**	Peak effect occurs at 4-6 hours; extrapyramidal effects are more likely above 3 mg.
Haloperidol, intramuscular, for the same delirium indication when oral treatment is not feasible	0.5-1 mg intramuscularly; observe for 30-60 minutes and repeat if necessary	Peak effect occurs at 20-40 minutes.
Quetiapine, oral, for severe agitation or psychotic symptoms in delirium in delirium	**12.5-50 mg twice daily; if tolerated, increase every 12 hours up to 200 mg daily**	Sedation and postural hypotension are common adverse effects.
Risperidone, oral, for severe agitation or psychotic symptoms in delirium in delirium	0.5 mg twice daily, with additional doses every 4 hours as needed; usual maximum 4 mg per day	Response may be poorer in older patients.
Olanzapine, oral, for severe agitation or psychotic symptoms in delirium in delirium	2.5-5 mg once daily, up to 20 mg per day	Sedation is the most commonly reported effect and may be useful when the presentation is markedly agitated.

For an older adult with delirium requiring behavioural control, in delirium, a conservative intravenous haloperidol schedule is 0.25-0.5 mg every 8 hours scheduled, with 0.25-0.5 mg every 6 hours as needed. If oral dosing is used, the corresponding schedule in delirium is 0.5-1 mg every 8 hours scheduled, with 0.5-1 mg every 6 hours as needed. If calm is achieved within 12-24 hours, continue for 2-3 days and taper over the next 2-3 days. This is a short symptom-control plan, not maintenance psychopharmacology.

Agent choice is secondary to indication discipline. Avoid combining agents merely because the first dose has not produced immediate tranquillity. Reassess the target, timing, route, accumulating adverse effects and the possibility that pain, hypoxia, fear or another untreated driver is sustaining the behaviour. Current local prescribing guidance and monitoring requirements should be checked before use.

16.8 QTc safeguards, exceptions and treatments to avoid

Obtain a baseline electrocardiogram before haloperidol. **Intravenous haloperidol QTc thresholds** are **450 ms or greater in a male and 470 ms or greater in a female**; at or beyond these values, intravenous haloperidol should not be used. Discontinue haloperidol if the QTc becomes prolonged by **more than 25% above baseline**. Interpret the tracing together with concurrent cardiac risk factors and other medicines rather than treating the number in isolation.

Antipsychotic sensitivity in Parkinson's disease and Lewy body dementia changes the plan: avoid haloperidol and antipsychotics generally. If a drug is genuinely needed here, a benzodiazepine such as lorazepam or diazepam is the usual alternative, used cautiously at the lowest effective dose because benzodiazepines can themselves worsen delirium; where an antipsychotic cannot be avoided, a low-dose agent with minimal dopamine blockade such as

quetiapine or clozapine is preferred under specialist guidance. Outside these neurological exceptions and sedative-hypnotic withdrawal, benzodiazepines should be avoided because they can exacerbate delirium, prolong it and increase falls risk, particularly in older adults. Withdrawal delirium, including its assessment and benzodiazepine regimens, belongs in the Substance use disorders notes.

Dexmedetomidine is setting-specific. Limited and mixed evidence suggests potential benefit in intensive-care populations, but cardiovascular adverse effects, particularly hypotension, confine its use to monitored intensive-care practice. Evidence should not be generalised to the ordinary ward, and no dose is supplied here because the permitted evidence does not provide one.

Cholinesterase inhibitors are not recommended for delirium. Adding rivastigmine to usual intensive-care treatment did not shorten delirium and was associated with a more severe presentation, longer intensive-care stay and higher mortality than placebo. Donepezil, rivastigmine and galantamine, used in Alzheimer disease, have not been adequately studied for delirium and should not be repurposed for it.

> Find and treat the precipitant, institute supportive care first, and reserve low-dose symptom medication for refractory severe distress or safety risk.

The safe endpoint is not simply a quiet patient. It is a patient whose cause has been identified as far as possible, whose physiology and comfort are being corrected, whose environment supports cognition, and whose temporary behavioural medication has a documented indication, monitoring plan and stopping decision. Failure to improve should reopen the causal formulation rather than automatically escalate sedation.

17 · Delirium prevention, outcomes, and substance-withdrawal delirium

Delirium prevention is active treatment of vulnerability before the syndrome appears. The marks lie in recognising that a substantial burden is avoidable, translating risk into a coordinated non-pharmacological bundle, and understanding that an episode is not necessarily transient in its consequences. Withdrawal delirium then supplies the crucial exception to ordinary symptomatic practice: the underlying withdrawal physiology must be treated, not merely the visible agitation.

> **IN INDIA**
>
> Give parenteral thiamine before or together with glucose in a malnourished or alcohol-dependent patient, without delaying treatment of hypoglycaemia, and treat alcohol-withdrawal delirium with a benzodiazepine rather than antipsychotic monotherapy.

This section names, but does not restate, delirium criteria and subtypes. It also uses the predisposing-versus-precipitating model only to explain why prevention is targeted; that model and delirium pathophysiology are taught in the dedicated aetiology section. Investigation and general management are addressed separately. Here the organising sequence is prevention, outcome surveillance, recognition of withdrawal, and safe exception management.

30% to 40%	OVER 200	35% to 40%	SIX-FOLD
CASES POTENTIALLY PREVENTABLE	HOSPITALS USING HELP	OLDER-PEOPLE MORTALITY AT ONE YEAR	MORTALITY ODDS WITH NEUROLEPTICS IN DT

17.1 Prevention begins with the vulnerability model

Multicomponent non-pharmacological prevention is the central approach. Delirium rarely reflects a single ward event that can be neutralised by a single tablet. Prevention instead reduces several modifiable pressures at the same time while protecting cognition, sleep, mobility, hydration, nutrition and sensory access. This is the practical consequence of the risk-factor model: a vulnerable brain may cross the threshold after several individually modest insults, so apparently ordinary elements of care become biologically important when they accumulate.

Among hospital cases, delirium may be preventable in **up to 30% to 40%**. This estimate makes prevention a patient-safety task rather than an optional refinement. The relevant question is not merely, "Does the patient have delirium now?" It is also, "Which foreseeable contributors can the team reduce before cognitive failure appears?" Screening identifies the population in whom prevention should be intensified, but the diagnostic criteria and screening instruments themselves belong in their dedicated delirium sections.

Prevention must be embedded in routine care. Risk is reviewed when the clinical context changes, and the bundle is adjusted to what the patient can safely do. Mobility, for example, is promoted within surgical and medical constraints; hydration and nutrition are supported in a manner compatible with the patient's treatment; sensory aids help only if they are available and usable. This is coordinated individualisation, not a rigid checklist detached from the illness.

RULE **Prevent delirium by reducing cumulative avoidable burden, not by searching for a universal prophylactic drug.** The bundle acts across several modifiable domains because risk is usually produced by interacting vulnerabilities and insults.

17.2 HELP: the ward-based prevention bundle

The most widely used strategy is the **Hospital Elder Life Program (HELP)**. Its design is clinically coherent: maintain meaningful cognitive engagement, keep the patient moving, reduce unnecessary psychoactive exposure, protect sleep without relying on medication, maintain oral intake, and correct the avoidable isolation produced by impaired hearing or vision. Each domain removes a source of cognitive or physiological stress; together they create a ward environment less likely to push a vulnerable patient into delirium.

HELP DOMAIN	WARD ACTION	WHY IT MATTERS
Cognition	Reorientation and therapeutic activities	Preserves contact with place, people and purposeful activity
Mobility	Early mobilisation with exercise or walking	Prevents avoidable immobility from becoming part of the risk burden
Medicines	Reduce psychoactive-drug use and doses	Limits avoidable drug-related cognitive disturbance
Sleep	Promote sleep through non-pharmacological measures	Protects the sleep-wake cycle without adding sedative burden
Intake	Maintain oral hydration and adequate nutrition	Supports physiological reserve during illness
Senses	Provide appropriate hearing and vision aids	Improves access to orientation, communication and reassurance

MNEMONIC

Mind, Move, Medicines, Midnight, Meals, Missing senses

The alliterative spine recalls the HELP domains: cognitive reorientation and activity, early mobility, reduced psychoactive exposure, non-drug sleep promotion, hydration and nutrition, and appropriate hearing and vision aids.

HELP has been implemented in more than 200 hospitals worldwide and has shown effectiveness and cost-effectiveness in reducing delirium and improving outcomes for hospitalised older people. Scale matters because a prevention bundle succeeds only when it survives ordinary ward practice. Its strength is not a proprietary object or a single specialist encounter; it is a repeatable pattern of nursing, medical, rehabilitative and family-supported care.

17.3 Adapt the bundle to intensive care and surgery

In intensive care, prevention is organised through the **ABCDEF bundle**: assess and manage pain; coordinate spontaneous awakening and breathing trials; choose sedation and analgesia deliberately; assess and manage delirium; promote early mobility and exercise; and engage and empower family. The bundle is associated with a decreased risk of delirium. Its logic is continuity across disciplines: ventilation, sedation, pain, cognition, movement and family involvement cannot be managed as unrelated silos.

The perioperative lesson is similarly practical. In older adults undergoing hip-fracture repair, lighter sedation produced an **approximately 50% reduction in postoperative delirium risk**. Minimising benzodiazepines and selected opioids, particularly meperidine, can further reduce postoperative incidence. The point is not to deny necessary analgesia or anaesthesia. It is to avoid greater sedative exposure than the clinical task requires and to review the postoperative medication plan as part of delirium prevention.

Implementation should make omissions visible. The team can document whether the patient received the indicated orientation, mobility, sleep, intake and sensory measures, and why any element could not be delivered. When delirium nevertheless develops, this record helps distinguish an unavoidable limitation from a preventable care gap and allows the bundle to be revised. It also prevents the label "non-pharmacological" from being mistaken for passive care. These interventions require assessment, coordination, repetition and accountability.

- Place prevention in the care plan before cognitive change appears, rather than adding it after agitation begins.
- Assign each bundle element to a team member, because an unowned intervention is easily omitted.
- Reconcile psychoactive exposure across anaesthesia, intensive care, ward prescriptions and as-needed medication.
- Preserve mobilisation, sleep, oral intake and sensory access within the constraints of the medical condition.
- Use family engagement to support orientation and baseline knowledge, while retaining professional responsibility for care.

GOOD TO REMEMBER

The prevention prescription is written in verbs: orient, mobilise, review medicines, protect sleep, support intake and restore sensory access. "Observe for delirium" detects failure; it does not itself prevent it.

17.4 Why routine pharmacological prophylaxis is not the answer

Routine pharmacological prophylaxis has no clear evidence base. Evidence is limited for routine haloperidol or the second-generation antipsychotics olanzapine and risperidone, and there is no clear support for cholinesterase inhibitors or melatonin in non-intensive-care settings. Medication minimisation is itself an effective preventive strategy. Prescribing a psychoactive drug to compensate for preventable ward-level risk therefore reverses the preferred hierarchy.

A frequently examined signal requires careful interpretation. In an acute-care study published in 2014, ramelteon given for delirium prevention at 8 mg at night was associated with 3% delirium compared with 32% in the placebo group. Four of five later trials of melatonin analogues reported benefit, but heterogeneity limited broad recommendations. This is a prevention-outcome finding, not a delirium-treatment dose and not authority for routine use in every setting.

The apparent tension is resolved by evidence hierarchy and scope. A promising individual trial can justify further study and informed local discussion, while the total evidence can remain insufficient for universal prophylaxis. Candidates should state the signal and its limitation without turning uncertainty into nihilism: the finding is clinically interesting, but the standard prevention answer remains a multicomponent non-pharmacological bundle plus reduction of deliriogenic medication.

PITFALL

Do not convert the ramelteon study into routine prescribing, and do not mislabel 8 mg at night as treatment for established delirium. The cited regimen concerns prevention in acute-care patients.

17.5 Outcomes: delirium is not a transient inconvenience

Clinical recovery from the acute behavioural state does not erase prognosis. In older people with delirium, the **one-year mortality is 35% to 40%**. The excess mortality risk persists at 12, 24 and 36 months, with a risk ratio of at least 2 at each time point; increased cognitive and functional impairment also remains evident at 24 months. These associations reflect a population with serious illness and vulnerable brains, but they still make delirium an important prognostic marker.

Persistence must be described by the outcome actually measured. A course account in the comprehensive psychiatry textbook reports residual delirium symptoms in 20% of older adults for up to 6 months; another overview in that textbook reports as many as 15% still symptomatic at 6 months. By contrast, the physical-illness prescribing guideline reports persistent cognitive impairment after delirium in up to 60% of individuals. Residual delirium and residual cognitive impairment are not interchangeable constructs, and their percentages must not be averaged or presented as competing estimates of the same endpoint.

OUTCOME CONSTRUCT	REPORTED FINDING	CORRECT INTERPRETATION
Persistent delirium symptoms	20% of older adults with residual symptoms for up to 6 months; another account gives as many as 15% symptomatic at 6 months	The syndrome or some of its symptoms remain present
Persistent cognitive impairment	Up to 60% following delirium	Cognitive deficit persists after the episode; this is broader than residual delirium
Mortality in older people	35% to 40% at one year	Delirium identifies a group requiring serious prognostic attention
Longer-term mortality association	Risk ratio at least 2 at 12, 24 and 36 months	The mortality association is sustained beyond discharge

TRAP **Do not collapse persistent delirium into persistent cognitive impairment.** The 15% and 20% reports concern residual delirium symptoms, whereas up to 60% concerns cognitive impairment after delirium. The denominators and measured outcomes differ.

17.6 Cognitive follow-up: delirium as a cerebral stress test

In vulnerable older adults, delirium may leave permanent cognitive impairment and increase incident dementia; affected patients have been reported to be three times more likely to develop dementia. Patients with Alzheimer disease may decline more rapidly after an episode. The relationship is bidirectional: pre-existing cognitive vulnerability increases susceptibility to

delirium, while delirium may accelerate subsequent decline. This is why an apparent return to behavioural calm should not end cognitive and functional observation.

The useful clinical metaphor is a **brain stress test**. Serious illness may expose cognitive deficits that were present but not obvious in ordinary life. The episode should therefore trigger careful reconstruction of premorbid function, review of recovery with an informant, and attention to whether cognition and daily functioning return toward baseline. It should not trigger a dementia diagnosis during an unstable confusional state. The dementia syndrome and its full workup belong in the Dementias and neurocognitive disorders notes.

Outcome assessment should separate several questions: Has the delirium itself resolved? Is cognition still impaired? Has mobility or self-care fallen below baseline? Is the family observing a new trajectory? Does the patient now require a different level of support? This separation prevents a quiet, dependent patient from being labelled “recovered” merely because disruptive behaviour has ceased. It also avoids treating every post-illness cognitive complaint as proof of a progressive neurocognitive disorder.

Discharge communication should preserve diagnostic uncertainty and the need for review. State the pre-illness baseline as far as known, the degree of recovery achieved, and the domains that remain impaired. The long-term outcome data justify follow-up, but they do not predict the fate of an individual patient with certainty.

Prognostic communication should be serious without becoming deterministic. Families can be told that lingering confusion and cognitive or functional decline are recognised outcomes, that recovery may be incomplete, and that a changed trajectory deserves reassessment. The clinician should also avoid attributing every later difficulty directly to delirium, because the underlying illness and premorbid vulnerability remain part of the causal picture. The episode is an event to recover from as well as a marker that future stress may expose limited cerebral reserve.

17.7 Recognising alcohol-withdrawal delirium within the differential

Delirium tremens is the severe agitated delirium of alcohol withdrawal. It occurs in around **3% to 5% of people admitted to hospital for alcohol withdrawal** and typically develops around 72 hours after the last drink. A careful alcohol history must therefore establish the last reliable intake, subsequent access to alcohol, prior severe withdrawal and the chronology of autonomic and behavioural change. A patient may be admitted for another illness and develop withdrawal only after alcohol access stops.

The broader withdrawal syndrome provides context without making delirium the expected outcome. Fewer than 10% of people who develop alcohol withdrawal ever develop dramatic manifestations such as severe autonomic hyperactivity, marked tremor or withdrawal delirium, and tonic-clonic seizures occur in fewer than 3%. Delirium tremens lies at the severe end of the alcohol-withdrawal spectrum and may emerge later than the initial withdrawal symptoms; its detailed symptom time course belongs in the Substance use disorders notes.

Previous seizures or delirium, low potassium, low magnesium, thiamine deficiency, systemic disease and undertreated withdrawal predispose to delirium tremens. These features increase vigilance; they do not replace bedside diagnosis or justify waiting for the full syndrome before treating escalating withdrawal.

The full withdrawal timeline, the content and scoring of the **Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar)**, and complete benzodiazepine regimens belong in the Substance use disorders notes. Within the delirium differential, the essential task is to recognise the withdrawal context because it changes the pharmacological principle.

17.8 Withdrawal delirium: LOCUS, FOCUS and MODUS

LOCUS: delirium tremens is a medical emergency requiring general-hospital care. NICE guideline CG100, updated in 2017, recommends nursing the patient in a general hospital and using lorazepam orally or intravenously. The setting must support medical assessment, repeated observation, correction of contributing illness and escalation when withdrawal remains uncontrolled.

FOCUS: in the acute phase, the target is the withdrawal state and its associated agitation, autonomic activation and risk, not tranquillity alone. As control is achieved, focus moves to preventing recurrence, correcting contributors and reassessing whether another cause of delirium is also present. A familiar low-dose rapid-tranquillisation protocol, particularly one that includes haloperidol, is explicitly inappropriate for delirium tremens because it is designed around a different clinical problem.

MODUS: benzodiazepines are the medications of choice for alcohol or sedative-withdrawal delirium. Delirium tremens may require larger benzodiazepine doses than ordinary rapid-tranquillisation practice. In reduced hepatic metabolic capacity, lorazepam or oxazepam may be preferred to chlordiazepoxide because they have shorter half-lives and do not depend on hepatic oxidative metabolism. Route and intensity are matched to urgency, clinical response and the capacity for monitoring.

Antipsychotics are not equivalent treatment. They do not correct the underlying GABA, glutamate and noradrenergic disturbance of withdrawal delirium. More importantly, a meta-analysis comparing sedative-hypnotics with antipsychotics in delirium tremens found an **approximately six-fold increase in the odds of mortality with neuroleptics**. This safety signal makes antipsychotic monotherapy a dangerous category error, not merely a weaker option.

The withdrawal-specific scoring and dosing, including any CIWA-Ar based titration, belong in the Substance use disorders notes and current local guidance; CIWA-Ar depends on patient participation and is in any case unreliable once established delirium prevents valid self-report. The delirious patient also requires the ordinary medical work of examining for concurrent illness, reviewing electrolytes and nutrition, maintaining supportive care and reassessing the diagnosis when the course is atypical. Withdrawal may be the central cause without being the only cause.

MODUS also includes non-drug care. Psychological support is brief, concrete and repeated: reduce stimulation, explain what is happening, reorient without confrontation and use calm human presence alongside medical treatment. Procedural care comprises the monitoring and access required to deliver treatment safely and respond to deterioration. Social input includes collateral history about alcohol and sedative use, involvement of a suitable caregiver, and continuity planning after the emergency settles. None of these modes replaces benzodiazepine treatment of the withdrawal state; they make that treatment safer and the surrounding care more complete.

In alcohol or sedative-withdrawal delirium, treat the withdrawal with benzodiazepines; antipsychotic monotherapy is not equivalent management and may be dangerous.

18 · Korsakoff syndrome: pathology, mammillary body and thalamic involvement

Korsakoff syndrome is the model diencephalic amnesia. The marks do not come from writing "alcohol causes memory loss." They come from linking thiamine deficiency to bilateral mammillary and thalamic pathology, placing those lesions within a distributed memory circuit, and then explaining why new learning fails while immediate recall and procedural learning can remain available. A strong answer therefore moves in a chain: antecedent deficiency, pathological structures, disrupted circuit, clinical memory profile, imaging correlate and prognosis.

IN INDIA

Give parenteral thiamine before or together with glucose in any at-risk patient, without delaying treatment of hypoglycaemia; the cost of missing it, a persistent and often irreversible amnestic syndrome, is out of all proportion to the simplicity of giving it.

The central anatomical distinction is easy to blur. The dorsomedial thalamic nuclei and mammillary bodies are sites of haemorrhagic pathology in the acute antecedent encephalopathy, while the anterior thalamic nuclei receive mammillary input and participate in an explicit-memory network with medial temporal and cingulate structures. Both thalamic regions belong in the answer, but they do not have identical circuit roles. The accompanying account keeps pathology, connectivity and clinical expression at their proper levels.

0.4% TO 2%	2%	25%
BOTH SYNDROMES, COUNTRY-SPECIFIC	WERNICKE, GENERAL POPULATION	KORSAKOFF RECOVERY

18.1 Definition, antecedent and diagnostic language

In 1889, **Sergei Korsakoff** described a syndrome combining polyneuritis, anterograde amnesia and confabulations in people with chronic alcohol use. The description did not separate the acute illness from the enduring memory disorder; Carl Wernicke had described the acute encephalopathy earlier. This history explains why the paired term Wernicke-Korsakoff syndrome remains common, but it must not make the candidate treat acute encephalopathy and chronic amnesia as interchangeable states.

Korsakoff syndrome usually develops after Wernicke encephalopathy, although some patients develop the chronic syndrome without a recognised initial acute stage. Absence of a documented acute episode therefore does not abolish the pathological link to thiamine deficiency. It may mean that the antecedent was not clinically recognised, but the permitted evidence does not quantify how often this occurs. The acute thiamine-deficiency emergency and its full treatment protocol are covered in the Endocrine and metabolic psychiatry notes.

In the setting of severe alcohol use disorder, **DSM-5** refers to the condition as alcohol-induced major neurocognitive disorder, amnestic-confabulatory type. This label describes the alcohol-related setting and the dominant cognitive phenotype. It should not be used to erase non-alcoholic thiamine deficiency, nor should it turn the bedside formulation into a mere coding exercise. The defining clinical problem remains a persistent amnestic syndrome arising from damage to a memory network.

RULE **Write the sequence, not a fused label.** Wernicke encephalopathy is the usual acute antecedent; Korsakoff syndrome is the enduring amnestic state, and the latter can appear without a recognised acute presentation.

18.2 Thiamine deficiency: the metabolic cause

Thiamine pyrophosphate is the active form of thiamine and a cofactor for enzymes central to glucose metabolism and neurotransmitter production. Its lack compromises the energy metabolism on which vulnerable diencephalic neurons depend, which is why deficiency itself, and not poor nutrition as a label, is the operative cause of the amnestic pathology.

Alcohol is the common context but not an obligatory one. Severe thiamine deficiency also arises from general malnutrition and from several non-alcoholic medical settings, which the Endocrine and metabolic psychiatry notes cover alongside the acute thiamine emergency. The clinical implication is diagnostic discipline: a patient need not fit the stereotype of long-standing alcohol misuse for thiamine-deficiency brain injury to be plausible, and chronic alcohol use does not by itself prove that an amnestic presentation is Korsakoff syndrome. The history supplies the deficiency context; the memory phenotype, neurological course, imaging and exclusion of competing causes build the localisation.

18.3 The pathological core: mammillary bodies and thalamus

The acute pathological substrate is **bilateral haemorrhage in the mammillary bodies and dorsomedial thalamic nuclei** in Wernicke encephalopathy secondary to thiamine deficiency. When chronic alcohol-related thiamine deficiency produces permanent injury to the mammillary bodies and thalamus, the resulting Korsakoff syndrome may be irreversible. The enduring memory disorder is therefore not adequately explained as intoxication, poor effort or a vague diffuse cognitive decline.

The anatomical field is wider than those two headline structures. Thiamine-deficiency lesions also include the fornix and cerebellum, and both the medial dorsal and anterior thalamic nuclei have been associated with the deficiency state. The mammillary complex and anterior thalamic nuclei are particularly important for explicit memory. The fornix matters because it carries

hippocampal fibres toward the mammillary bodies, while the anterior thalamic nucleus carries the mammillary signal onward toward cingulate components of the memory circuit.

Two distinctions protect the answer from overstatement. First, "thalamic involvement" is not a single undifferentiated dot. The dorsomedial nucleus is named in the haemorrhagic pathology; the anterior nucleus is named as a thiamine-deficiency lesion site and as a connected relay for explicit memory. Second, the permitted evidence does not adjudicate which thalamic nucleus is the unique critical lesion for diencephalic amnesia. The safest high-level formulation is network injury involving mammillary and thalamic structures, with disruption of their connections to medial temporal and cingulate regions.

TRAP **Do not choose between "mammillary bodies" and "thalamus," or between dorsomedial and anterior thalamus.** Thiamine-deficiency pathology includes mammillary, medial dorsal and anterior thalamic structures, while the anterior nucleus has the explicit mammillothalamic circuit role.

18.4 The mammillothalamic memory circuit

The circuit of Papez provides the anatomical spine for understanding the amnesia. Fibres arise in the mammillary body, travel through the mammillothalamic tract and reach the anterior thalamic nucleus. The anterior nucleus projects to the cingulate cortex and cingulum, which connect onward with entorhinal and subicular cortices on the medial temporal surface. From there, the pathway enters the hippocampal formation and eventually returns through the fornix to the mammillary body.

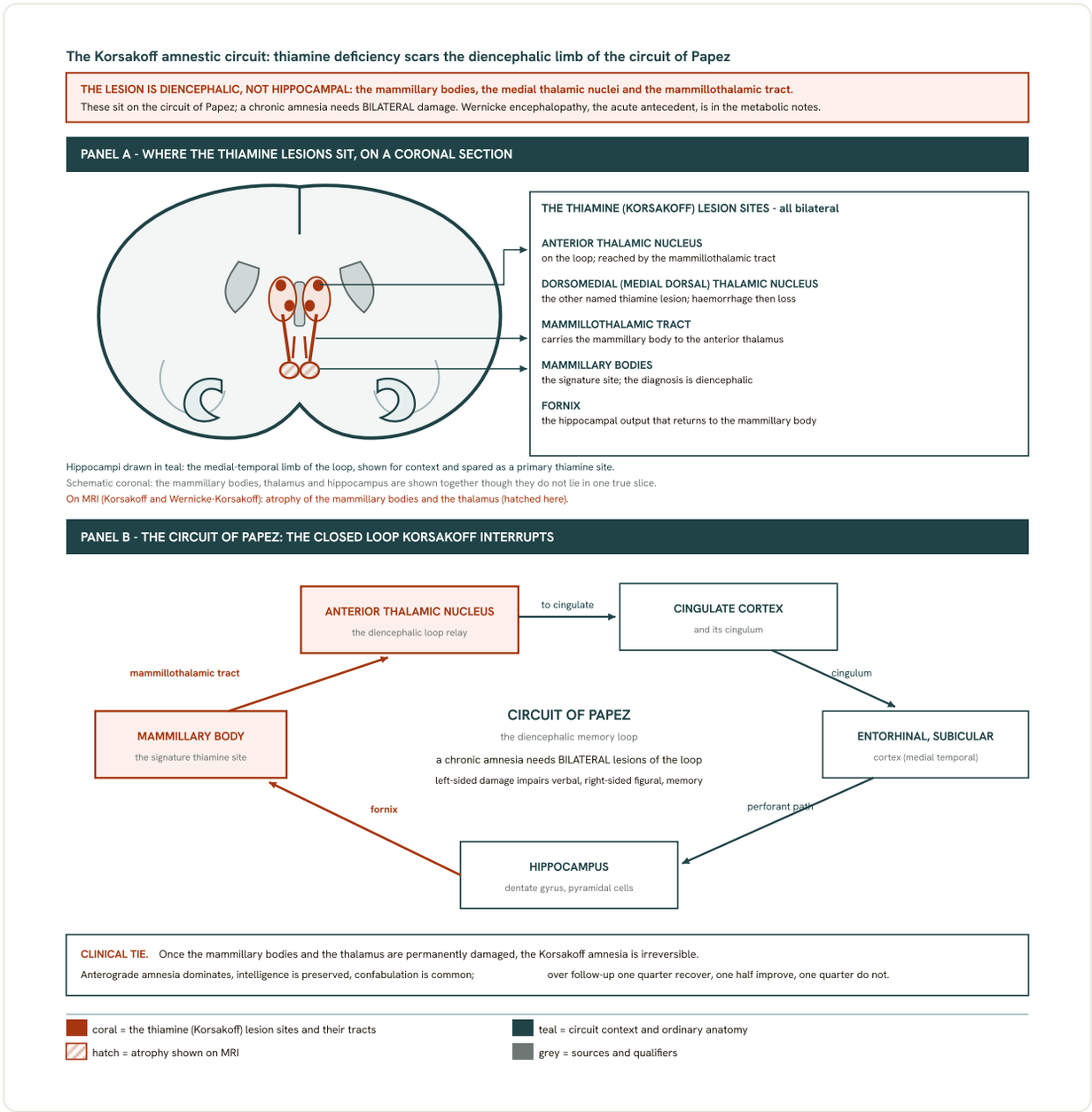


Fig 34.6 **The Korsakoff amnestic circuit.** Thiamine deficiency scars the diencephalic midline, the mammillary bodies, the medial (dorsomedial and anterior) thalamic nuclei and the mammillothalamic tract, which form the diencephalic limb of the circuit of Papez. A chronic amnesia needs bilateral lesions of the loop, and once the mammillary bodies and thalamus are permanently damaged it is irreversible. The hippocampus is the medial-temporal limb, shown for context and spared as a primary thiamine site. (Kaplan and Sadock CTP 2024, and Tasman Psychiatry.)

The accompanying figure should be read as a loop rather than a list of unrelated nuclei. The entorhinal cortex projects through the perforant pathway to the dentate gyrus; fibres then reach the pyramidal cells of the hippocampus proper, and hippocampal fibres enter the fornix before terminating in the mammillary body. The loop links diencephalic structures with the medial temporal memory system and cingulate cortex. Damage at a relay or connecting tract can therefore disturb explicit memory even when the entire circuit is not destroyed.

NODE OR TRACT	SUPPORTED CONNECTION	WHY IT BELONGS IN THE ANSWER
Mammillary body	Origin of the mammillothalamic tract; receives the returning fornix pathway	Major site of thiamine-deficiency pathology
Mammillothalamic tract	Mammillary body to anterior thalamic nucleus	Part of the anterior-thalamic pathway damaged in amnesia
Anterior thalamic nucleus	Projects to cingulate cortex and cingulum	Connected with explicit-memory impairment when injured
Entorhinal, subicular and hippocampal structures	Perforant pathway to dentate gyrus and hippocampus	Medial temporal portion of the loop
Fornix	Carries hippocampal fibres back toward the mammillary body	Also named among thiamine-deficiency lesion sites

MNEMONIC

MAMMILLARY - TRACT - ANTERIOR THALAMUS - CINGULATE - MEDIAL TEMPORAL - FORNIX

Follow the loop from **mammillary** body through the mammillothalamic **tract** to **anterior thalamus**, then **cingulate** and **medial temporal** structures, before the **fornix** carries the return pathway.

18.5 Network logic, bilaterality and material-specific laterality

Bilateral circuit injury is usually required for chronic amnesia involving the circuit of Papez, although exceptions occur. This principle fits the bilateral pathological emphasis in thiamine-deficiency disease. It also explains why the syndrome is better conceived as disconnection of a distributed memory network than as loss of a single isolated "memory centre." Mammillary injury, thalamic injury and tract interruption can converge on the same failure of new explicit learning because they interrupt different positions in the loop.

Bilaterality does not mean that hemispheric specialisation disappears. Left-sided hippocampal or thalamic damage produces predominantly verbal memory impairment, whereas right-sided damage produces predominantly figural memory impairment. These lateralised deficits describe the type of material most affected after unilateral or asymmetric damage. The chronic global amnestic syndrome, by contrast, generally points toward bilateral disruption. Thus, "left verbal, right figural" and "bilateral for chronic amnesia" answer different localisation questions.

The same evidence clarifies why immediate retention can survive. Short-term or working memory depends on frontoparietal mechanisms distinct from the hippocampal and thalamic pathways damaged in the amnestic syndrome. A patient may therefore hold a small amount of information briefly yet fail to establish a durable new memory from it. This apparent contradiction is diagnostically useful: intact immediate performance does not demonstrate intact learning across a delay.

This dissociation also prevents a common bedside misreading. A coherent conversation samples attention, language, general knowledge and immediate maintenance as well as memory, so conversational fluency can mask the amnestic deficit. The examiner must introduce material, allow the immediate moment to pass and then test whether it was retained. Failure of delayed new learning despite preserved immediate recall is more informative than repeatedly asking the patient whether memory feels poor. Likewise, improvement on a practised procedure without conscious recollection of the learning episode demonstrates preserved implicit learning rather than recovery of explicit episodic memory. The network account thus predicts a selective pattern, not uniform failure of every task containing the word “memory.”

The network model also disciplines interpretation of imaging. Atrophy in a characteristic structure supports the formulation, but a scan is not a direct photograph of a cognitive operation. The clinician still has to show that the bedside pattern is amnestic, that the relevant history supports thiamine deficiency, and that alternative causes have been considered. Anatomy explains the pattern; it does not replace phenomenology.

18.6 The clinical memory profile

The dominant deficit is **anterograde amnesia**: a striking inability to form new memories despite broadly intact overall intelligence. The failure becomes clearest when information must be retained beyond immediate registration and later retrieved as an episode. The patient may participate coherently in the interview, repeat material in the moment and appear socially intact, yet be unable to retain what has just been discussed.

Several capacities are characteristically spared, which sharpens the contrast with the failure of new episodic learning:

- immediate registration and repetition within the moment;
- procedural and skill learning acquired without conscious recollection;
- broadly preserved general intelligence and language;
- a socially intact surface that can mask the severity of the deficit.

Retrograde amnesia is present but less severe, and it usually affects events shortly before the illness began. This temporal pattern should not be flattened into “both recent and remote memory are lost.” The asymmetry matters: new learning is the striking impairment, while loss of previously formed memories is more limited. The exact boundary of lost autobiographical material must be established clinically rather than inferred from the label.

MEMORY DOMAIN	TYPICAL FINDING	INTERPRETIVE MEANING
New explicit learning	Strikingly impaired	Core anterograde amnesia
Memory for pre-illness events	Less severely impaired, especially near onset	Retrograde component is present but subordinate
Immediate recall	Preserved	Working-memory mechanisms are relatively distinct
Implicit or procedural learning	Preserved	Performance can improve without normal explicit recollection
Overall intelligence	Broadly intact	The syndrome is not synonymous with global intellectual failure

Confabulation is a classical accompanying feature and is commonly understood as an attempt to cover the memory deficit. Its presence may draw attention to the syndrome, but its phenomenological types and mechanisms are taught in the dedicated confabulation section. It should not displace direct examination of acquisition, retention and delayed retrieval.

GOOD TO REMEMBER

Separate registration from learning. Preserved immediate recall can coexist with profound failure to form new memories, and preserved procedural learning can coexist with poor conscious recollection of having practised. Test performance across a delay rather than concluding from an intact immediate response.

18.7 Imaging and diagnostic integration

Mammillary-body and thalamic atrophy is the typical imaging correlate in Wernicke-Korsakoff syndrome. Mammillary-body atrophy is particularly useful as an anatomical clue within the imaging differential of amnestic syndromes. The finding coheres with the pathological account: structures that link hippocampal output with anterior thalamic and cingulate components of the memory network have undergone enduring injury.

Imaging is supportive and discriminative, not self-sufficient. Neuroimaging helps distinguish several causes of amnestic syndrome, but the alternative structural and transient amnesias are covered in their dedicated section. For Korsakoff localisation, the correct inference is narrower: mammillary and thalamic atrophy supports a thiamine-deficiency diencephalic amnesia when the history and memory phenotype agree. Absence of a quoted sensitivity or specificity prevents a stronger diagnostic claim.

At the bedside, build the formulation in layers. Identify a disproportionate failure of new learning; verify that immediate recall, procedural learning and overall intellectual function are not being mistaken for normal episodic memory; look for the less severe retrograde component; and integrate nutritional or alcohol-related risk with imaging. The full ordered cognitive examination and standardised cognitive instruments belong in the Psychotherapies, clinical

assessment, MSE and nosology notes. The dementia syndrome and its broader workup belong in the Dementias and neurocognitive disorders notes.

PITFALL

Do not diagnose the syndrome from alcohol history plus forgetfulness. The localisation becomes persuasive when severe anterograde amnesia coexists with preserved immediate recall and implicit learning, and when mammillary or thalamic atrophy supports the expected diencephalic network injury.

18.8 Prevention, treatment boundary and prognosis

The decisive therapeutic principle lies before fixed amnesia is established. Vitamin B1, particularly by the intravenous route, can prevent cognitive impairment and Wernicke-Korsakoff syndrome in people at risk because of long-standing alcohol misuse or severe malnutrition. In an emergency or inpatient locus, the immediate focus is recognition and treatment of the acute deficiency state; in later care, the focus shifts to persistent memory impairment, safety and support. The exact acute repletion regimen belongs in the Endocrine and metabolic psychiatry notes.

The treatment boundary matters because high-dose intravenous thiamine is likely to reverse Wernicke encephalopathy partly or completely, whereas benefit in established chronic Korsakoff syndrome is not established. This does not make late care futile. It means that thiamine treatment of the acute state and rehabilitation of chronic memory disability are different targets. Drug treatment addresses the deficiency emergency; psychological, environmental and social modes must then be aligned with the enduring functional consequences, although the permitted evidence does not provide a validated rehabilitation programme.

Long-term outcome is heterogeneous. **About one-quarter recover**, one-half improve to some degree, and the remaining one-quarter show no recovery. A parallel source summarises recovery at about 25% and notes that the others retain varying degrees of memory impairment. A significant minority require permanent placement. These figures are best presented as an outcome distribution, not as a prediction for an individual patient.

The prognostic message follows directly from the pathology. Permanent mammillary-body and thalamic damage can make the syndrome irreversible. Prevention and early treatment of the antecedent deficiency therefore carry disproportionate value. Once chronic amnesia is present, care planning should not be based on an assumption of either inevitable full recovery or inevitable complete non-response. The observed range includes recovery, partial improvement and persistent impairment.

Epidemiological figures require equally careful scope. Reported rates for Wernicke encephalopathy and Korsakoff syndrome range from 0.4% in France to 2% in the United States, Scandinavia and Australia. A separate estimate places Wernicke encephalopathy prevalence in the general population at 2%. These are distinct estimates and should not be merged into a single

universal rate. The syndrome is usually seen in people over 40 years of age after 20 or more years of alcohol use, but non-alcoholic deficiency remains clinically important.

> Korsakoff syndrome is a predominantly anterograde amnesia caused by permanent disruption of a bilateral mammillary-thalamic memory network, with immediate recall and procedural learning relatively preserved.

19 · Confabulation: types and mechanisms

Confabulation is a disorder of remembering in context, not merely an inaccurate statement. The examiner is looking for a disciplined distinction between accounts elicited by a memory question and accounts produced spontaneously, followed by an explanation of why frontal monitoring failure changes their content, persistence and resistance to correction. The marks lie in describing the behaviour before naming a lesion: what prompted the account, what kind of narrative appeared, how the patient responded to contradiction, and whether the anatomical setting fits the proposed type.

The useful clinical stance is descriptive. An account may conflict with the verified situation, yet its surface falsity alone does not explain the cognitive process that produced it. The psychiatrist should establish the memory context, compare the account with collateral information, and observe belief revision without turning the interview into an argument. The core distinction comprises **two** patterns: **provoked confabulation** and **spontaneous or fantastic confabulation**. They overlap enough that no single sentence should classify the phenomenon; the pattern across prompting, narrative quality and correction is more informative.

PROMPT	CONTENT	CHECK	LOCUS
WHAT ELICITED IT?	PROSAIC OR FANTASTIC?	DOES BELIEF REVISE?	DOES ANATOMY FIT?

19.1 What the term means at the bedside

Confabulation in chronic amnesia becomes visible when a patient supplies an account that conflicts with the established circumstances. The account is clinically meaningful because it is offered as memory, not because it is dramatic or bizarre. A routine answer about recent activity can therefore be more informative than an elaborate story. The clinician first asks what memory demand preceded it, whether the answer is anchored to the current setting, and how readily it changes when accurate contextual information is supplied.

This approach prevents several conceptual errors. Confabulation should not be reduced to ordinary factual inaccuracy; the relevant question is how an erroneous recollection is generated and accepted. Implausibility is not required, because a simple, everyday account may be a classic provoked example. Plausibility likewise does not establish accuracy. Verification comes from records, staff observation and collateral history, while phenomenology comes from the patient's manner of production and response to correction.

The word is also not a complete diagnosis. It describes a memory-related phenomenon whose clinical value depends on the surrounding amnestic state and neuroanatomical context. The

pathology of Korsakoff syndrome belongs in the dedicated section on mammillary-body and thalamic involvement. Other causes of amnestic syndrome and the transient amnesias are discussed separately. The full ordered cognitive examination and standardised cognitive instruments belong in the Psychotherapies, clinical assessment, MSE and nosology notes; here the examination is limited to the operations needed to characterise confabulation.

RULE **Classify the production pattern, not the truth value alone.** Prompting, content, response to correction and lesion context together distinguish the clinically useful forms.

19.2 Provoked confabulation

Provoked confabulation is typically elicited by a question. The examiner asks about a recent event, and the patient provides an answer despite the account being inconsistent with what actually occurred. Its content is usually **prosaic, simple and straightforward**. Ordinary routines, familiar social activity or other plausible autobiographical material may be recruited into the answer. Because the narrative resembles everyday life, it can escape notice unless the interviewer has reliable knowledge of the patient's actual circumstances.

The second defining feature is **little resistance to correction**. When the discrepancy is pointed out calmly and the true context is supplied, the patient may pause, reconsider and accept that the initial account was probably wrong. The correction does not necessarily restore the missing memory. What changes is the patient's commitment to the proposed account. This distinction matters: revisability shows that the account is not being defended with the persistence typical of the spontaneous pattern.

Provoked confabulation can be understood as an error exposed by retrieval demand. A question requires an answer about a time and situation that the damaged memory system cannot adequately reconstruct. Familiar material may be selected because it is coherent and available, but its fit to the requested episode is poor. The resulting narrative may therefore be internally sensible while externally misplaced. The interviewer should not mistake coherence for accurate episodic placement.

At the bedside, use neutral questions before offering alternatives. Record the exact question, the gist of the response, the verified context and the reaction to correction. Repeated leading questions can manufacture apparent consistency by repeatedly supplying the same cues. A calm correction is more informative than confrontation because the observation sought is whether the patient can update the account when contextual evidence becomes available.

19.3 Spontaneous or fantastic confabulation

Spontaneous confabulations often emerge independently of prompting, although they may also appear in response to a question. Their defining contrast extends beyond speech beginning uninvited. The narratives often have a **fantastic or dream-like quality**, extending beyond the ordinary substitutions seen in provoked confabulation. A patient may describe an implausible plan as if it belongs to the current situation and may organise behaviour around that account.

Correction is characteristically resisted. When the clinician supplies the verified context, the patient may become irritated and continue to insist on the account. Resistance is therefore part of the phenomenology, not an interpersonal nuisance to be ignored. It suggests that the false account has passed whatever internal process would normally reject material that is temporally misplaced, contextually inappropriate or incompatible with current reality.

The classic clinical setting in the permitted evidence is a patient assessed after clipping of an anterior communicating artery aneurysm, in the context of basal forebrain damage. The value of this example is anatomical and phenomenological. The narrative is spontaneously relevant to action, fantastic in content and maintained despite direct contradiction. The clinician should learn the pattern rather than reproduce the anecdote as a substitute for explanation.

Spontaneous confabulation occurs in only a minority of amnestic patients. Amnesia alone is therefore insufficient as a mechanism. The additional clue is failure of frontal systems that normally evaluate when and from where a recollection arose, and whether it is appropriate to the present situation. The account is not merely retrieved inaccurately; it is insufficiently checked before it is accepted and acted upon.

PITFALL

Do not label every implausible statement in an amnestic patient as spontaneous confabulation. Establish whether it emerged as memory, whether it was produced without prompting, whether its quality was fantastic or dream-like, and whether it persisted when the verified context was supplied.

19.4 The comparison that earns marks

The highest-yield discrimination rests on **three** bedside axes: prompt dependence, narrative quality and response to correction. Localisation then tests whether the classification is coherent. None of these axes should be read in isolation. Spontaneous confabulation can occasionally follow a question, so an elicited response is not automatically provoked. Conversely, a plausible account is not necessarily accurate. The whole production pattern decides the label.

CLINICAL AXIS	PROVOKED CONFABULATION	SPONTANEOUS OR FANTASTIC CONFABULATION
How it appears	Usually elicited by a memory question	Often volunteered, but may follow a question
Narrative quality	Prosaic, simple and straightforward	Fantastic and sometimes dream-like
Correction	Little resistance; the account is readily reconsidered	Resistance and irritation may occur; the account is maintained
Lesion association	May accompany lesions anywhere in the circuit of Papez	Generally associated with bilateral basal forebrain lesions
Interpretive emphasis	Retrieval under demand with weak episodic fit	Retrieval plus failure to monitor context and reject the account

MNEMONIC

PROMPT - PLOT - PUSHBACK

Prompt: was the account elicited or volunteered? **Plot:** was it ordinary or fantastic? **Pushback:** did accurate contextual information lead to revision or resistance? Use lesion localisation as the coherence check after describing these features.

The table also shows why "confabulation equals lying" is not an adequate examination answer. Truth value is only the starting observation. The diagnostic work is to analyse the memory operation and the checking failure. Equally, "confabulation equals gap filling" is too vague unless the candidate states which form, what elicited it and how the patient responded when reality was clarified.

19.5 Lesion localisation and the amnesia substrate

Provoked confabulation may occur with chronic amnesia caused by lesions anywhere in the **circuit of Papez**. It is most commonly encountered in Korsakoff syndrome secondary to thiamine deficiency. This broad association fits the clinical picture: disruption within an established memory circuit can leave the patient unable to retrieve the requested episode accurately, yet does not by itself imply the more severe monitoring disturbance that sustains fantastic accounts.

By contrast, spontaneous confabulation generally occurs in chronic amnesia associated with **bilateral basal forebrain lesions**. The laterality and regional restriction are important. They explain why spontaneous confabulation is not simply the more colourful end of ordinary amnesia. It reflects an amnestic substrate plus damage in a region closely related to frontal systems that evaluate relevance, temporal placement and behavioural meaning.

These anatomical statements should be held together, not memorised as disconnected lists. A distributed memory-circuit lesion can support provoked errors. The spontaneous form points more specifically toward bilateral basal forebrain involvement and its relationship with ventromedial frontal monitoring. Thus localisation follows phenomenology: first decide what kind of account was observed, then ask whether the lesion pattern is expected. Working backwards from a scan to a behavioural label risks circular reasoning.

Confabulations are more frequent in **diencephalic amnesia**, exemplified by Korsakoff syndrome, than in **hippocampal amnesia**. This relative-frequency statement reinforces that equally severe-looking memory failure need not produce the same confabulatory tendency. It does not justify diagnosing a lesion from confabulation alone. Rather, it tells the candidate that the organisation of the damaged memory system matters, not merely the presence of forgetting.

19.6 Mechanism: source and temporal-context failure

The most economical mechanism begins with **source memory**: the ability to identify where information came from and the circumstances to which it belongs. A recollection may contain familiar people, places or actions yet be assigned to the wrong episode. If its origin is not

recovered, familiarity can be mistaken for evidence that the event occurred in the requested context.

Frontal damage impairs memory for temporal context and source, and this deficit is relevant to confabulation. Temporal-context memory answers “when did this belong?” Source memory answers “where did this information arise?” A patient may retain fragments of autobiographical knowledge while losing the tags that separate past routine, imagined plan and current event. The error is therefore not necessarily absence of content. It may be failure to bind available content to its proper context.

This model separates availability from attribution. Material may feel familiar because it belongs somewhere in the person’s experience, yet familiarity does not specify its source or time. The memory system must still decide whether the material was perceived, planned, imagined or recalled from another occasion, and whether it answers the question now being asked. Failure at that stage creates an account whose components can be individually ordinary while their assembly is wrong for the present episode. A further monitoring failure allows the assembled account to survive obvious conflict with the current setting.

Correction tests the final part of this sequence. Acceptance suggests that external context can still overrule the initial reconstruction. Resistance suggests that the internally generated account continues to govern judgment despite contrary information. The response therefore gives the examiner a behavioural window into monitoring: it does not directly measure the missing memory, but it shows whether the patient can use supplied evidence to revise what has just been claimed.

The next operation is evaluation. Retrieved material must be checked against the present environment, recent experience and other available evidence. When this monitoring works, an initially plausible candidate memory can be rejected or held with uncertainty. When it fails, the candidate account may be accepted as current fact. Provoked confabulation can be conceptualised as weak reconstruction under demand with enough checking capacity remaining for later revision. Spontaneous confabulation adds a more consequential failure of monitoring, so contextually inappropriate material survives contradiction.

Spontaneous confabulation depends on **ventromedial frontal damage**. This localisation is consistent with, rather than opposed to, the bilateral basal forebrain association. The ventromedial frontal and basal forebrain region provides the anatomical bridge between memory failure and defective evaluation. The mechanism therefore has paired levels in the answer: an amnestic disturbance supplies poorly contextualised material, while frontal monitoring failure permits that material to be believed, maintained and potentially translated into action.

19.7 Bedside elicitation and interpretation

A useful assessment samples autobiographical material whose correct context can be independently established. The purpose is not to catch the patient out. It is to observe how an account is generated, qualified and revised. Begin with open, neutral questions, then clarify time

and setting. Compare the response with reliable collateral information. Finally, offer the verified context calmly and note whether the patient incorporates it, remains uncertain or resists it.

- Record whether the account was volunteered or followed a direct memory question.
- Describe its content as ordinary and plausible, or fantastic and dream-like, without using those adjectives as diagnoses by themselves.
- Document the response to correction, including reflection, acceptance, persistence or irritation.
- Integrate the observation with the amnestic state and lesion context rather than inferring anatomy from a single reply.

The interview should minimise suggestion. Closed alternatives may insert content that later sounds like the patient's own recollection. Repeated challenge may produce defensiveness that resembles resistance to correction but reflects the interpersonal method rather than the memory disorder. The clean observation is obtained when the examiner states the verified context once, respectfully, and watches whether belief revision occurs.

Collateral verification is indispensable because plausibility can mislead in either direction. A prosaic story may be false, and an unusual story may occasionally be true. Clinical classification must not depend on the examiner's intuition about what "sounds possible." Documentation should separate observed speech from verified facts and from interpretation. This preserves the chain of reasoning for colleagues and prevents a colourful narrative from becoming a diagnostic shortcut.

GOOD TO REMEMBER

Use correction as a bedside probe, not as a contest. The clinically useful observation is whether contextual evidence modifies the account. Escalating confrontation obscures that signal and can turn an assessment of memory monitoring into an assessment of the interview relationship.

19.8 Integration, differential framing and answer construction

Confabulation should be placed within the amnestic formulation before broader psychiatric explanations are invoked. Delirium, primary psychotic phenomena, the dementia syndrome, deliberate fabrication and ordinary memory error may all enter the differential, but their full diagnostic criteria belong to their respective sections and chapters. The dementia syndrome and its workup are covered in the Dementias and neurocognitive disorders notes. Delirium criteria and subtypes are covered in the dedicated delirium section of this chapter.

The candidate's answer can proceed in a compact causal sequence. Define confabulation descriptively as an inaccurate account offered in a memory context. Contrast provoked and spontaneous forms using prompting, content and correction. State the lesion associations. Then explain temporal-context and source-memory failure, adding ventromedial frontal monitoring failure for the spontaneous form. Finish by showing how collateral verification and response to correction convert the theory into bedside assessment.

TRAP **Do not equate confabulation with a confidently told falsehood.** Confidence, plausibility and factual error do not classify the phenomenon. The provoked-spontaneous distinction requires the production pattern, correction response and anatomical context.

The final conceptual distinction is between production and checking. Memory-network damage makes accurate reconstruction difficult; frontal-contextual dysfunction makes an erroneous reconstruction harder to reject. Provoked confabulation is usually exposed by a question and remains revisable. Spontaneous confabulation emerges more independently, becomes fantastic or dream-like, and resists correction. This is why the second pattern has a narrower basal forebrain and ventromedial frontal association.

Provoked confabulation is prompted, prosaic and readily revised; spontaneous confabulation is often unprompted, fantastic, correction-resistant and linked to bilateral basal forebrain with ventromedial frontal dysfunction.

20 · Other causes of amnestic syndrome and the transient amnesias

The useful distinction is anatomical first, temporal second. A persistent, disproportionate failure of episodic learning points toward damage within the medial temporal, diencephalic, basal forebrain or retrosplenial memory network; a self-limited attack demands separation of transient global, epileptic and ischaemic amnesia. The examination marks lie in connecting the memory phenotype to lesion locus and course, not in writing an undifferentiated list of causes.

Chronic amnesic syndrome describes enduring impairment in acquiring or retrieving episodic memories that is prominent enough to require anatomical explanation. It is not synonymous with delirium, because stable amnesia can remain after any acute confusional state has cleared. It is also not synonymous with the dementia syndrome, which is broader and is covered with its full workup in the Dementias and neurocognitive disorders notes. This section instead asks a narrower question: which memory-system lesion best explains the pattern, and when does an apparently isolated attack require a seizure or vascular formulation?

5.2 TO 10 CASES PER 100,000 PER YEAR	NOT OVER 24 HOURS	MINUTES; UNDER 1 HOUR
TGA INCIDENCE	TGA DEFINITION	TEA USUALLY

20.1 A lesion-locus map of persistent amnesia

The network approach prevents the familiar error of treating memory as a function of the hippocampus alone. Persistent episodic-memory impairment may follow hippocampal, diencephalic or retrosplenial damage, while bilateral injury to the medial temporal lobe, diencephalon or basal forebrain can produce a profound amnesic syndrome. These regions are linked components of an extended limbic memory system. A lesion at a node or connecting pathway can therefore create a similar headline complaint while leaving a different retrograde profile and different accompanying signs.

PRINCIPAL LOCUS	GROUNDED CAUSES	LOCALISING EMPHASIS
Hippocampal or medial temporal	Herpes simplex encephalitis, limbic encephalitis, anoxia and temporal-lobe removal	Failure of durable new episodic learning
Diencephalic or basal forebrain	Bilateral thalamic infarction, lesions around the third ventricle and post-subarachnoid-haemorrhage injury	Encoding weakness may coexist with defective retrieval
Retrosplenial	Tumour or haemorrhage	Posterior network disruption can also impair episodic memory

This is a localisation framework, not a claim that all causes are clinically interchangeable. Establish whether registration and attention are adequate, demonstrate failure across a delay, examine the extent of retrograde loss, and use the neurological course and imaging to decide which network component is implicated. The full ordered bedside cognitive examination and standardised instruments belong in the Psychotherapies, clinical assessment, MSE and nosology notes.

Encoding and retrieval language adds precision to that map. A weak delayed response may reflect a memory trace that was never laid down effectively, difficulty gaining access to a stored trace, or both. Diencephalic amnesia can combine weak encoding with defective retrieval; the hippocampal pattern is more closely centred on failure to consolidate new episodic material. This distinction should guide the examiner's explanation, but it should not be overclaimed from a single bedside task. Converging evidence comes from adequate initial attention, performance after a delay, the benefit or absence of benefit from retrieval support, the temporal extent of retrograde loss, collateral history and lesion-compatible imaging. The result is a neurobehavioural formulation rather than a score-labelled complaint.

20.2 Medial temporal injury: infection, autoimmunity and hypoxia

Hippocampal amnesia is classically dominated by impaired anterograde learning with a comparatively limited retrograde deficit. Autobiographical recall may be affected mainly for the most recent **2 to 5 years**, rather than across much of adult life. The practical lesson is that a patient may lose the ability to establish new episodic memories while retaining a large body of older personal knowledge. Immediate conversational coherence does not refute this formulation because immediate maintenance and durable consolidation are different operations.

Herpes simplex encephalitis preferentially injures the medial temporal lobes, including the hippocampus, and produces haemorrhagic necrosis; magnetic resonance imaging may show bilateral temporal-pole T2 hyperintensity. The well-known case of Clive Wearing illustrates the resulting dense anterograde amnesia. The point of the vignette is anatomical: destruction of medial temporal memory structures can leave each present moment poorly connected to the next, even when other aspects of interaction remain recognisable.

Autoimmune disease reaches the same functional system by another route. In anti-NMDA-receptor encephalitis, autoantibodies target the GluN1 subunit of the receptor, a subunit essential

for hippocampal memory consolidation. Cognitive dysfunction therefore belongs within a wider neuropsychiatric presentation rather than being dismissed as poor engagement. Hypoxic-ischaemic injury, whether arising from respiratory, cardiovascular or metabolic compromise or carbon monoxide intoxication, selectively threatens the CA1 hippocampal region. Attempted hanging, cardiorespiratory arrest, carbon monoxide intoxication and inhalational anaesthesia are documented settings in which chronic amnesia may dominate the post-hypoxic picture. The shared endpoint is hippocampal vulnerability, but the causal history remains indispensable.

20.3 Diencephalic, basal forebrain and vascular amnesia

Basal forebrain amnesia may follow rupture of an anterior communicating artery aneurysm, the associated subarachnoid haemorrhage or surgical clipping. The mechanism is injury to small perforating arteries that supply basal forebrain structures, including the fornices. The anatomical label "basal forebrain" should be unpacked rather than left vague: the septal nucleus and diagonal band of Broca are named components, and the fornix links this region to the broader episodic-memory network.

Vascular amnesia is similarly site-dependent. Infarction involving the thalamus, medial temporal lobe or fornices may produce amnesia. A thalamic infarct may initially present with delirium, but the enduring memory deficit must be assessed after attention and arousal have stabilised. This protects against describing a fluctuating failure to register information as if it were a fixed storage disorder. Delirium criteria, mechanisms and management are taught in the dedicated delirium sections of this chapter.

Diencephalic amnesia, exemplified by Korsakoff syndrome, has a different retrograde contour from the relatively focal hippocampal pattern. It can extend back across decades while showing relative sparing of more distant memories, creating a temporal gradient; both encoding and retrieval may be defective. This contrast is a discriminator, not a complete account of Korsakoff pathology. Mammillary-body and thalamic pathology, nutritional antecedents and confabulation are covered in their dedicated sections. For the present differential, extensive temporally graded retrograde loss favours diencephalic network dysfunction, whereas a shorter recent retrograde loss fits hippocampal amnesia more closely.

20.4 The transient-amnesia problem

A transient memory gap is a syndrome description, not a diagnosis. The clinician must reconstruct the episode from a witness wherever possible because the patient may be unable to encode the very events being investigated. The high-yield axes are onset, duration, recurrence, state on waking, preservation of personal identity, attention and consciousness, associated neurological or epileptic phenomena, repetitive questioning, and the memory left after recovery.

The major distinction is between **transient global amnesia**, which is prolonged but self-limited and usually isolated, and transient epileptic amnesia, which is brief and recurrent. A vascular transient amnesia is briefer still: a transient ischaemic attack involving the thalamus or medial temporal lobe may produce 15 to 20 minutes of amnesia. Duration alone cannot make the diagnosis, but it sharply changes the prior formulation.

TGA is uncommon. Its reported incidence is 5.2 to 10 cases per 100,000 people per year. It occurs mainly in later life, peaks around the sixth and seventh decades, and is exceptional below 40 years of age. TEA is usually seen in a similar age range but can occur in younger people; no numerical incidence or age-of-onset estimate is stated here. Epidemiology therefore supports context but must not substitute for the observed attack pattern.

RULE **Classify transient amnesia by the whole episode.** Duration, recurrence, waking relationship, identity, attention, questioning, seizure history and the residual memory gap belong in one reconstruction; no isolated feature is a sufficient label.

20.5 Transient global amnesia: the clinical phenotype

The fundamental event is abrupt inability to retain new factual information. **Anterograde amnesia** is more profound than the accompanying retrograde loss, which chiefly affects recently acquired information. General knowledge and fundamental personal information remain available, so patients can ordinarily state who they are and supply familiar biographical facts. This preservation of identity is diagnostically valuable: the patient is bewildered by the memory failure, not emptied of a personal self.

Working memory remains available, but new material disappears after only a very short interval. The patient is disoriented and repeatedly cycles through the same questions, while consciousness, attention, language and visuospatial function remain intact. Repetitive questioning is therefore not mere anxiety. It is the behavioural signature of repeated registration without durable retention. The preserved attention and language distinguish the episode from a global confusional state.

An operational bedside synthesis, without attaching an unsupported named criteria set, is:

- acute, prominent anterograde amnesia with a less marked recent retrograde component;
- preserved personal identity and general knowledge;
- repetitive questioning despite preserved working memory;
- no clouding of consciousness or impairment of attention;
- no accompanying language or visuospatial deficit;
- complete resolution of the acute syndrome within the defining time ceiling.

Frightening events, physical exertion and sexual activity may immediately precede an attack; stressful emotional or physical events and migraine are also associated. These are contextual clues, not diagnostic proofs. The observed cognitive pattern and course remain primary.

20.6 TGA course, prognosis and disputed mechanism

TGA lasts **3 to 24 hours** and is most severe during the initial 1 to 2 hours; by definition, the acute attack must not exceed 24 hours. Another account places typical restoration of new learning at 4 to 8 hours. Recovery is gradual: retrograde loss contracts as anterograde learning returns, leaving a dense gap for the attack and often for the couple of hours immediately before

it. The patient may therefore look recovered while remaining unable to remember the episode itself.

The aetiology remains unsettled. Proposed mechanisms include transient posterior-cerebral-artery ischaemia affecting medial temporal structures, migraine, seizure, and impaired cerebral venous outflow. Different mechanisms may operate in different patients. Yet the vascular hypothesis must not be promoted to established fact: another account argues that thromboembolic cerebrovascular disease does not explain the usual syndrome, and TGA itself is not a risk factor for stroke. Acute focal or atypical presentations still require a vascular differential; that clinical precaution is separate from claiming that classic TGA is a transient ischaemic attack.

TRAP **Do not flatten the source discrepancies.** The exam-tested acute definition is no more than 24 hours, supported by the account that typical recovery occurs within 4 to 8 hours; a major psychiatry text instead uses the outlying phrase “improving over the course of several days.” Recurrence is also framed differently: one source gives approximately **10% overall**, while another gives **2 to 3% per year**. Preserve “overall” versus “per year.” Both formulations convey low recurrence and need not be forced into one figure.

The general prognosis is excellent. Reassurance is appropriate after the attack pattern has been established and competing urgent causes have been considered. Recurrent, very brief or waking-related events should reopen the diagnosis rather than being repeatedly called TGA.

20.7 Transient epileptic amnesia

Transient epileptic amnesia resembles TGA because confusion, disorientation and repetitive questioning can occur, but its temporal signature is different. Attacks are recurrent, generally last less than 1 hour and commonly only a few minutes; they often occur immediately on waking or after a catnap. Partial recollection of the ictus may survive, and the episodes may evolve into complex partial seizures. Seizure classification and anticonvulsant pharmacology belong in the Epilepsy and psychiatry notes.

The disorder is not confined to attacks. Patients may discover large autobiographical gaps when they try to retrieve holidays or family events from preceding years. A further hallmark is **accelerated long-term forgetting**: new material can be recalled normally after a short delay measured in hours or days, yet be lost after a delay of weeks. Standard short-delay testing can therefore appear reassuring while the patient describes a genuine long-interval failure. This discrepancy should prompt testing and collateral history across ecologically meaningful intervals rather than an inference of poor effort.

A separate source uses **pure epileptic amnesia** for a partial seizure consisting only of anterograde and variable retrograde amnesia. It emphasises paroxysmal onset, brevity, absence of anxious questioning and a history of complex partial or grand mal seizures. The terminology and questioning description are not perfectly identical across sources, so the safer synthesis is clinical: brief recurrent attacks with seizure evidence favour an epileptic mechanism, whether or not repetitive questions occurred.

MNEMONIC

GLOBAL: LONGER, CLEAR, IDENTITY KEPT. EPILEPTIC: BRIEF, RECURRENT, WAKING.

In TGA, the attack lasts longer while attention and identity remain clear. In TEA, brevity, recurrence and onset after sleep carry more discriminating weight.

PITFALL

A normal routine EEG does not exclude TEA. Routine recordings may be normal, whereas sleep EEG usually reveals temporal-lobe spikes or sharp waves. If the history is compelling, the state sampled by the recording matters.

20.8 Assessment, investigation and management

Locus. A patient with active unexplained transient amnesia belongs in an emergency or acute medical setting until dangerous neurological and metabolic alternatives have been addressed. Once stable, outpatient review is appropriate for reconstructing recurrence, long-interval autobiographical loss and sleep-related attacks. Persistent amnesia requires the care setting dictated by its underlying encephalitic, hypoxic, vascular or structural cause.

Focus. During the attack, establish attention, consciousness, identity, language, visuospatial function, focal neurological findings and the ability to retain new material. In the short term, obtain a precise witness account and define onset, offset, precipitant, recurrence, waking relationship, questioning and residual gap. Over longer follow-up, ask specifically about autobiographical holes and accelerated forgetting. Thorough history, neuropsychological evaluation and EEG recordings are required to distinguish TGA from TEA.

Construct the history as a timeline rather than asking whether the patient “was confused.” Ask what the patient was doing immediately before the gap, which question was repeated, whether answers were understood, whether identity and familiar knowledge were retained, whether ordinary speech and navigation were preserved, and what the first durable memory after the event was. Then ask separately about earlier similar spells, sleep or waking, exertion or emotional stress, seizure phenomena and vascular symptoms. This sequence reduces retrospective blending of the attack with the distress around it. It also prevents a normal examination after recovery from erasing an abnormal witnessed event. For persistent amnesia, interview collateral informants about day-to-day learning and remote autobiographical loss, because apparent social fluency may conceal repeated forgetting.

PATTERN	DURATION AND RECURRENCE	POSITIVE CLUES	AFTER THE EVENT
TGA	3 to 24 hours; recurrence is low	Identity and general knowledge retained; attention clear, repetitive questions	Dense gap for the attack
TEA	Under 1 hour, often minutes; recurrent	Often on waking, sometimes partial ictal recall; sleep EEG abnormalities	Autobiographical gaps and accelerated forgetting may persist
Thalamic or medial-temporal TIA	15 to 20 minutes	Vascular localisation must be sought	Do not relabel a vascular event as classic TGA

Modus. Treatment follows the mechanism. Persistent amnesia requires treatment of the underlying medical or structural disease and rehabilitation directed at functional memory problems. For classic TGA, the expected course justifies explanation and follow-up after urgent mimics have been excluded; do not infer a disease-specific drug regimen from the diagnostic label. For TEA, anticonvulsant treatment typically prevents further attacks but may not improve established remote-memory loss. Drug selection belongs with current guidance and the Epilepsy and psychiatry notes.

GOOD TO REMEMBER

Ask beyond the attack. Recurrent waking episodes suggest TEA, but remote autobiographical gaps and accelerated long-term forgetting may be the complaints that expose it. Pair collateral history with sleep EEG when routine recording is unrevealing.

TGA is a longer, self-limited amnesia with preserved identity and attention and a strict 24-hour ceiling; TEA is brief, recurrent, often waking-related and may require sleep EEG to reveal temporal epileptiform activity.

The bedside examination and the focal lobe syndromes

21 · Frontal lobe syndromes: dorsolateral, orbitofrontal and medial subtypes

Frontal lobe syndromes are disorders of organised behaviour, not merely failures on a cognitive screen. The examiner is trying to recognise which aspect of goal-directed conduct has broken down: planning and mental flexibility, inhibition and social regulation, or initiation and drive. This framing matters in psychiatry because the presentation may resemble depression, mania, a personality disorder or a global neurocognitive syndrome even when the primary disturbance is focal prefrontal dysfunction.

The traditional clinical framework describes at least **three** prefrontal syndromes: dorsolateral or frontal-convexity, orbitofrontal or inferior-ventral, and medial frontal or anterior cingulate. They overlap considerably and commonly occur in combination rather than as discrete entities. The

useful answer therefore identifies a dominant pattern, states the expected accompanying signs, and then acknowledges mixed presentations. These syndromes are usually described with bilateral or large unilateral prefrontal damage, so a neat behavioural label provides insufficient evidence for a tiny, isolated lesion.

21.1 The clinical map: plan, restrain and initiate

A practical way to enter the topic is to ask what the patient cannot regulate. The dorsolateral system is expressed clinically through organisation, problem solving and flexible control of a mental set. The orbitofrontal system is expressed through inhibition, appraisal of social context and restraint of behaviour. The medial frontal and anterior cingulate system is expressed through initiation, sustained engagement and the conversion of intention into action. These are clinical organising ideas, not claims that any complex human behaviour resides in a single cortical patch.

PLAN	RESTRAIN	INITIATE
DORSOLATERAL	ORBITOFRONTAL	MEDIAL

The accompanying figure should be read as a map of dominant clinical signatures. It helps organise recall, but the patient in front of you may show apathy together with disinhibition, or executive rigidity together with poor initiation. Such mixtures are expected because the traditional syndromes overlap. Localisation becomes persuasive when the behavioural pattern, neurological signs and lesion context converge.

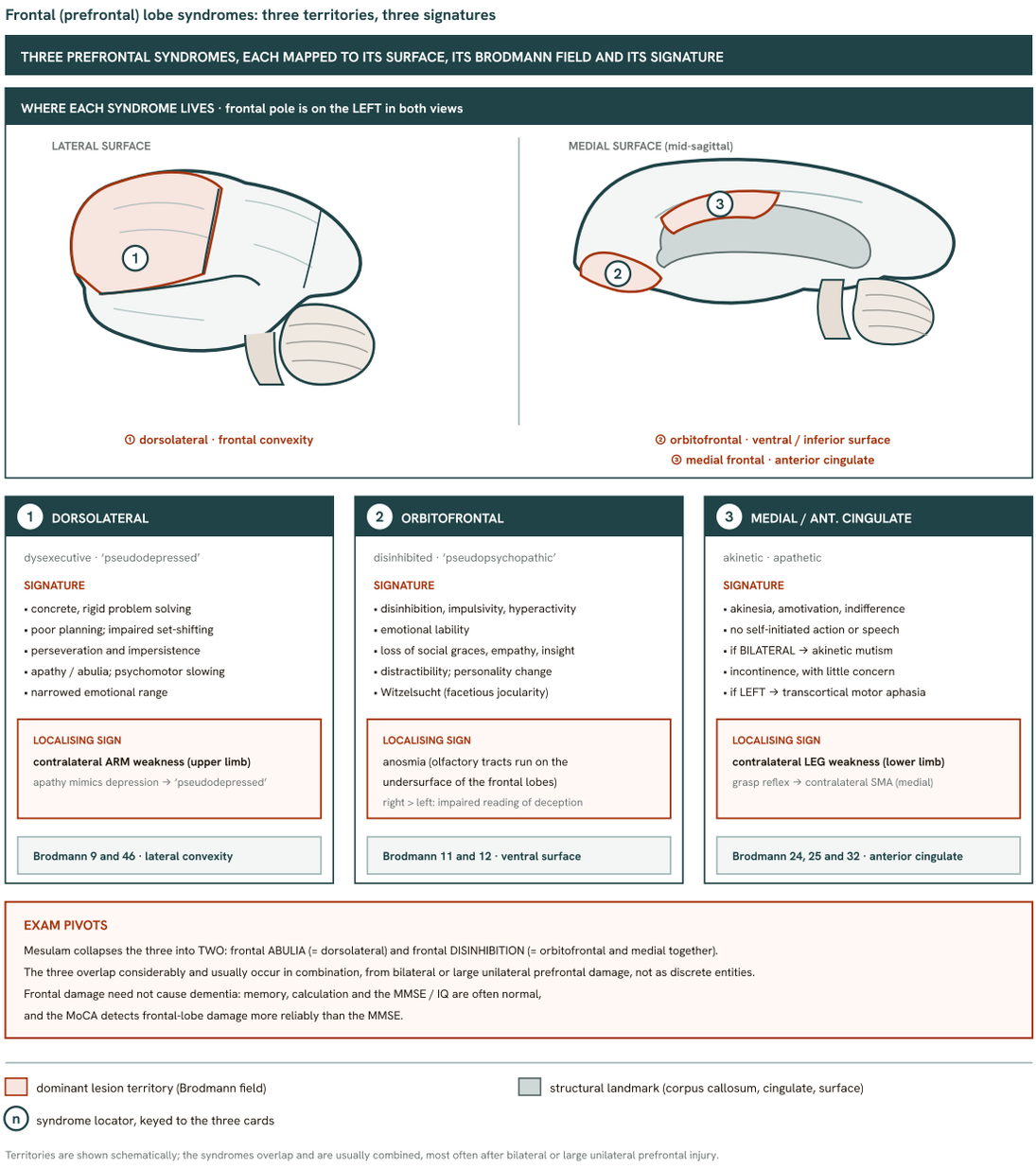


Fig 34.7 **The three frontal-lobe syndromes and their territories.** Dorsolateral (frontal convexity) damage gives a dysexecutive, apathetic picture; orbitofrontal (ventral) damage gives disinhibition and loss of social judgement; medial-frontal and anterior-cingulate damage gives akinesia, apathy and, if bilateral, akinetic mutism. The three overlap and usually occur together (after Kaufman's Clinical Neurology for Psychiatrists and Frontal Lobe Functions).

MNEMONIC

PLAN - RESTRAIN - INITIATE

Plan points to the dorsolateral dysexecutive pattern, **restrain** to orbitofrontal disinhibition, and **initiate** to medial frontal apathy and akinesia. Add the characteristic motor, language, continence and olfactory associations after naming the dominant behavioural change.

RULE **Localise from a convergent syndrome, not from a single behaviour.** Describe the dominant failure, search for the predicted associated signs, and expect overlap when damage is extensive.

21.2 Shared frontal phenomena and behavioural polarity

Across frontal-lobe dysfunction, the patient may become apathetic and indifferent, think and move slowly, struggle to change from one mental set to another, and speak little. **Bradyphrenia** denotes slowed cognition, while **bradykinesia** denotes slowed movement. Paucity of spontaneous speech and action may range from reticence to **abulia**. At the severe end, voluntary movement and speech may disappear together, producing **akinetic mutism**. These features form a low-output pole of frontal dysfunction.

The contrasting pole reflects loss of inhibition. The patient may be distractible, pulled toward whatever is immediately present, socially inappropriate or facetiously jocular. The term **stimulus-bound behaviour** captures environmental capture: conduct is governed by an available cue rather than by an internally maintained goal. This helps explain why a patient can converse fluently yet fail to regulate what is said or done.

These poles are not mutually exclusive. A patient may show sparse self-initiated activity until an external cue triggers an impulsive or inappropriate response. That apparent contradiction becomes intelligible when initiation and inhibition are treated as separable control problems. It is one reason collateral history is essential: ward behaviour, family observations and the patient's functioning outside the interview may reveal abnormalities that a quiet consultation does not.

Observation should distinguish capacity from self-regulation. If the patient completes an action after repeated prompting but does not initiate it independently, the available capacity is greater than the spontaneous output. If the patient understands a boundary yet repeatedly crosses it when a cue appears, comprehension is greater than behavioural restraint. If the patient knows the component steps of an activity but cannot arrange, revise or complete them, stored knowledge is greater than executive organisation. These discrepancies are the clinical texture of a frontal syndrome. They prevent the examiner from reducing all poor performance to memory loss, all inactivity to sadness, or all impropriety to deliberate misconduct.

The tempo and setting of assessment also matter conceptually. A short formal encounter supplies structure, reminders and an explicit goal, all of which can temporarily support a patient whose internally guided behaviour is impaired. Less structured settings may reveal failure to begin, drift from purpose, capture by environmental cues or inability to stop. Collateral examples should therefore be translated into operations: what goal was intended, what cue diverted behaviour, whether correction changed the response, and whether the patient recognised the consequence. This is more localising than a global description such as "personality changed."

The terms apathy, abulia and akinetic mutism should not be used interchangeably. Apathy describes reduced motivation and concern; abulia emphasises marked reduction in spontaneous action and speech; akinetic mutism denotes the extreme combination of absent voluntary movement and absent speech. The medial syndrome supplies the clearest anatomical setting for the severe state, but lower-output features also occur within the dorsolateral pattern.

21.3 Dorsolateral syndrome: the dysexecutive pattern

Damage to the dorsolateral frontal convexity produces the **dysexecutive syndrome**. Problem solving becomes concrete and rigid. Organisational strategies are poor, the patient struggles to shift set, and behaviour may alternate between perseveration and failure to persist. The core problem is not absence of stored knowledge. It is impaired control over how knowledge and action are selected, sequenced, revised and carried through toward a goal.

Perseveration is continued use of a response or strategy after the situation requires change. Impersistence is the complementary failure to maintain an appropriate effort. Together they explain a common bedside impression: the patient may become stuck when flexibility is required, yet abandon a task that needs sustained organisation. Concrete answers and rigid strategies should therefore be interpreted as parts of a control disorder rather than as isolated intellectual deficits.

The affective and motor tempo is often reduced. Apathy or abulia, psychomotor slowing and a restricted emotional range can make the patient look depressed. For this reason, the same phenotype is called the **pseudodepressed syndrome**. The label is a localisation clue, not a claim that depressive illness and frontal dysfunction cannot coexist. Look for the quality of reduced output, executive rigidity and neurological accompaniment rather than deciding from sadness or low activity alone.

Anatomically, the syndrome is associated with Brodmann areas 9 and 46 on the lateral frontal convexity. A lesion may also produce contralateral upper-extremity weakness. The side of weakness matters: it points across the body to the affected hemisphere. When executive disorganisation, psychomotor slowing and this motor pattern occur together, the localisation is stronger than any behavioural feature considered alone.

> **PITFALL**
>
> Do not diagnose primary depression solely from reduced speech, slowed activity and a flat emotional range. Ask whether the patient also shows concrete problem solving, poor organisation, set-shifting failure, perseveration or impersistence, and examine for a contralateral upper-extremity deficit.

21.4 Orbitofrontal syndrome: disinhibition and social dysregulation

Orbitofrontal damage produces the **disinhibited syndrome**, also described as pseudopsychopathic. The patient may become impulsive, hyperactive, distractible and emotionally labile. Social graces, insight and empathy are reduced, so a striking personality change may be more obvious to relatives and staff than to the patient. The deficit is not simply "bad behaviour." It is failure to use context, likely consequences and interpersonal meaning to restrain an immediately available response.

A characteristic manner is **Witzelsucht**: hollow, superficial jocularity with inappropriate joking or laughter. The humour may be socially ill-timed and lacking in genuine emotional depth. An

inappropriate laugh must be interpreted within the wider behavioural context rather than assigned a mechanism from its surface appearance alone.

The lesion lies on the inferior or ventral frontal surface, associated with Brodmann areas 11 and 12, the orbitofrontal cortex proper, with the exact numbering varying by atlas. Poor smell discrimination or **anosmia** may accompany the syndrome because the olfactory nerves lie on the undersurface of the frontal lobes. Smell disturbance is therefore not a decorative extra in the answer. It is an anatomical bridge between the behavioural syndrome and the ventral location.

Laterality can refine the interpretation. Orbitofrontal damage on the right more than the left particularly impairs appreciation of deception.

This association should remain supporting evidence; stand-alone localisation needs the wider syndrome. In practice, extensive lesions commonly blur boundaries, and impaired insight can make self-report reassuring when behaviour has changed profoundly.

GOOD TO REMEMBER

When relatives report a new loss of tact, empathy or restraint, obtain concrete examples and ask about smell. A socially polished interview does not exclude orbitofrontal dysfunction, especially when the patient lacks insight into the change.

21.5 Medial frontal syndrome: failure of initiation

Damage to the medial frontal and anterior cingulate region produces the **akinetic-apathetic syndrome**. The patient is amotivated, apathetic and indifferent, with little self-initiated behaviour or speech. The central clinical question is whether action begins without external prompting. A patient may possess the motor and language capacity required for a response yet fail to generate it spontaneously.

Severity and laterality determine the associated pattern. Bilateral medial frontal damage can produce akinetic mutism, in which the patient is akinetic and mute. A unilateral lesion may cause contralateral lower-extremity weakness, while bilateral damage may weaken both legs. The distribution of weakness is therefore different from the upper-extremity association of the dorsolateral convexity syndrome.

Urinary and bowel incontinence may occur, accompanied by strikingly little concern. The combination of reduced initiation, leg weakness and indifferent incontinence should direct attention toward the medial surface rather than being dismissed as poor cooperation or a nonspecific behavioural problem. Each element reinforces the same localisation when it appears within a coherent syndrome.

Language provides an additional lateralising clue. A left medial frontal lesion involving the anterior cingulate can produce transcortical motor aphasia. The syndrome is anatomically associated with Brodmann areas 24, 25 and 32 in the anterior cingulate gyrus. Extension into the corpus callosum may add alien hand; the disconnection syndrome itself is taught in the dedicated section on alien hand, disconnection and visual association syndromes.

The behavioural description must remain distinct from weakness, aphasia or reduced consciousness. A patient who does not act may be unable, may not understand, may be insufficiently awake, or may lack initiation. The medial frontal formulation becomes credible only after those alternatives are considered and the full pattern aligns.

21.6 Comparison at the bedside

The examination answer is strongest when the syndromes are compared on shared axes rather than presented as separate lists. Start with the dominant control failure, then add behavioural tone, neurological accompaniment and surface anatomy. The table deliberately separates signature from supporting signs so that a single finding is not mistaken for the whole syndrome.

AXIS	DORSOLATERAL	ORBITOFRONTAL	MEDIAL FRONTAL / ANTERIOR CINGULATE
Dominant failure	Planning, organisation, set shifting and persistence	Inhibition, impulse control and social regulation	Initiation of behaviour, movement and speech
Characteristic behaviour	Concrete, rigid problem solving with perseveration or impersistence	Impulsivity, distractibility, emotional lability and social impropriety	Apathy, indifference, amotivation and scant spontaneous output
Memorable descriptive label	Dysexecutive or pseudodepressed	Disinhibited or pseudopsychopathic	Akinetic-apathetic
Motor association	Contralateral upper-extremity weakness	No defining motor association in the permitted account	Contralateral leg weakness, or bilateral leg weakness with bilateral damage
Additional clue	Reduced emotional range and psychomotor slowing	Anosmia and hollow jocularity	Indifferent incontinence; akinetic mutism with bilateral damage
Anatomical surface	Lateral frontal convexity	Inferior or ventral frontal surface	Anterior cingulate on the medial surface

A compact clinical sequence is useful:

- Identify whether the dominant failure concerns planning, restraint or initiation.
- Seek the predicted motor, olfactory, continence, language and affective accompaniments.
- State whether the observed picture is a dominant subtype or a mixed frontal syndrome.

The sequence protects against paired errors. The first is overlocalisation from a colourful isolated behaviour. The second is underrecognition because the patient does not reproduce a complete textbook phenotype. A syndrome is a pattern with internal anatomical coherence, and overlap is part of that pattern rather than evidence against it. Documentation should name the dominant pattern and retain discordant findings, because mixed damage can make those discrepancies clinically meaningful. The final formulation should explain apparent contradictions instead of forcing every finding into the dominant label, and should state which signs remain unexplained.

21.7 Why routine global testing may mislead

A normal global score does not neutralise a compelling frontal history. Frontal-lobe damage does not necessarily cause dementia. Memory, simple calculation and visuospatial perception may remain relatively preserved because they depend substantially on parietal, temporal or distributed systems. Normal results on IQ tests or the MMSE do not exclude frontal damage.

This dissociation explains why the interview must examine behaviour in context. A patient may answer factual questions, calculate simply and copy visuospatial material, yet be unable to organise a plan, shift strategy, inhibit an inappropriate response or initiate purposeful activity. The deficit lies in governing cognition and conduct rather than in the complete loss of the component abilities sampled by a global screen.

The danger is particularly important with indolent disease. A slowly growing lesion in the nondominant frontal lobe may become enormous before producing any sign. The statement is not permission to order imaging indiscriminately. It is a warning that apparently preserved conversation and routine cognition cannot, by themselves, exclude frontal pathology when personality, initiative or executive conduct has changed.

Detailed administration, scoring and interpretation of standardised cognitive instruments belong to the Psychotherapies, clinical assessment, MSE and nosology notes. The bedside cognitive examination, executive testing and frontal release signs are taught in the dedicated section of this chapter. Here the localising lesson is narrower: global preservation and focal behavioural failure can coexist.

TRAP **A normal MMSE does not exclude frontal lobe disease.** Global tests may remain normal because the disabling abnormality is executive, motivational or socially regulatory. History and behavioural observation remain central.

21.8 Alternative model and examination synthesis

The traditional framework is not the only way to organise prefrontal behaviour. The **two**-syndrome model associated with Mesulam describes frontal abulia and frontal disinhibition. Frontal abulia corresponds to the dorsolateral syndrome, while frontal disinhibition combines orbitofrontal and medial-frontal features because both are often present in the same patient.

This alternative should be presented as a teaching compression, not as a contradiction. The more detailed map separates planning, inhibition and initiation because each has a useful dominant anatomical association. The compressed map emphasises the clinically recurring contrast between diminished output and poorly restrained output. Each framework acknowledges that real lesions can produce mixed behaviour.

A high-quality written answer can therefore proceed in a disciplined order. Define frontal syndromes as dominant prefrontal behavioural patterns with substantial overlap. Name the traditional subtypes. For each, state the signature, localisation and associated neurological clue. Contrast the pseudodepressed appearance of dorsolateral damage with the pseudopsychopathic appearance of orbitofrontal damage, then distinguish each from the profound initiation failure of

medial frontal disease. Finish with the alternative model and the warning that global cognition may appear preserved.

At the bedside, avoid moral language. “Lazy,” “rude,” “uncooperative” and “attention-seeking” convert neurological observations into judgements and destroy localisation. Describe initiation, inhibition, set shifting, persistence, emotional range, insight and social regulation in operational terms. Obtain collateral examples and integrate them with the neurological examination. A scan can demonstrate a lesion, but the syndrome is established by the coherent clinical pattern.

Dorsolateral disease impairs planning and set shifting, orbitofrontal disease impairs inhibition and social restraint, and medial frontal disease impairs initiation; mixed syndromes are common.

22 · The bedside cognitive examination, executive testing and frontal release signs

The bedside cognitive examination is a method of clinical localisation, not a ritual list of questions. A good examination asks whether the patient is sufficiently awake to engage, identifies the cognitive process that fails, checks whether a more elementary deficit explains that failure, and then looks for a coherent pattern across interview, testing and behaviour. This matters in psychiatry because fluent conversation, preserved social polish or an acceptable global screen can conceal a disabling problem with initiation, inhibition, set maintenance or self-monitoring.

IN INDIA

Use a brief cognitive test in a version matched to the patient's language and schooling, rather than defaulting to an English instrument.

The marks lie in method. State the prerequisite of arousal, proceed through the domains in an explicit order, choose brief probes that answer a clinical question, and interpret errors rather than merely recording them. The examination should end with executive tasks, behavioural observation, social cognition, judgement, insight and relevant neurological signs. Standardised screens support this process; they do not replace it.

22.1 Establish validity before testing

The bedside cognitive examination begins before a formal question is asked. Observe whether the patient can be engaged, sustain wakefulness, hear and understand the examiner, tolerate the encounter and make an effort that is interpretable. Arousal or consciousness is the prerequisite for valid testing. When that foundation is unstable, an apparent failure of memory, language or executive control may simply reflect an invalid testing state. The proper response is to document the limitation and repeat or adapt the examination, not to construct an elaborate localisation from unreliable performance.

Interpretability also depends on how the task was delivered. Use language the patient can understand, confirm that instructions were grasped, allow for educational and cultural familiarity, and attend to sensory, motor, pain and fatigue barriers. These are not excuses for poor

performance; they are competing explanations that must be tested. Record what the patient actually did: lost the rule, stopped initiating, became stimulus-bound, repeated a previous response, misunderstood the words, or could not execute a motor answer. Such description preserves clinical information that a total score discards.

RULE **Test the process, not just the answer.** First establish arousal and task comprehension; then identify the cognitive operation that failed and ask whether a simpler deficit accounts for it.

Testing is therefore iterative. A surprising error should prompt clarification, a simpler instruction or a non-verbal route where appropriate. Concordance among history, spontaneous behaviour and several bedside probes strengthens an inference. Discordance is useful too: it signals that language, attention, motivation, sensory limitation or task novelty may be influencing the result.

22.2 Use an ordered domain sweep

The examination proceeds from basic engagement toward increasingly integrated functions. After arousal, assess orientation, **attention and concentration**, **working memory**, language, learning and memory, perceptual-motor or visuospatial function, **executive function**, social cognition, and judgement and insight. The order protects interpretation: later tasks often depend on capacities examined earlier.

STAGE	CLINICAL QUESTION	INTERPRETIVE PURPOSE
Arousal	Can the patient remain awake and engage?	Determines whether subsequent performance is valid.
Orientation	Can the patient place the self and situation in context?	Provides a broad anchor, but must be interpreted with attention and memory.
Attention and concentration	Can a mental set be selected and sustained?	Checks the gateway needed by most later tasks.
Working memory	Can information be held while it is manipulated?	Links attention with goal-directed performance.
Language	Can the patient understand and formulate meaningful responses?	Prevents language failure being mislabeled as global cognitive failure.
Learning and memory	Can information be acquired, retained and accessed?	Separates acquisition difficulty from later retrieval difficulty by observing the process.
Perceptual-motor and visuospatial function	Can visual information guide organised action?	Identifies whether a visually mediated task is suitable for executive interpretation.
Executive function	Can behaviour be organised, shifted and inhibited?	Tests control over action rather than stored knowledge alone.
Social cognition, judgement and insight	How is cognition used in interpersonal and real-world decisions?	Reconnects test performance with everyday function and self-appraisal.

Standardised batteries may be comprehensive, but their length can consume time and fatigue the patient. A brief, hypothesis-led bedside examination combined with a suitable screening tool is often the practical clinical approach recommended for the resident. Brevity should come from choosing discriminating probes, not from omitting domains.

AROUSAL	DOMAIN	ERROR	PATTERN
VALIDITY	PROCESS	INTERPRETATION	LOCALISATION

22.3 Attention, concentration and working memory

Attention is not a single observable behaviour. At the bedside, ask whether the patient can register the rule, maintain it, resist distraction, detect a change and continue until the task ends. Concentration is inferred from sustained goal-directed performance. Working memory adds an active demand: information must remain available while the patient reorders, updates or acts upon it. These capacities are best judged from accuracy together with the manner of responding.

Useful probes include:

- digit span forward and backward, comparing simple retention with the additional demand of reversing the sequence;
- months backward, which requires maintenance of a familiar ordered sequence while proceeding against its usual direction;
- alphanumeric sequencing, which places an explicit manipulation demand on working memory; and
- observation across the interview for losing the question, drifting from the task, requiring repeated prompts or abandoning an effort prematurely.

Do not interpret a failed complex task before checking these gateway functions. Poor attention can impair encoding, make recall inconsistent, disrupt comprehension and produce disorganised construction. Conversely, a patient may remain socially engaged yet fail when the task requires holding and manipulating information. This is why a conversational impression is insufficient.

The examiner should note whether errors are immediate or emerge with continued demand, whether the rule is forgotten or merely violated, whether cueing restores performance, and whether the patient recognises the lapse. These observations convert a pass-or-fail exercise into a cognitive formulation. They also guide the next probe: simplify the task when comprehension is uncertain, reduce perceptual or motor demand when output is constrained, and repeat under better conditions when fatigue has made the result uninterpretable.

Documentation should preserve this reasoning. Begin with the testing conditions and degree of engagement, then give a domain-by-domain account of performance and the characteristic errors. Separate what was observed from what is inferred. For example, “lost the alternating rule despite restatement” is an observation; “impaired set maintenance” is an interpretation. Note adaptations, prompting and self-correction because they change what a response means. End with a synthesis that identifies the strongest pattern, the important confounders and the findings that do not fit. This style is more clinically portable than a string of scores: another examiner can

understand the basis of the conclusion, repeat the crucial probes and judge whether change reflects cognition, context or testing conditions. It also guards against circular reasoning, in which a presumed diagnosis dictates the meaning of every error. Bedside examination generates a localising hypothesis; history, neurological examination and appropriate investigation must test that hypothesis.

22.4 Language, memory and visually mediated probes

Domain-specific tools are chosen to clarify a question raised by the bedside examination, not to decorate it. For language, the bedside Western Aphasia Battery-Revised and the Boston Naming Test are named clinical options. For memory, the Hopkins Verbal Learning Test provides a verbal learning probe. Their item content and scoring are not reproduced here. The clinician still has to decide whether poor performance reflects language comprehension, inadequate attention, failed acquisition, retrieval difficulty or an unsuitable testing context.

Visually mediated tasks broaden the examination beyond verbal interaction. Line bisection and target cancellation are bedside probes for neglect. The clock-drawing test and Navon figures probe visuospatial function. A poor result is not self-interpreting: visual perception, spatial organisation, motor output, instruction comprehension and executive planning may all affect the finished response. Describe the error pattern and test the relevant components before assigning a lobe syndrome.

This is also the point at which examination boundaries matter. Hemispatial neglect, apraxia and agnosia require the dedicated assessment taught with the parietal lobe syndromes. Temporal and occipital syndromes likewise need their own focal examination. Here, these bedside probes serve the general method: they reveal which domain needs expansion and prevent a verbal screening encounter from being mistaken for a complete cognitive examination.

PITFALL

A malformed drawing is often labeled “executive dysfunction” at sight. First ask whether the patient saw the material, understood the instruction and could perform the motor act. Executive interpretation becomes credible only after the task’s perceptual, language and output requirements are accounted for.

22.5 Standardised screens: know what each samples

A screening instrument is a structured sample, not the whole examination. Its value depends on the domains it includes, the clinical question and the validity of performance. The recognised multi-domain tools overlap, but their emphasis is not identical.

INSTRUMENT	DOMAINS SAMPLED	BEDSIDE IMPLICATION
Mini-Mental State Examination (MMSE)	Orientation, verbal registration and recall, attention, naming and repetition, verbal comprehension, praxis and visuospatial function	Use as a multi-domain screen; do not treat it as a comprehensive executive examination.
Montreal Cognitive Assessment (MoCA)	Orientation, attention, memory, naming, fluency, verbal repetition and visuospatial-executive function	Its domain sampling includes explicit executive content.
Addenbrooke's Cognitive Examination-Revised and current Addenbrooke's Cognitive Examination-III (ACE-R and ACE-III)	Attention and orientation, memory, fluency, language and visuospatial function	Provides a broad domain profile without replacing hypothesis-led bedside testing.

When frontal-lobe damage is the question, the MoCA is more reliable for detection than the MMSE. That relative advantage does not make either instrument a stand-alone localisation test. A discrepant history, behavioural observation or executive probe still requires explanation.

The Frontal Assessment Battery and antisaccades are named tools for frontal executive assessment, but their item content and scoring are intentionally outside this fragment. The standardised instruments themselves, including administration, scoring, interpretation and licensing boundaries, belong to the Psychotherapies, clinical assessment, MSE and nosology notes.

TRAP **Do not equate a global screening result with an executive examination.** State what the selected screen samples, then add bedside probes of sequencing, rule conflict, inhibition, fluency and behaviour according to the clinical question.

22.6 Executive testing at the bedside

Executive function is the control architecture of goal-directed behaviour. It is inferred from how the patient establishes a set, organises a sequence, maintains a rule, shifts when demands change, suppresses a prepotent response, monitors errors and persists to completion. No **single** probe screens every executive dysfunction. The defensible bedside approach is therefore a small set of tasks with different demands, interpreted alongside spontaneous behaviour.

Motor sequencing or Luria tasks examine whether an ordered motor programme can be learned and maintained. Watch for **perseveration**: the patient may continue a previous element or remain trapped in an established response despite correction. Do not reduce the finding to clumsiness. Check that the component movements are physically possible, demonstrate the sequence clearly, and distinguish failure to acquire the programme from failure to sustain it.

The conflicting-instructions tapping task asks the patient to tap once when the examiner taps twice and twice when the examiner taps once. Success requires holding the rule and overriding direct imitation. The go/no-go tapping task asks the patient to tap once when the examiner taps once but not to tap when the examiner taps twice. Here the critical demand is response

inhibition. Record anticipatory tapping, imitation, rule loss, correction after feedback and awareness of error. Similar-looking failures may arise from different points in the control process.

Verbal fluency samples strategic search and self-monitoring. Semantic generation can use an "animals" cue, while phonemic generation can use "words with s". The clinically useful information is not merely output volume. Note whether production starts readily, clusters around a narrow theme, becomes repetitive, breaks the rule or stops despite encouragement. Language capacity and educational familiarity must be considered before calling the pattern executive.

Finally, observe the patient between explicit tasks. **Utilisation behaviour** is suggested when visible objects pull action toward their use without an appropriate goal. Echopraxia and echolalia reveal excessive capture by another person's movement or speech. **Motor impersistence** is difficulty sustaining a requested motor act. These signs may be more revealing than a polished verbal response because they test control in the presence of competing environmental cues.

MNEMONIC

Sequence, Conflict, Stop, Search, Sustain

The executive bedside spine: organise a motor **sequence**, reverse the examiner under **conflict**, **stop** a primed response, strategically **search** for words, and **sustain** a motor set while watching for environmental capture.

22.7 From error pattern to frontal localisation

Localisation should follow the cognitive analysis, not precede it. A patient who fails sequencing because the instruction was not understood has not demonstrated a frontal deficit. A patient who repeatedly understands the rule, can execute its components, yet cannot maintain, shift or inhibit the response provides a more coherent executive pattern. The same principle applies to fluency and working memory: interpret the mechanism of failure and seek convergence across tasks.

The anatomical associations also differ among probes. Go/no-go performance depends on the orbitofrontal cortex. The other executive tasks, including sequencing and fluency, depend chiefly on the dorsolateral prefrontal cortex and its circuit. Motor impersistence is associated with right-hemisphere dysfunction. These are associations for clinical reasoning, not a licence to localise from an isolated error. The accompanying figure places focal bedside signs in a broader lobe and hemisphere framework.

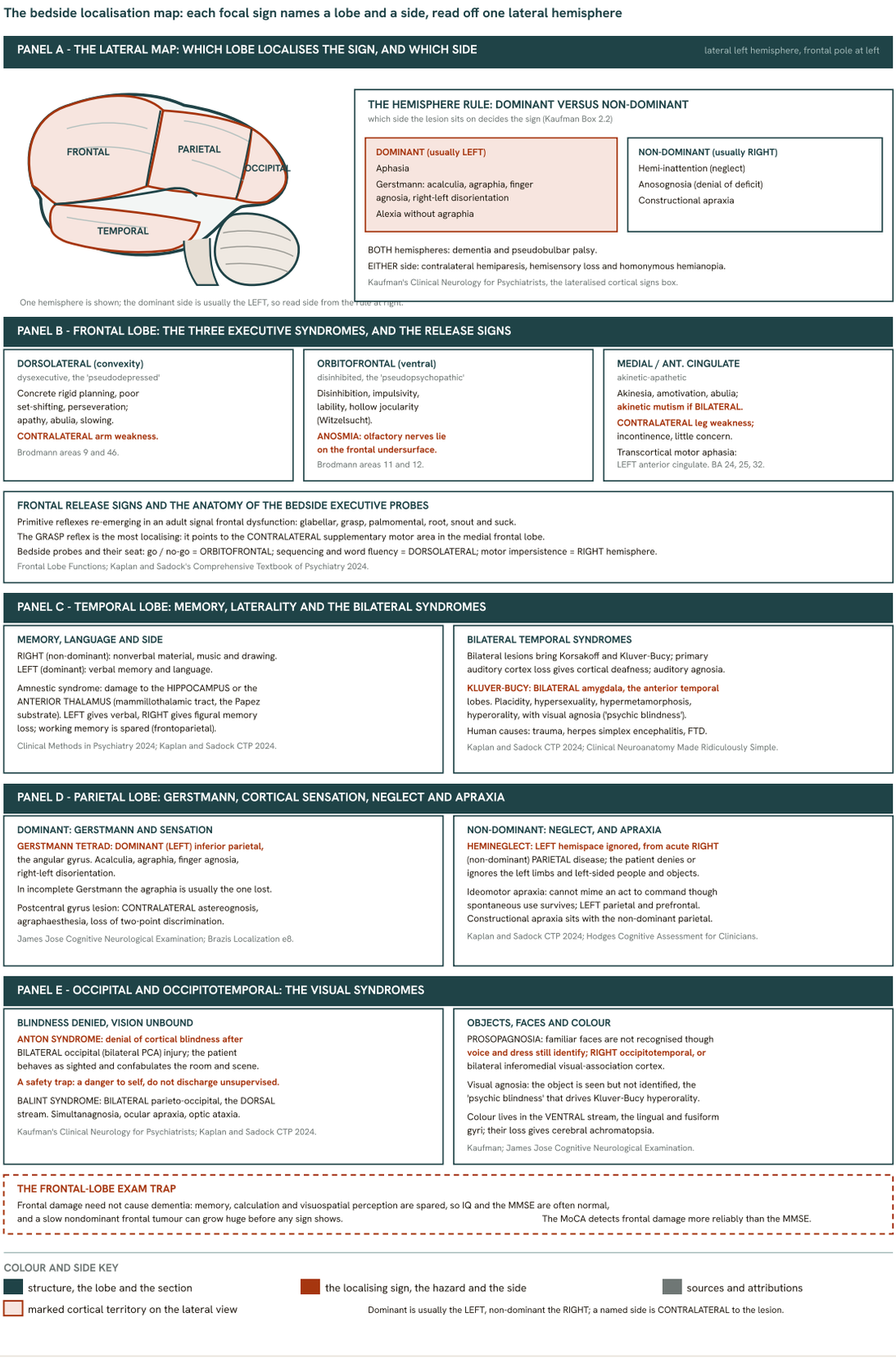


Fig 34.8 **The bedside localisation map.** Each focal sign is read back to a lobe and a side on one lateral hemisphere: frontal for the executive syndromes and release signs, temporal for memory and the Kluver-Bucy syndrome, parietal for the Gerstmann tetrad and neglect, occipital for the visual syndromes; the hemisphere rule fixes dominant against non-dominant. (Kaufman's Clinical Neurology for Psychiatrists; Frontal Lobe Functions; Kaplan and Sadock's Comprehensive Textbook of Psychiatry 2024; Clinical Methods in Psychiatry 2024; James Jose Cognitive Neurological Examination.)

Behavioural observation supplies ecological corroboration. Difficulty initiating the task, stimulus-bound responding, failure to stop, repetition after correction and poor awareness of error may reveal different aspects of impaired control. Their interpretation is strengthened when they agree with the interview and structured probes. The full phenomenology of dorsolateral, orbitofrontal and medial frontal syndromes belongs with the frontal lobe syndromes; this section owns the examination used to detect and localise their cognitive signs.

GOOD TO REMEMBER

If an executive task is abnormal, repeat the instruction in simpler language and verify the elementary motor or language capacity needed for the response. A reproducible failure of rule maintenance or inhibition is more informative than an unexplained wrong answer.

22.8 Frontal release signs

Frontal release signs, also called primitive reflexes, are responses present in infancy and normally suppressed through development. Their re-emergence in an adult suggests frontal-lobe dysfunction. They are most often encountered with acute or severe injury and may be absent when frontal disease is less severe or sub-acute. Presence therefore supports a frontal hypothesis, while absence does not dispose of it.

The bedside repertoire includes the following:

The glabellar response is failure of blinking to extinguish during repeated tapping above the nose. The palmomental response is contraction of the ipsilateral chin or mentalis after stimulation over the thenar region. The snout response is puckering of the lips after the upper lip is tapped. The root, suck and grasp reflexes complete the named group. Elicit them deliberately, explain the manoeuvre, avoid startling the patient, and document the observed movement rather than writing “release signs positive” without qualification.

The **grasp reflex** is particularly useful because it is fairly specific for frontal-lobe injury and carries localising value. Stroke the palm distally toward the base of the fingers and observe for grasping. A grasp response points to dysfunction of the contralateral supplementary motor area in the medial frontal lobe. Laterality is essential: the pathological response is on the side opposite the implicated supplementary motor area.

No **single** frontal release sign is pathognomonic. A response must be interpreted with age and clinical context, the quality and reproducibility of the manoeuvre, associated executive findings and the rest of the neurological examination. A cluster of convergent abnormalities is more persuasive than an isolated equivocal movement. Equally, a normal release-sign examination cannot exclude sub-acute or less-severe frontal disease.

Arousal validates the examination; ordered domains identify the failed process; convergent executive probes and release signs support localisation, but no isolated task or primitive reflex makes the diagnosis.

23 · Temporal lobe syndromes and the Kluver-Bucy syndrome

Temporal-lobe syndromes become manageable when the answer is organised by domain, side and lesion extent. The temporal lobes participate in auditory perception, language, memory and emotion, so their disorders can present to psychiatry as forgetting, altered recognition, disturbed behaviour or an apparent language problem rather than as an obvious motor deficit. The marks lie in showing that these manifestations are related but not interchangeable. A strong formulation names the impaired operation, lateralises it where possible, and asks whether the lesion must be unilateral or bilateral.

> **IN INDIA**
>
> Start aciclovir early on clinical suspicion of herpes simplex encephalitis rather than waiting for laboratory confirmation, because delay worsens the amnestic outcome.

The central contrast is between dominant, non-dominant and bilateral involvement. Dominant temporal dysfunction preferentially disturbs verbal material and language; non-dominant dysfunction preferentially disturbs figural, visual and other nonverbal material; bilateral injury can disrupt auditory recognition or produce a much broader memory-emotion-behaviour syndrome. The most distinctive bilateral behavioural pattern is the **Kluver-Bucy syndrome**, whose feature names are often remembered better than their meanings. The examiner should therefore translate each term into observable behaviour and state the bilateral anterior-temporal or amygdala localisation.

23.1 Functional map and the logic of laterality

The **temporal-lobe syndrome** is not a single uniform phenotype. It is the clinical expression of failure within a lobe that supports auditory perception, language, memory and emotion. The patient may therefore complain of hearing without understanding, remembering some kinds of material better than others, difficulty finding words, or a marked change in emotional and motivational behaviour. These complaints must be converted from everyday language into the specific operation that has failed.

Dominant temporal-lobe dysfunction, usually represented clinically by the left side, interferes with language and verbal memory. The critical word is verbal: difficulty retaining a story, names or spoken material is more lateralising than the global statement that "memory is poor." **Non-dominant temporal-lobe dysfunction**, usually represented by the right side, impairs nonverbal information such as drawing and music. This is not merely a weaker version of the dominant syndrome. The material being processed is different.

LEFT	RIGHT	BILATERAL
VERBAL AND LANGUAGE	FIGURAL AND NONVERBAL	AUDITORY AND LIMBIC SYNDROMES

Laterality is useful only when the task matches the material. A verbal task cannot adequately test the non-dominant temporal contribution, and a figural task cannot by itself establish dominant verbal-memory failure. At the bedside, compare learning across material types, relate the result to

language competence, and seek convergence from history and neurological findings. The aim is not to infer an exact lesion from a single failed item. It is to establish a coherent side-sensitive pattern.

RULE **Localise by operation, material and side.** "Poor memory" is too broad. Verbal learning and word retrieval point toward dominant temporal dysfunction; figural, visual and other nonverbal learning point toward non-dominant dysfunction; broader auditory or behavioural syndromes raise the question of bilateral involvement.

23.2 How to examine a suspected temporal syndrome

A temporal-lobe examination begins before formal testing. Clarify what the patient means by "I cannot remember," "I cannot hear properly," or "words do not come." Determine whether information was understood at presentation, whether it can be maintained briefly, whether it remains available after distraction, and whether the difficulty changes with verbal versus visual material. Ask relatives for concrete examples, because fluent conversation can coexist with failure to retain new events and the patient may not appreciate the pattern accurately.

The examination should sample the owned temporal domains without reproducing a general cognitive battery. Test acquisition and later recall with verbal material, then use nonverbal or figural material to look for a side-sensitive dissociation. Assess ordinary language and word retrieval so that an apparent verbal-memory deficit is not interpreted without considering language performance. Present meaningful environmental sounds and ask what they signify, while separately establishing whether sound is perceived at all. When bilateral anterior-temporal disease is plausible, observe emotional responsiveness, stimulus-driven attention, oral exploration, sexual disinhibition and placidity.

This sequence separates closely neighbouring questions. Perception asks whether the stimulus reaches awareness. Recognition asks whether the percept has meaning. Memory asks whether newly encountered material becomes durably available. Language asks whether verbal material can be understood and expressed. Behavioural observation asks whether emotional and motivational regulation has changed. A patient can fail one operation while retaining another, so a global label such as "organic behaviour" or "cognitive decline" throws away localising information.

Formal test administration and scoring belong to the Psychotherapies, clinical assessment, MSE and nosology notes. The temporal examination uses the same disciplined approach but asks a narrower anatomical question. Repeat an apparently abnormal task in a different form, document whether the material was verbal or nonverbal, and record the type of error rather than only success or failure. A side-sensitive dissociation is more persuasive when language, attention and immediate maintenance have been considered.

GOOD TO REMEMBER

When a patient reports “hearing loss,” ask separately whether sound is detected and whether it is recognised. When the complaint is “memory loss,” ask what kind of material is lost and whether it disappears immediately or only after a delay. Those distinctions turn a vague psychiatric complaint into a localising examination.

23.3 The amnestic syndrome and medial-temporal memory

The **amnestic syndrome** consists of anterograde amnesia for new material together with variable retrograde amnesia. The core clinical problem is impaired formation of durable new memories, not loss of every mental operation. A patient may follow the interview, hold a question in mind and answer coherently, yet later fail to retain the encounter. This apparent paradox is expected because short-term or working memory is spared through its dependence on frontoparietal mechanisms.

Anatomically, damage to the hippocampus can produce the syndrome. The permitted anatomical differential also includes the anterior thalamus and the mammillothalamic tract. That comparison matters because a severe new-learning disorder is not uniquely temporal. Detailed thalamic and mammillary pathology in Korsakoff syndrome belongs in its dedicated section of this chapter; here the useful point is that medial-temporal and diencephalic injury can converge on an amnestic presentation.

The memory deficit is lateralised by material. Left-sided damage produces predominantly verbal memory impairment, whereas right-sided damage produces predominantly figural or visual memory impairment. This is the same material-sensitive logic that organises the broader temporal syndrome. It prevents the common mistake of treating “memory” as anatomically indivisible. In practice, language failure can contaminate verbal learning, and poor initial engagement can mimic defective retention, so the examiner should establish comprehension and adequate acquisition before interpreting delayed recall.

A bedside formulation should state the operation, the material and the preserved capacity. For example, describe impaired acquisition of durable verbal information with intact immediate maintenance, rather than simply recording forgetfulness. If figural learning is selectively poor while verbal learning is relatively stronger, state that contrast explicitly. The full causes, transient amnesias, confabulation and rehabilitation of amnestic disorders are taught in their dedicated sections; the temporal-lobe question is the hippocampal contribution and its laterality.

PITFALL

Do not dismiss medial-temporal amnesia because the patient can repeat information or converse normally for a short interval. Immediate maintenance may be preserved while durable learning is profoundly impaired. Test retention after interference and obtain collateral examples of repeated forgetting.

23.4 Cortical deafness and auditory agnosia

Auditory syndromes demonstrate why perception and recognition must be separated. **Cortical deafness** follows damage to the primary auditory cortex in the setting of bilateral temporal involvement. The ears are structurally intact, yet the person cannot hear. The syndrome therefore localises failure beyond the peripheral organ. It should not be described as inattention merely because the patient does not respond to spoken material.

Auditory agnosia is different: sound recognition is impaired while language remains intact. Sound reaches awareness, but its significance is not identified. The patient's difficulty is therefore not equivalent to deafness, and preserved language argues against explaining the entire problem as a language disorder. At the bedside, first establish whether a sound is perceived, then ask the patient to identify or explain it. This order prevents failure of perception from being mislabelled as failure of recognition.

CLINICAL AXIS	DOMINANT TEMPORAL PATTERN	NON-DOMINANT TEMPORAL PATTERN	BILATERAL TEMPORAL PATTERN
Material most affected	Verbal information and language	Drawing, music and other nonverbal information	Broader failure that cannot be reduced to a unilateral material preference
Memory expression	Predominantly verbal impairment with left-sided damage	Predominantly figural or visual impairment with right-sided damage	Bilateral lesions may produce major amnestic syndromes
Epilepsy-associated cognitive profile	Verbal-memory and word-retrieval deficits	Visuospatial and visual-memory deficits	Classify seizures in the dedicated epilepsy chapter
Auditory consequence	No isolated auditory syndrome is assigned here	No isolated auditory syndrome is assigned here	Cortical deafness after primary auditory-cortex damage, or impaired sound recognition in auditory agnosia
Behavioural consequence	Interpret emotion and behaviour within the whole syndrome	Interpret emotion and behaviour within the whole syndrome	Anterior-temporal or amygdala damage may produce the characteristic placid, oral, sexual and stimulus-bound pattern

The table is a localisation framework, not a substitute for examination. Hearing, recognition, language and memory must each be tested at the level appropriate to the complaint. A bilateral label should be reserved for a pattern whose anatomy and breadth demand bilateral temporal involvement, not applied merely because several symptoms coexist.

23.5 Temporal-lobe epilepsy as a lateralising context

Temporal-lobe epilepsy provides a clinically useful demonstration of the same hemispheric specialisation. In dominant temporal-lobe epilepsy, verbal-memory and word-retrieval deficits

are associated features. In non-dominant temporal-lobe epilepsy, visuospatial functioning and visual memory are preferentially affected. The pattern does not create a separate rule for epilepsy; it confirms that the side and the kind of information remain linked.

The psychiatric assessment should not turn this association into a diagnosis from cognitive testing alone. Word-retrieval difficulty or weak visual memory can support lateralisation within a known clinical context, but neither establishes that episodes are epileptic. Reconstruct the event history, determine whether cognitive problems are persistent or episodic, and seek neurological corroboration. Seizure classification, electroencephalographic interpretation and anticonvulsant pharmacology belong to the Epilepsy and psychiatry notes.

There is also an important acquired-lesion overlap. Herpes simplex encephalitis has a predilection for the temporal lobes and the undersurface of the frontal lobes. When its temporal damage is bilateral, the human behavioural syndrome may coexist with amnesia and complex partial seizures. This cluster should be read anatomically: memory structures, limbic behaviour and seizure susceptibility can be affected within the same regional disease. It does not justify importing the entire classification or treatment of epilepsy into the temporal-lobe answer.

TRAP **Do not equate every temporal cognitive deficit with epilepsy.** Dominant verbal-memory and word-retrieval difficulty, or non-dominant visual-memory difficulty, may lateralise dysfunction in temporal-lobe epilepsy; they do not by themselves prove an epileptic mechanism.

23.6 Kluver-Bucy syndrome: anatomy and feature meanings

The defining anatomical principle is **two-sided** injury. The syndrome depends on damage to the amygdala in the anterior temporal lobes on both sides, producing a mixture of emotional, perceptual and motivational change. A unilateral amygdala lesion should not be offered as the classic localisation. The description arose from the captive-monkey syndrome, but in clinical practice each term must be translated into behaviour rather than recited as an unexplained list.

The cleanly grounded behavioural core contains **four** elements:

- **Tameness or placidity:** reduced aggression and striking docility.
- **Hypersexuality:** excessive and indiscriminate sexual behaviour.
- **Hypermetamorphosis**: compulsive or forced attention to environmental stimuli, so behaviour is repeatedly captured by what is present.
- **Hyperorality**: mouthing of nonfood objects, an abnormal oral exploration of the environment.

A separately grounded associated feature is **visual agnosia**, meaning inability to recognise objects visually despite seeing them. Its anatomical wording requires care: the amygdala lesion accounts for placidity, hypersexuality and hypermetamorphosis, while visual agnosia reflects injury to nearby areas. Thus the perceptual feature belongs in the taught clinical picture, but it should not be simplistically attributed to the amygdala alone.

MNEMONIC

PLACID - SEXUAL - STIMULUS-BOUND - ORAL - SEES BUT DOES NOT KNOW

Placid recalls reduced aggression, **sexual** recalls indiscriminate hypersexuality, **stimulus-bound** unpacks hypermetamorphosis, and **oral** recalls mouthing of nonfood objects; **sees but does not know** captures the separately grounded visual agnosia.

23.7 Human presentations and causes

Humans usually show an incomplete phenotype rather than the full experimental picture. The human Kluver-Bucy syndrome usually occurs in partial form. This is clinically important because insisting on every named manifestation will miss plausible cases, while using one colourful behaviour as proof will overdiagnose them. The formulation should identify the observed features, state what is absent or unknown, and demonstrate compatible bilateral anterior-temporal involvement.

The permitted causes are trauma, herpes simplex encephalitis and frontotemporal dementia. These diagnoses supply different clinical contexts, but the localisation question is shared: can the pathology affect the anterior temporal-amygdala system bilaterally? The syndrome should therefore direct anatomical reasoning without replacing the aetiological assessment.

Herpes simplex encephalitis is especially instructive because it preferentially affects the temporal lobes and the undersurface of the frontal lobes. Bilateral temporal damage can then produce the human syndrome together with amnesia and complex partial seizures. Behaviour that appears disinhibited, sexually inappropriate, orally exploratory or unusually placid must therefore be interpreted alongside memory change and the neurological context rather than assigned prematurely to a primary psychiatric disorder.

Conversely, none of the listed causes can be inferred from the syndrome alone. The behavioural pattern localises a network; the history, examination and appropriate investigation establish the pathology. Human partiality also means that absence of a feature is less decisive than the anatomical coherence of those present. Documentation should avoid claiming a complete syndrome when only a subset is observed.

23.8 Bedside synthesis and examination answer

A concise long-answer structure begins with function, proceeds to laterality, then separates focal domain syndromes from the bilateral behavioural syndrome. State that the temporal lobes support auditory perception, language, memory and emotion. Contrast dominant verbal-language deficits with non-dominant figural and nonverbal deficits. Add hippocampal amnesia with preserved working memory, distinguish cortical deafness from auditory agnosia, and then describe the bilateral amygdala basis and clinical meaning of the characteristic behavioural features.

At the bedside, use a disciplined synthesis. Name the failed operation: perception, recognition, language, durable learning, emotional regulation or stimulus control. State the material involved: verbal, figural, visual, musical or environmental sound. Use side-sensitive findings to distinguish

dominant from non-dominant temporal dysfunction. Reserve the bilateral formulation for cortical deafness, major bilateral memory syndromes, or the anterior-temporal amygdala pattern. Describe each observed behavioural feature in plain clinical terms and record whether the human presentation is partial. Finally, separate localisation from aetiology: the pattern identifies the involved system, while the clinical context identifies trauma, encephalitis, degeneration or another pathology.

The main differentials are operational rather than merely diagnostic. Failure to perceive sound is not failure to recognise it. Failure to recognise a visual object is not blindness. Failure to retain new information after a delay is not disproved by intact immediate repetition. Verbal-memory impairment is not interpretable without language assessment. A striking behavioural change is not enough for the bilateral syndrome unless the feature cluster and anatomy cohere.

Keep ownership boundaries equally clear. Korsakoff syndrome pathology and confabulation are taught in their dedicated sections of this chapter. The general dementia syndrome and its workup belong to the Dementias and neurocognitive disorders notes. Seizure classification and drug selection belong to the Epilepsy and psychiatry notes. These cross-references preserve the focal temporal answer: what operation failed, which side is implicated, whether bilateral damage is required, and how the behavioural terms translate at the bedside.

> Temporal localisation follows material and laterality: left dominant lesions impair verbal memory and language, right non-dominant lesions impair figural and nonverbal memory, and the characteristic placid, hypersexual, stimulus-bound and hyperoral syndrome requires bilateral anterior-temporal amygdala damage.

24 · Parietal lobe syndromes: Gerstmann syndrome, neglect, apraxia and agnosia

Parietal syndromes are best understood as failures of integration. Strength, primary sensation, coordination, comprehension and willingness may be adequate, yet the patient cannot combine symbols, spatial attention, learned action or higher sensory information into an effective response. That contrast is why these syndromes are disproportionately useful at the bedside: a brief task can reveal the impaired operation as well as the likely hemisphere.

The marks lie in disciplined distinctions. The dominant inferior parietal region points toward the Gerstmann cluster; the non-dominant parietal region points toward contralateral hemispatial neglect; praxis must be tested only after elementary motor and sensory failure has been excluded; and cortical sensory loss must be distinguished from loss of primary sensation. A good answer therefore moves from definition, through bedside demonstration, to localisation, while stating what the finding is not.

DOMINANT	NON-DOMINANT	COMMAND	TOUCH
GERSTMANN PATTERN	NEGLECT	IDEOMOTOR FAILURE	CORTICAL SENSORY SIGN

24.1 The parietal map: domain before label

The parietal examination samples several related but separable domains. Symbolic operations include writing, calculation, finger representation and right-left orientation. Spatial attention determines whether the full environment and body enter awareness. Praxis converts an understood intention into a learned act. Higher somatosensory processing converts intact elementary sensation into recognition of form, identity or a traced symbol. A lesion may disturb a particular domain more than the others, so "parietal syndrome" is a localisation hypothesis rather than a uniform behavioural phenotype.

Laterality gives the initial organising axis. Dominant-hemisphere cortical signs include aphasia, the Gerstmann pattern and alexia without agraphia, whereas non-dominant signs include neglect, anosognosia and constructional apraxia. Either hemisphere can also produce contralateral weakness, hemisensory loss or a homonymous field defect. Those elementary findings support a side but do not by themselves identify the higher parietal operation that has failed. Extensive or distributed disease may blur these teaching patterns.

CLINICAL AXIS	DOMINANT PARIETAL EMPHASIS	NON-DOMINANT PARIETAL EMPHASIS	EITHER SIDE / SUPPORTING SIGN
Core higher function	Calculation, writing, finger recognition and right-left orientation	Attention to contralateral hemispace	Interpret as a pattern, not from an isolated task
Characteristic syndrome	Gerstmann syndrome	Hemi-inattention and constructional apraxia	Contralateral motor, sensory or visual-field signs
Common conceptual error	Calling every writing failure aphasic	Calling every left-sided omission a primary sensory loss	Localising from an abnormal response without checking prerequisites

RULE **Define the failed operation, verify its prerequisites, and only then localise.** A higher cortical sign becomes convincing when the patient is sufficiently alert, understands the task, cooperates, and has enough elementary motor, sensory and visual capacity to attempt it.

24.2 Gerstmann syndrome: the tetrad

Gerstmann syndrome is a **four**-component syndrome comprising **acalculia**, **agraphia**, **finger agnosia** and right-left disorientation. Its classic localisation is the dominant, usually left, inferior parietal lobule in the region of the angular gyrus. The value of the tetrad is not merely memorising a list. The components converge on learned symbolic and body-schema operations that are anatomically close enough to fail together.

At the bedside, examine each component directly and document the nature of the error. Calculation should sample more than rote recitation and should separate misunderstanding from faulty manipulation of numerical information. Writing should be spontaneous or elicited in a way that allows inspection of letter formation and organisation, rather than judged from the patient's signature alone. Finger recognition requires the patient to identify or indicate fingers reliably.

Right-left orientation should be tested on the patient's body and interpreted cautiously if language comprehension is doubtful.

MNEMONIC

WRITE - CALCULATE - FINGERS - SIDES

The compact sweep is: ask the patient to write, perform a calculation, identify fingers, and distinguish right from left. The mnemonic preserves the whole tetrad without pretending that an isolated error establishes the syndrome.

The localisation statement should follow the findings, not substitute for them: a coherent tetrad indicates dominant inferior parietal dysfunction near the angular gyrus. If aphasia, weakness, sensory loss, visual impairment or poor attention makes a task uninterpretable, record that limitation rather than scoring the response as another cortical deficit. In an examination answer, this caveat shows clinical maturity because the same apparent failure can arise from different broken prerequisites.

24.3 Gerstmann components can dissociate

The classical tetrad is a pattern, not an all-or-none bedside law. In incomplete Gerstmann syndrome, agraphia is usually the absent component. Therefore, the remaining concordant elements should prompt careful retesting and an anatomically reasoned formulation rather than reflex rejection of the localisation. Conversely, an isolated element should retain a broader explanation until the other components and their prerequisites have been examined.

The nature of the writing disorder is a favourite discriminator. The agraphia in this syndrome is considered apraxic rather than aphasic and need not be accompanied by alexia. The patient's problem is therefore not automatically reducible to loss of language formulation. Examine spoken language and reading separately, and describe how the written output fails. This prevents a visible writing problem from being swept into "aphasia" without analysis.

The same discipline applies to the other elements. Poor calculation may reflect failure to understand the instruction, impaired attention or educational familiarity rather than a focal symbolic deficit. Incorrect finger naming may become uninterpretable when naming itself is impaired. Right-left errors may arise because the patient did not understand the relational language. The examiner should simplify instructions, demonstrate the task when demonstration does not destroy the construct, and seek consistency across repeated responses without turning the encounter into a formal psychometric assessment.

PITFALL

Do not diagnose the full syndrome from an isolated classroom-like error. Establish that the patient understood the instruction, could see and move adequately, and was attending. Then test all components and state whether the pattern is complete, incomplete or only suggestive.

Detailed administration and scoring of standardised cognitive instruments belong to the Psychotherapies, clinical assessment, MSE and nosology notes. The present task is focal localisation: identify the operation that failed, show that the failure is reproducible, and integrate it with the rest of the neurological examination.

24.4 Hemispatial neglect: an attentional disorder

Hemispatial neglect, or hemi-inattention, is a focal disorder of attention. It almost always affects left hemispace in acute right, non-dominant hemisphere disease, most characteristically from a parietal lesion. Distinguishable neglect patterns may also follow frontal or cingulate lesions, so the bedside sign is strongly lateralising but must still be integrated with the wider syndrome.

Gross neglect may be visible before formal testing. The patient may fail to attend to people or objects on the left, ignore the left limbs, or deny that those limbs belong to the self. Observe spontaneous orientation during conversation, approach from each side, and note whether grooming, interaction or response consistently excludes a hemispace. Structured paper-and-pencil or copying tasks may make subtle asymmetry easier to see, but interpretation still depends on adequate vision, motor output and task comprehension.

The decisive conceptual distinction is between inattention and elementary loss. A patient with neglect behaves as though information from a side does not gain sufficient access to ongoing behaviour. A primary sensory or visual deficit, by contrast, concerns the incoming signal itself. The disorders can coexist, which is why the examiner compares visual, tactile and auditory behaviour, checks elementary function, and looks for a consistent spatial bias across modalities and activities. Do not convert every omission into neglect before this groundwork.

Neglect must also not be equated with anosognosia. The former is a spatial-attention disorder owned here; the latter concerns unawareness or denial of deficit and is taught with post-stroke psychosis, emotional incontinence and denial of deficit. They may accompany the same non-dominant hemisphere syndrome, but either term retains its distinct meaning.

> **GOOD TO REMEMBER**
>
> When the patient repeatedly misses material on the left, change the mode of presentation and verify vision, sensation, movement, comprehension and arousal. A cross-modal leftward attentional bias carries more localising weight than an untidy drawing or a missed touch.

24.5 Apraxia: definition and classification

Apraxia is inability to perform complex motor acts despite intact motor and sensory systems, coordination, comprehension and cooperation. These exclusions belong inside the definition because weakness, ataxia, sensory loss, misunderstanding and refusal can each mimic a failed learned action. “Could not do it” is therefore an observation; apraxia is the reasoned conclusion reached after the simpler explanations have been tested.

A useful clinical classification describes **four** principal motor apraxias. The table is a map of dominant associations, not permission to force a patient into a rigid compartment.

TYPE	DOMINANT CLINICAL PROBLEM	LOCALISATION IN THE PERMITTED ACCOUNT	BEDSIDE EMPHASIS
Limb-kinetic apraxia	Execution of a skilled limb act	Basal ganglia or supplementary motor area	Inspect the quality of the learned movement after excluding weakness and incoordination
Ideomotor apraxia	Translating an understood command into a correctly selected and oriented gesture	Left parietal lobe	Compare command, imitation, spontaneous action and object use
Ideational apraxia	Conceptual organisation of an intended action	Contested localisation	Describe the conceptual failure and acknowledge the source conflict
Orobuccal apraxia	Performance of learned oral movements	Left inferior frontal lobe	Separate voluntary task failure from elementary weakness and poor comprehension

TRAP **Do not give a falsely settled localisation for ideational or conceptual apraxia.** The temporal account places it in the left temporal lobe, while the competing account places the stored movement formulae in the left inferior parietal lobule; their only agreement is the left, dominant hemisphere. State the conflict explicitly rather than silently choosing a site.

24.6 Ideomotor apraxia: command, imitation and spontaneous action

The hallmark of ideomotor apraxia is a dissociation: the patient cannot carry out an act to command but may perform the same act spontaneously. The failure concerns selection, sequencing or spatial orientation of the motor act rather than loss of the intention itself. Meaningful as well as meaningless gestures can be affected, as can demonstration of how an imagined tool is used.

Bedside examination should exploit that dissociation. Give a clear verbal command, ask for imitation of a demonstrated gesture, observe spontaneous use, and, where appropriate, compare imagined with real-object use. Imitation and provision of the real object may improve performance. Improvement is informative because it reduces the need to generate the action from a verbal instruction alone. Describe the error: wrong sequence, wrong orientation, an approximation, use of a body part as though it were the object, or inability to initiate a recognisable gesture. Description is safer than merely marking pass or fail.

In right-handed patients, the associated lesions are in the left hemisphere, particularly inferior parietal and prefrontal regions. This fits the broader principle that learned action systems can be dominant-hemisphere functions even when the tested limb itself is not weak. The finding should be interpreted alongside language, sensation and motor examination, because verbal-command testing becomes ambiguous when comprehension is impaired.

A particularly localising dissociation occurs with disconnection. An anterior callosal lesion may leave one limb, usually the left, unable to perform on command while the other limb performs normally. This asymmetric command failure is not ordinary bilateral clumsiness. It points to failure of information transfer to the motor system controlling the affected limb. Alien hand and the wider disconnection syndromes are taught in the dedicated section on alien hand, disconnection, occipital and visual association syndromes.

24.7 Agnosia and cortical sensory signs

In this parietal context, agnosia is best approached through touch. Elementary sensation must reach the cortex, but the patient fails to convert that information into a higher percept or an identified object. This is why the examiner initially establishes that the stimulus is felt and only then asks what its shape, size, traced form or identity means.

Astereognosis is failure to identify a palpated object because perception of its size and shape is impaired. A postcentral-gyrus lesion produces this deficit contralateral to the lesion and may also impair two-point discrimination and graphaesthesia. The patient's inability to name the object is not sufficient by itself. Vision should not be used to solve the task, elementary sensation must be adequate, and a naming disorder must not be mistaken for failed tactile recognition.

Agraphaesthesia refers to inability to recognise a letter or digit traced on the skin. It samples the conversion of a felt trajectory into a learned symbolic form. Compare sides under similar conditions and document whether the patient perceived contact but could not recognise the traced symbol. This distinction turns a vague "sensory problem" into a cortical sensory sign.

Persistent tactile object-recognition failure, or tactile agnosia, follows lesions of the secondary sensory area. The distinction from astereognosis is conceptual: impaired analysis of size and shape prevents recognition in the latter, whereas persistent failure of tactile object recognition defines the former in the permitted account. In either case, the deficit is contralateral to the relevant parietal sensory lesion.

Visual agnosias and other visual association syndromes belong to the dedicated section on alien hand, disconnection, occipital and visual association syndromes. Keeping that boundary matters: "agnosia" names a family of recognition failures, while this section owns the tactile and body-representation signs that localise parietal dysfunction.

24.8 Integrated bedside synthesis

The final answer should sound like a localisation argument, not a catalogue. Begin with the domain that failed, then state the decisive exclusion and the lateralising pattern. A calculation, writing, finger and right-left cluster supports the dominant inferior parietal region. A consistent left-sided attentional bias supports right non-dominant disease. Failure of learned action despite preserved prerequisites establishes apraxia, with the command-spontaneous dissociation sharpening ideomotor apraxia. Contralateral failure of higher tactile recognition supports parietal sensory cortex.

A compact examination sequence is:

- Confirm arousal, comprehension, cooperation, primary sensation, power, coordination and adequate vision for the selected task.
- Test the complete Gerstmann cluster rather than stopping after an isolated writing or calculation error.
- Seek neglect across spontaneous behaviour and sensory modes, then distinguish it from elementary loss and from anosognosia.
- Compare action to command, imitation, spontaneous action and object use; finish with cortical sensory testing on each side.

The formulation should preserve uncertainty. Say “incomplete Gerstmann pattern” when the supported elements cluster but a component is absent; say “possible neglect” when an elementary field or sensory deficit remains unresolved; and say “apraxia cannot be assessed reliably” when comprehension or weakness invalidates the task. These are not evasions. They prevent an invalid test from acquiring false anatomical precision.

Documentation should make the inference auditable. Record the instruction, the patient’s response, the prerequisite that was checked, and the interpretation. “Failed gesture” is weak documentation; “understood the command, had adequate power and coordination, produced a spatially disorganised gesture, then improved with imitation” shows why an ideomotor formulation was considered. Likewise, “ignored the left” is strengthened by noting that elementary input was detected but did not consistently guide behaviour. This style separates observation from localisation and allows another clinician to decide whether the same evidence supports the conclusion.

When findings disagree, resist tidying them into a perfect syndrome. Retest the questionable domain with a simpler instruction, look for a competing prerequisite failure, and describe the residual mismatch. Focal cortical syndromes are valuable precisely because their components can dissociate. Honest discordance is more informative than an overconfident label built from ambiguous tasks.

Finally, integrate associated signs without allowing them to replace the syndrome. Contralateral weakness, hemisensory loss and homonymous hemianopia may follow a lesion in either hemisphere. Constructional apraxia and neglect favour the non-dominant side, while the Gerstmann cluster favours the dominant side. The general ordered bedside cognitive examination is taught in the dedicated section on bedside cognitive examination, executive testing and frontal release signs. Here, the examiner’s task is narrower: use a small set of internally coherent higher cortical signs to identify the parietal operation and hemisphere involved.

Dominant inferior parietal disease produces the Gerstmann pattern; right non-dominant parietal disease produces left hemispatial neglect; apraxia requires preserved elementary function before it can localise, as do cortical sensory signs.

25 · Alien hand, disconnection, occipital and visual association syndromes

Why this cluster belongs together. These syndromes show that intact elementary function is not the same as integrated function. A limb may move and feel yet escape experienced control; vision may be present at the sensory level yet fail to yield recognition; or an entire visual scene may collapse into one attended element. The examination question is therefore not simply whether the patient can move, see or speak. It is whether specialised cortical systems can exchange information and convert perception into ownership, recognition and visually guided action.

The marks lie in a disciplined sequence: define the failed operation, demonstrate it without supplying the answer, identify what remains intact, and localise the interrupted network. Autonomous movement, denial of blindness and recognition failure can otherwise acquire vague psychiatric labels. Bedside analysis replaces them with a testable clinico-anatomical formulation.

RULE **Localise the broken link, not just the visible failure.** In a disconnection or visual-association syndrome, explicitly state the preserved input or output, the higher operation that fails, and the pathway or association cortex whose interruption explains the mismatch.

25.1 Disconnection as a clinical principle

A **disconnection syndrome** arises when an injury severs communication pathways between cortical centres. The relevant centres may each retain some capacity, but information available to one cannot reach the system that must interpret it or act upon it. This produces a characteristic dissociation: the patient succeeds when a task uses an intact route and fails when the same task depends on the disconnected route. That internal contrast is more localising than a general statement that cognition is impaired.

The recognised family includes alexia without agraphia, conduction aphasia, and buccofacial or limb forms of ideomotor apraxia. A comparable connectional principle operates outside the cerebral hemispheres in internuclear ophthalmoplegia from a medial longitudinal fasciculus syndrome. These examples should not be flattened into one mechanism or re-taught as though their bedside signs were interchangeable. Their shared lesson is that a pathway lesion can isolate otherwise functional systems.

The bedside method follows that lesson. First establish that the sensory channel required for the task is usable. Then show that the relevant motor response can occur in another context. Finally, vary the route by which the instruction or object reaches the patient. A route-dependent failure argues for disconnection; failure across every route suggests a more primary sensory, motor or broadly cognitive problem. Language comprehension, attention and cooperation must be considered before assigning a focal label.

Neuroanatomical inconsistency is orderly: performance changes with the pathway demanded by the task. Map that pattern before interpreting the behaviour psychologically. The full assessment of parietal apraxia and agnosia is handled in the dedicated parietal-lobe section.

CALLOSAL	BILATERAL OCCIPITAL	DORSAL	VENTRAL
OWNERSHIP AND INTERHEMISPHERIC CONTROL	CORTICAL BLINDNESS WITH DENIAL	SCENE, GAZE AND VISUAL GUIDANCE	COLOUR PROCESSING

25.2 Alien hand: ownership, agency and control

In **alien hand syndrome**, also called alien limb syndrome, the affected hand retains at least rudimentary motor and sensory function, yet its movements are not under the patient's control and its sensations are not appropriately appreciated. The hand may act in a semi-purposeful, autonomous fashion, such as scratching or unbuttoning. The striking point is not simple involuntary movement. The movement appears organised enough to suggest an intention, but the patient does not experience that intention as his or her own.

The definition contains **two** linked misperceptions: the patient experiences the hand as not belonging to the self, and experiences another agent as governing it. This separates alien hand from a purely motor disorder. Abnormal movement alone does not establish alienness; the disturbance of ownership and agency is central. Conversely, an unusual verbal description should not be accepted without observing the limb and establishing the preservation of basic function.

The affected limb is usually the left hand. It may reach toward or explore objects outside apparent volitional control. It may also counteract the other hand, producing **intermanual conflict**: one hand initiates or completes an act while the other reverses or obstructs it. This opposition gives a visible example of hemispheric intentions failing to remain coordinated.

Bedside description should separate observation from interpretation. Record what the hand did, whether the action was stimulus-bound or apparently spontaneous, whether the patient noticed it, and how ownership and agency were described. Examine elementary motor and sensory capacity, ask for purposeful action, and observe bimanual activity. The aim is to show the mismatch between retained capacity and impaired voluntary integration.

> **GOOD TO REMEMBER**
>
> When an apparently purposeful hand behaves “on its own,” ask separately about **ownership**, **agency** and **control**. Alien hand requires more than an involuntary movement; the patient's experience of possession and authorship is part of the syndrome while rudimentary motor and sensory function remains.

25.3 Callosal and medial-frontal localisation

Alien hand can follow injury to the corpus callosum, and callosal damage within a medial-frontal syndrome can leave the left extremities outside volitional control. The medial-frontal and callosal observations are complementary. Medial-frontal systems contribute to initiation and voluntary control, while the callosum allows the hemispheres to coordinate intention, sensory information and action. Damage at their interface can therefore produce autonomous exploration rather than paralysis.

The classic teaching image is “the right hand not knowing what the left hand is doing,” but the useful anatomy runs in the opposite explanatory direction: language-mediated awareness and control cannot be assumed to reach the systems organising the other limb. This is why laterality matters. The syndrome usually affects the left hand, controlled predominantly by the non-dominant hemisphere, when interhemispheric communication is disrupted by callosal or medial-frontal injury.

Callosal alien hand is an integration disorder. The hand is neither mechanically powerless nor simply insensate. Its activity may look purposive, but the action is not incorporated into the patient's plan. Opposition between hands exposes motor programmes no longer reconciled across the hemispheres.

This distinction prevents psychiatric over-reading. A patient's report that another agent controls the hand resembles the language of passivity, but the clinician should first determine whether there is an observed, lateralised limb phenomenon with retained basic function and a coherent neurological pattern. The statement is then interpreted within ownership and motor-control failure, rather than treated in isolation as evidence of a primary disorder of belief.

PITFALL

Do not diagnose alien hand from the phrase “someone controls my hand” alone. Look for an actual autonomous, semi-purposeful limb action, preserved rudimentary function, impaired ownership and agency, and a reproducible lateralised pattern compatible with medial-frontal or callosal damage.

25.4 The callosal command-apraxia model

A particularly clear disconnection model follows occlusion of both anterior cerebral arteries. The resulting injury involves both frontal lobes and the anterior corpus callosum at the genu. The left arm and leg can move spontaneously, yet they fail to follow verbal or written commands. This is a **left-sided limb apraxia** defined by the route through which action is requested.

The anatomical explanation is an information-transfer failure. Language centres in the left hemisphere cannot pass the command to motor centres in the right hemisphere that organise movement of the left limbs. A command delivered through language therefore fails, while spontaneous movement can remain. The contrast is precisely what makes the syndrome more than weakness: the motor apparatus demonstrates capacity, but the linguistically specified action cannot reach it.

At the bedside, compare spontaneous use with action to spoken and written command. Confirm that the patient understood the instruction and that the limb can move. Describe the deficit as left-sided and command-dependent before offering the callosal localisation. Demonstration by the examiner may use a different route and can help clarify whether the failure is specifically language-mediated, but the interpretation must remain anchored to the observed pattern rather than to one failed gesture.

The broader apraxia taxonomy and parietal examination belong in the parietal-lobe syndromes section. The high-yield point here is narrower: anterior callosal injury can disconnect a comprehended command from the hemisphere controlling the contralateral limbs. Preserved spontaneous movement plus failed command performance supplies the bedside logic.

25.5 Cortical blindness with denial: the Anton presentation

Anton syndrome is denial of cortical blindness. The patient behaves as though vision were normal and may deny blindness directly or reveal the denial through conduct. Confabulation is frequent: the patient may describe the room, clothing or objects despite being unable to see them. The syndrome is therefore not merely blindness plus a verbal claim. It is cortical blindness accompanied by unawareness of the deficit, expressed verbally or through behaviour.

The localisation requires bilateral occipital damage in the posterior cerebral artery territories. An illustrative vascular pattern is a new right posterior cerebral artery stroke superimposed on an earlier left-sided stroke, leaving bilateral occipital injury and cortical blindness. The sequence teaches an important principle: a patient can appear visually confident because awareness of loss is itself impaired.

Examination begins with behaviour, not confrontation. Observe navigation, reaching and responses to the environment; then establish visual failure and ask the patient to explain any errors. If the patient supplies confident visual descriptions, record them as confabulatory responses only after confirming that the stated information could not have been obtained visually. The examiner should distinguish a failure to acknowledge the deficit from an ordinary attempt to preserve dignity or from uncertainty during testing.

The immediate consequence is safety. Denial of blindness commonly undermines adherence to ward arrangements, prompts demands for early discharge and can lead to dangerous behaviour. A cortically blind patient acting as though fully sighted may endanger self and others and must not leave unsupervised. Capacity and disposition decisions require the actual functional risk to be documented, not merely the diagnostic label.

25.6 Visual agnosia and recognition of objects

Visual agnosia is inability to comprehend or identify an object that is seen despite an intact visual system. The dissociation lies between seeing features and knowing what those features mean. A patient may describe a stop sign as red, octagonal and bearing the letters S-T-O-P, yet be unable to state what a driver should do. Elementary visual analysis has supplied colour, shape and lettering, but the percept has not acquired usable object meaning.

This distinction guides examination. First ensure that the patient can access the visual features needed for the task. Ask for a description before asking for the object's name or use; this reveals whether shape, colour or component detail is available. Then test whether identification improves through a nonvisual route. The resulting profile should be described rather than reduced prematurely to “poor vision” or “memory loss.” The defining problem is recognition from vision despite an intact visual system.

Visual agnosia is detected most often in association with multiple small strokes or Alzheimer disease. That association does not make either diagnosis from the bedside sign alone. The syndrome identifies the failed cognitive operation; aetiology requires the broader history, examination and investigation. The full dementia syndrome and its diagnostic workup belong to the Dementias and neurocognitive disorders notes.

Severe visual agnosia, termed "psychic blindness," is a major component of Kluver-Bucy syndrome and can drive oral examination of objects. This is a connection to, not a substitute for, the dedicated temporal-lobe discussion of that syndrome. For the present section, its value is conceptual: when vision no longer yields object identity, the patient may seek information through another sensory route.

25.7 Prosopagnosia: a selective failure of face recognition

Prosopagnosia is inability to recognise familiar faces despite an intact visual system. The deficit is selective rather than a failure to recognise the person in every modality. Patients can identify individuals from voice, dress and mannerisms, while object recognition and reading remain intact. The examiner should therefore ask how recognition occurred instead of accepting a correct name as proof that facial recognition is preserved.

The clean localisation is occipitotemporal dysfunction. Lesions may involve bilateral inferomedial visual-association cortices or the right occipitotemporal lobe. Structural injury and neurodegeneration, including Alzheimer disease and frontotemporal dementia, can produce the syndrome. These alternatives again separate syndrome from cause: the same selective recognition failure can arise in an acute focal setting or during a progressive disorder.

Bedside assessment requires familiar stimuli whose identity can be checked without giving contextual clues. Ask the patient to identify the person from the face, then establish whether voice, dress or mannerisms permit recognition. Also confirm that reading and ordinary object recognition are usable. The characteristic dissociation is not "cannot name a photograph"; it is impaired identification by face with successful identification through other personal cues.

Localisation language must remain precise. Occipitotemporal cortex, bilateral inferomedial visual-association cortex and the right occipitotemporal lobe provide the regional formulation. Do not add a narrower gyral label.

TRAP **Do not collapse all visual-association failure into "visual agnosia."** Object meaning, familiar-face identity, awareness of blindness, attention to a scene, voluntary gaze, visually guided reaching and colour perception are separable operations with different clinico-anatomical patterns.

25.8 Balint syndrome and the dorsal visual pathway

Balint syndrome is the archetypal disorder of the dorsal visual pathway and follows bilateral parieto-occipital damage, which may arise from strokes or Alzheimer disease. It contains a **three**-part syndrome: simultanagnosia, psychic paralysis of gaze or ocular apraxia, and optic ataxia.

Each component examines a different transformation of visual information, so merely naming the triad earns less than showing how its parts fit together.

Simultanagnosia is inability to grasp more than one visual object at once. When shown a complex scene, the patient may report only a single element, which may even be peripheral. This is not simply poor visual acuity. The failure concerns simultaneous visual attention and integration: isolated parts can enter awareness, but the scene does not become a coherent whole.

Ocular apraxia, also described as psychic paralysis of gaze, is inability to direct gaze voluntarily. **Optic ataxia** is misreaching under visual guidance. Together they show why the dorsal pathway is clinically concerned with more than static perception. It helps organise attention, gaze and action in relation to the visible world. The patient may see an object yet fail to orient the eyes toward it or guide the hand accurately to it.

Examine the components separately. Use a complex scene to assess whether more than one element can be integrated; ask the patient to shift gaze voluntarily toward selected targets; and observe reaching to visible objects. Before interpreting failure, ensure that the patient has understood the task and that gross movement and elementary vision are adequate for it. The triad is strongest when its parts converge on the same bilateral parieto-occipital, dorsal-stream account.

25.9 Ventral colour processing and an integrated bedside map

Colour is processed through the ventral visual stream. The human colour-perception area lies along the collateral sulcus and fusiform gyrus. **Cerebral achromatopsia** follows bilateral or non-dominant inferior occipitotemporal lesions involving the lingual and fusiform gyri while sparing the calcarine cortex. The pattern differs from cortical blindness because primary visual cortex is spared, and from prosopagnosia because the failed visual attribute is colour rather than familiar-face identity.

The examination should isolate colour perception from language and object recognition as far as the clinical setting allows. Establish that the patient can see the material, then ask for comparison, matching or description of colours without relying on a single naming response. The purpose is to determine whether colour itself is unavailable or whether the patient sees it but cannot retrieve a verbal label. This is a clinical reasoning sequence, not a substitute for formal visual assessment.

SYNDROME	FAILED OPERATION	PRESERVED CLUE	SUPPORTED ANATOMY OR ASSOCIATION
Alien hand	Ownership, agency and voluntary integration of limb action	Rudimentary movement and sensation	Medial frontal or corpus callosum
Anton syndrome	Awareness of cortical blindness	Confident behaviour may conceal the loss	Bilateral occipital cortex
Visual agnosia	Meaning of a seen object	Elementary visual features can be described	Most often detected with multiple small strokes or Alzheimer disease
Prosopagnosia	Identity from a familiar face	Voice, dress, mannerisms, reading and object recognition	Bilateral inferomedial or right occipitotemporal cortex
Balint syndrome	Scene integration, voluntary gaze and visually guided reaching	Individual capacities may be demonstrable when isolated	Bilateral parieto-occipital dorsal pathway
Cerebral achromatopsia	Colour perception	Calcarine cortex is spared	Inferior occipitotemporal lingual and fusiform regions

MNEMONIC

SEE - KNOW - FACE - SCENE - COLOUR

See: establish cortical vision and awareness. **Know:** test object meaning. **Face:** test familiar-face identity without voice or dress cues. **Scene:** test simultaneous attention, gaze and visually guided reach. **Colour:** test colour perception separately. The sequence keeps neighbouring syndromes from being collapsed into one vague “visual problem.”

Build the integrated answer from dissociations. Ask what the patient can detect, what meaning can be extracted, whether awareness of loss is present, and whether vision can guide gaze and reach. Test each operation separately, then seek a coherent pattern of preserved and impaired functions.

- Describe the behaviour before naming the syndrome.
- Establish elementary sensory and motor capacity required by the task.
- Change the input route or response demand to expose a disconnection.
- State the failed operation, preserved function and supported localisation in one formulation.

Disconnection syndromes are diagnosed by dissociation: demonstrate what remains intact, identify the higher operation that fails, and localise the pathway that should have joined them.

26 · Pseudobulbar affect: phenomenology, pathophysiology and treatment

Why this syndrome earns bedside marks. **Pseudobulbar affect** is a disorder of emotional expression in which laughing or crying escapes voluntary regulation and no longer maps reliably onto the patient's prevailing mood. The same construct is described as pathological laughing and crying, involuntary emotional expression disorder, emotional incontinence or emotional lability. Its dramatic appearance invites a psychiatric shortcut, especially when crying is mistaken for depression. The better answer separates expressed emotion from experienced emotion, demonstrates the associated neurological syndrome, and then explains the disrupted motor-affective network.

IN INDIA

For pseudobulbar affect, options include an SSRI or a tricyclic such as amitriptyline; no comparative hierarchy is established, so individualise the choice. Explain the treatment to the family as reducing the outbursts rather than as treating low mood.

The topic joins phenomenology, examination and mechanism. Phenomenology establishes that the episode is brief, stereotyped, excessive and uncontrollable. Examination asks whether corticobulbar upper motor neuron signs or a broader cerebral disorder are present. Pathophysiology then moves from the traditional release model to a distributed fronto-ponto-cerebellar account, while treatment targets the expression disorder without assuming that the patient's mood has changed. This sequence is clinically useful because pseudobulbar affect and depressive illness can coexist.

RULE **Diagnose a mismatch between emotional display and underlying mood, not crying alone.** Establish the abrupt, uncontrollable and disproportionate episode; ask what the patient actually felt before, during and after it; and examine for the neurological disorder that makes impaired emotional regulation plausible without requiring residual sadness or happiness.

26.1 The emotional burst: core phenomenology

The conspicuous clinical feature is **emotional lability**. An episode begins suddenly, usually as crying and less often as laughter, and is excessive in relation to the conversation or situation. It may be triggered by something emotionally relevant, but the magnitude and persistence of the display exceed what the patient feels. At other times the outburst appears unprovoked. The defining abnormality is therefore not the presence or absence of a trigger; it is loss of proportional, voluntary control over expression with an increased frequency of laughing or crying.

Episodes are stereotyped for the individual and last **from a few seconds to a few minutes**. The patient cannot reliably suppress them once they begin, yet often recognises that the display is inconsistent with, or excessive relative to, the underlying feeling. When the burst ends, there is no persisting sadness after crying and no persisting happiness after laughter. That rapid return to the premorbid emotional state is among the most useful bedside clues.

Interview the event as an event. Ask for its onset, observable form, trigger, controllability, duration, stereotypy, frequency and emotional aftermath. Then obtain an informant account when available, because embarrassment, poor recall or adaptation may lead patients to underdescribe visible episodes. Record the patient's own appraisal: “I was not that sad,” “I could not stop,” or “the laughter did not fit” is more informative than a global report of being emotional. Avoid leading questions that collapse felt mood and motor expression into the same construct.

MNEMONIC

BURST

Brief; **U**ncontrollable; **R**ecurrent or unusually frequent; **S**tereotyped and stronger than the felt emotion; **T**erminates without a residual corresponding mood. Each element is supported by the characteristic episode phenomenology of pathological laughing and crying.

26.2 Clinical diagnosis and the depression differential

There are no established formal diagnostic criteria for pseudobulbar affect. Diagnosis remains clinical: identify the characteristic expressive episodes, establish their relationship to subjective mood, and interpret them in the context of neurological disease. Rating scales can quantify symptoms, but a score cannot replace the interview or the observation of an episode. Among available measures, the **Pathological Laughter and Crying Scale** was developed specifically for pathological emotion after stroke. Its proper role is structured severity assessment rather than conversion of a heterogeneous phenomenon into a stand-alone criterion set.

The main psychiatric distinction is from depression after stroke or brain injury. Pseudobulbar crying is abrupt, brief, stereotyped, difficult to control and out of proportion to the trigger. It may be incongruent with the prevailing mood and stops without residual sadness. Depression is organised around sustained low mood, with congruent affect and accompanying neurovegetative symptoms. The same logic separates pseudobulbar laughter from a sustained elevation of mood: the visible act alone is not the mood state.

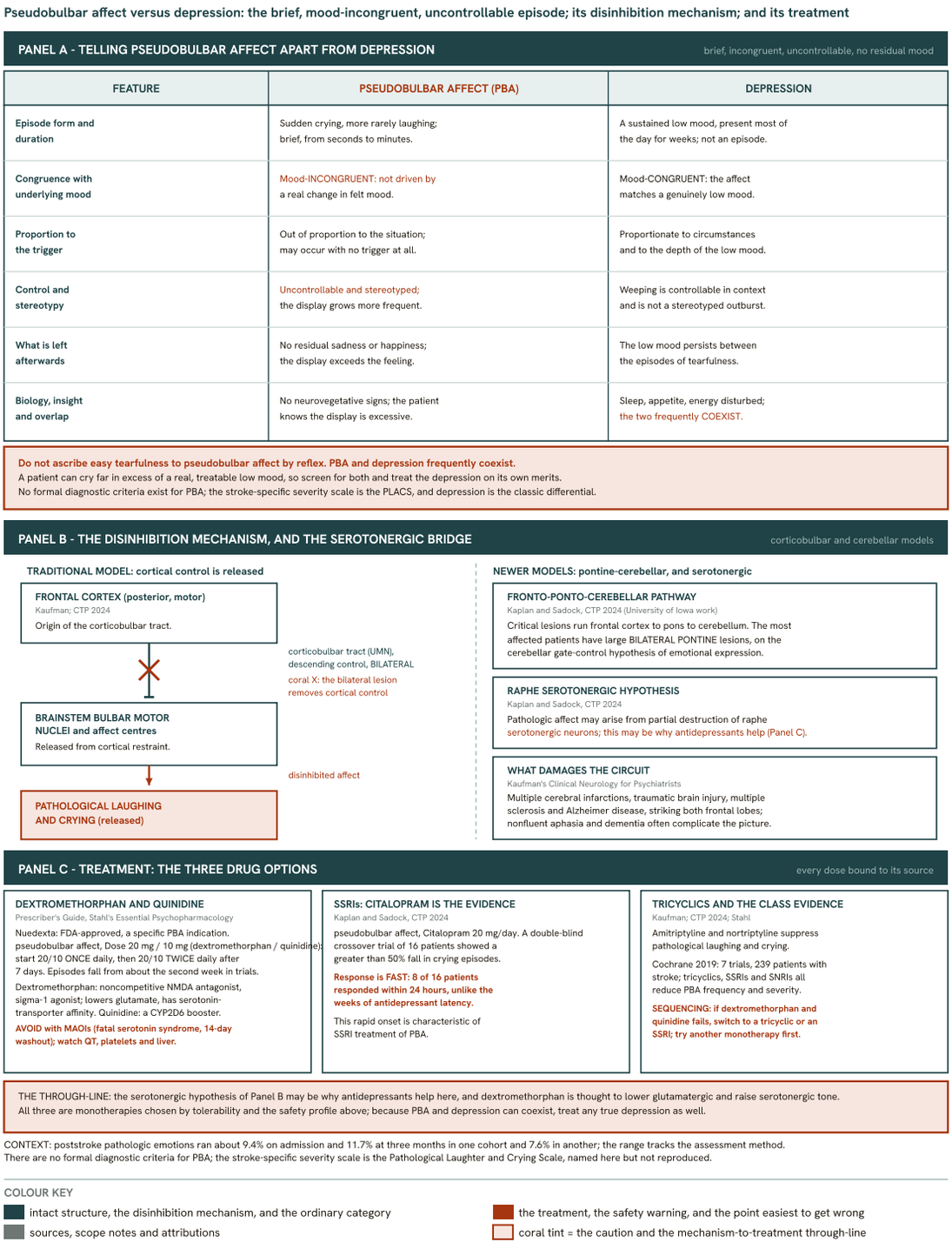


Fig 34.9 Pseudobulbar affect versus depression: the episode, the mechanism, and the treatment. Pseudobulbar affect is a brief, stereotyped, mood-incongruent and uncontrollable outburst of crying or laughing that is out of proportion to its trigger and leaves no residual feeling, unlike the sustained, congruent low mood of depression, though the two frequently coexist. It is traditionally read as bilateral corticobulbar lesions releasing brainstem affect centres from cortical control, with newer fronto-ponto-cerebellar and raphe-serotonergic models; the serotonergic account may explain why SSRIs and tricyclics help, while dextromethorphan acts mainly through NMDA and sigma-1 mechanisms, with quinidine added as a pharmacokinetic booster. (Kaufman's Clinical Neurology for Psychiatrists; Kaplan and Sadock, CTP 2024; Prescriber's Guide, Stahl's Essential Psychopharmacology.)

The accompanying figure reinforces the crucial separation between episode and syndrome. The following table turns it into an answer that can be used at the bedside.

AXIS	PSEUDOBULBAR AFFECT	DEPRESSIVE ILLNESS
Temporal pattern	Sudden, brief, stereotyped outbursts	Sustained low mood
Relation to trigger	Disproportionate or apparently unprovoked	Affect is generally understandable within the mood syndrome
Display versus feeling	Display exceeds, or is incongruent with, the felt emotion	Affect is congruent with the low mood
After the episode	No residual sadness or happiness attributable to the burst	Low mood persists beyond an individual crying spell
Associated symptoms	Neurological context and impaired control of emotional expression	Neurovegetative features support the mood syndrome
Relationship between them	Pseudobulbar affect and depression may coexist; demonstrating one does not exclude the other.	

PITFALL

Do not re-label every easy tear as pseudobulbar affect in a patient with a neurological lesion. Ask about sustained mood and neurovegetative change as well as the episode itself. Conversely, do not diagnose depression merely because the patient cries. The expression disorder and depressive illness frequently coexist and require separate formulations.

26.3 Neurological setting and the bulbar examination

Pseudobulbar affect can accompany disorders that injure frontal systems, descending corticobulbar pathways or more extensive cerebral networks. Supported settings include multiple cerebral infarctions, traumatic brain injury, multiple sclerosis and Alzheimer disease. When both frontal lobes or a wider area of cerebrum is affected, nonfluent aphasia and dementia may complicate assessment. The examiner may then need collateral description and direct observation because the patient cannot give a detailed account of internal mood or loss of control.

Pseudobulbar palsy reflects upper motor neuron corticobulbar disease. Pseudobulbar and **bulbar palsy** share dysarthria, dysphagia and absent voluntary palate movement, but their accompanying signs differ. The distinction matters because emotional lability belongs to the pseudobulbar pattern, whereas bulbar palsy is a lower motor neuron syndrome and does not explain pathological emotional expression.

BEDSIDE FEATURE	PSEUDOBULBAR PALSY	BULBAR PALSY
Motor level	Upper motor neuron, corticobulbar	Lower motor neuron
Shared bulbar difficulty	Dysarthria, dysphagia and loss of voluntary palate movement	
Gag reflex and jaw jerk	Hyperactive	Hypoactive
Respiratory impairment	Absent	Present
Intellectual impairment	May be present	Absent in the defining comparison
Emotional lability	Present	Absent

Post-stroke frequency estimates vary with timing and who supplies the history. This is not statistical clutter; it explains why a patient-only interview may miss a public, episodic behaviour.

9.4%	11.7%	17.9%	6.3%
DURING STROKE ADMISSION	SAME COHORT, THREE-MONTH FOLLOW-UP	CAREGIVER-ASSISTED, THREE-MONTH ASSESSMENT	PATIENT-ONLY ESTIMATE IN THAT STUDY

A consecutive cohort of 508 people with ischaemic stroke generated the admission and later estimates, while a separate assessment of 127 people showed the caregiver-versus-patient contrast. Another cohort of 516 people assessed three months after stroke yielded an estimate of 7.6%. These figures should remain explicitly post-stroke; the evidence supplied here does not justify exporting them to other neurological diseases.

26.4 From corticobulbar release to a distributed circuit

The traditional explanation is **corticobulbar disinhibition**. The corticobulbar tract originates in the posterior frontal motor cortex and descends to brainstem motor nuclei, which then innervate the muscles of the head and neck. In the classical model, bilateral interruption of descending neocortical upper motor neuron control releases brainstem affective motor centres. Emotional expression can then be triggered too readily and cannot be shaped or stopped by cortical intention in the same way that bilateral corticobulbar injury produces pseudobulbar palsy.

That account is valuable but incomplete. A major clinical text states that the bilateral lesion pattern is not uniform: frontal or temporal lesions in either hemisphere are also associated with pathological emotion. The observed syndrome therefore cannot be reduced to a single tract cut at a fixed point. It is better viewed as loss of regulation within a network that estimates the emotional context, selects an appropriate motor response, scales it and corrects it while it unfolds.

TRAP **"Pseudobulbar affect requires bilateral corticobulbar lesions" is the textbook rule, not a universal clinical law.** The classic pseudobulbar-palsy account specifies bilateral corticobulbar tract damage, but clinical observations report pathological emotion with unilateral frontal or temporal lesions in either hemisphere. State the rule and the exception. Do not erase the conflict or resolve it by assertion.

The broader model places the critical disturbance along the **fronto-ponto-cerebellar pathway**. Frontal systems provide contextual and intentional signals; pontine relays carry them toward the cerebellum; and the cerebellar contribution can be understood as modulation of the intensity and timing of the emotional motor response. In a lesion analysis of 12 patients with pathological crying, the heaviest episode burden occurred with relatively large bilateral pontine lesions. This supports a gate-control formulation without making one lesion site obligatory.

A complementary **serotonergic hypothesis** proposes partial destruction of raphe serotonergic neurons or their projections, particularly in relation to pontine damage. It provides a mechanistic bridge between lesion anatomy and the rapid benefit observed with serotonergic antidepressants. The hypothesis should be presented as explanatory support, not as a proven biomarker or a complete account of every case.

26.5 Management frame: locus, focus and modus

Treat the target that is actually present. LOCUS depends on medical and neurological stability. A patient with an established, stable neurological disorder and characteristic recurrent episodes can usually be assessed and followed in outpatient care. A new presentation with an evolving focal deficit, altered consciousness, swallowing risk or diagnostic uncertainty requires urgent neurological and medical assessment; suppressing the visible crying is not a substitute for identifying a new lesion or systemic problem.

FOCUS begins with the acute burden: loss of control, episode frequency and severity, embarrassment, interrupted communication and risk during swallowing, mobility or care. In the short term, establish whether the chosen treatment reduces episodes without producing disproportionate adverse effects. Longer-term review separates residual pseudobulbar episodes from depression, cognitive decline and the underlying neurological disease. Improvement in crying does not prove that a comorbid depressive syndrome has remitted.

MODUS combines explanation, environmental adaptation and pharmacotherapy. Explain to the patient and family that the expression is involuntary and may exceed the actual feeling. This reduces moral interpretations such as weakness, rudeness or emotional manipulation. Agree on a simple way to pause conversation during an episode, allow recovery, and resume without repeatedly demanding an explanation. Address the consequences in rehabilitation, family interaction and public settings while continuing care of the underlying neurological disorder.

- Define the treatment target in observable terms: frequency, severity, controllability and disruption caused by episodes.
- Assess sustained mood independently, because depression and pseudobulbar affect may coexist.
- Choose a supported monotherapy, review benefit and tolerability, and avoid confusing rapid control of expression with an antidepressant response.
- Recheck diagnosis, adherence, interactions and the neurological course before declaring treatment failure.

Pharmacological options supported in the supplied evidence are dextromethorphan with quinidine, selective serotonin reuptake inhibitors and tricyclic antidepressants; selective serotonin-norepinephrine reuptake inhibitors also have class-level trial support after stroke for reducing the frequency and severity of pathological affect. Use current product information and local prescribing guidance for screening and monitoring because the combination treatment has clinically important cardiac, hepatic, haematological and interaction risks.

26.6 Dextromethorphan with quinidine

Dextromethorphan with quinidine is FDA-approved specifically for pseudobulbar affect under the trade name Nuedexta. Dextromethorphan is a noncompetitive NMDA receptor antagonist and sigma-1 receptor agonist; it reduces glutamatergic neurotransmission and also has affinity for the serotonin transporter. These actions provide several plausible routes by which it may alter the dysregulated emotional-expression circuit without implying that pseudobulbar affect is simply a glutamate or serotonin disorder.

Quinidine is not included here to treat an arrhythmia. It acts as a **pharmacokinetic booster** by inhibiting CYP2D6 metabolism of dextromethorphan, thereby increasing dextromethorphan exposure. This distinction predicts efficacy variation as well as interaction risk. People who are poor CYP2D6 metabolisers may gain little additional dextromethorphan availability while remaining exposed to quinidine adverse effects.

For pseudobulbar affect, begin dextromethorphan 20 mg with quinidine 10 mg once daily. **After 7 days, for pseudobulbar affect, increase to dextromethorphan 20 mg with quinidine 10 mg twice daily**, which is the usual regimen. Some patients may tolerate and respond to doses above the approved regimen, but controlled evidence for such dosing is limited, and the supplied source gives no explicit numerical maximum for pseudobulbar affect.

Set expectations around the target rather than promising mood change. In clinical trials, episode frequency fell significantly beginning on **day fifteen**, with benefit expressed as reduced frequency and severity of uncontrollable laughing or crying. The permitted evidence does not provide a placebo-adjusted effect size, so a precise percentage reduction should not be quoted. Review an episode record and collateral observations alongside tolerability.

26.7 Antidepressants and treatment sequencing

Antidepressants can suppress pathological laughing and crying even when the clinical target is not a depressive disorder. The serotonergic lesion hypothesis offers one rationale, while the characteristically rapid response in pseudobulbar affect helps distinguish control of emotional expression from the slower change expected when treating a sustained mood syndrome. This does not make antidepressants diagnostic tests; response remains supportive and must be interpreted with the original phenomenology.

A Cochrane Review published in 2019 included seven trials and 239 people with stroke. Across the small evidence base, tricyclic antidepressants, selective serotonin reuptake inhibitors and selective serotonin-norepinephrine reuptake inhibitors significantly reduced the frequency and

severity of pathological affect. The finding supports a class-level treatment option after stroke, but does not erase differences in adverse effects, interactions or patient vulnerability.

The most concrete selective serotonin reuptake inhibitor example is post-stroke pathological crying treated with citalopram. In a double-blind, placebo-controlled crossover study of 16 patients, crying episodes decreased by more than 50%. For pseudobulbar affect, citalopram 20 mg per day produced a response **within 24 hours in eight patients**; three responded within 3 days and four required more than a week. The rapid onset is the memorable point, not a promise that every patient will respond immediately.

Tricyclic antidepressants are also established options. Amitriptyline is reported to suppress pathological laughing and crying, and an illustrative post-stroke case improved greatly with nortriptyline. No treatment dose for either tricyclic is provided in the permitted evidence, so none should be inferred from general antidepressant prescribing.

GOOD TO REMEMBER

If dextromethorphan with quinidine is ineffective, consider switching to a tricyclic antidepressant or a selective serotonin reuptake inhibitor. With a partial response, try another appropriate monotherapy before moving to augmentation as the preferred sequencing principle. Reassess whether the residual problem is pseudobulbar affect, depression or their coexistence.

26.8 Safety, follow-up and the integrated answer

Dextromethorphan with quinidine demands an interaction and cardiac screen before prescribing. It must not be combined with a monoamine oxidase inhibitor because the combination can cause fatal serotonin syndrome, and it must not be started for **at least 14 days after stopping a monoamine oxidase inhibitor**. It is also contraindicated in complete atrioventricular block without a pacemaker, or when the risk of complete block is high, and with a QT-prolonging drug metabolised by CYP2D6, such as thioridazine or pimozide.

CYP2D6 inhibition is clinically relevant beyond dextromethorphan: quinidine can raise concentrations of other CYP2D6 substrates, with desipramine as a supported example. Medication reconciliation should therefore include prescribed, over-the-counter and recently stopped drugs. The interaction review is not a paperwork exercise: it is part of deciding whether this otherwise targeted treatment is suitable for the individual patient.

Dangerous adverse effects include immune-mediated thrombocytopenia, hepatotoxicity and dose-dependent QT prolongation. Thrombocytopenia may be severe or fatal; if it occurs, discontinue immediately unless it is clearly unrelated to the drug, and do not restart in a sensitised patient. Quinidine is also associated with a lupus-like syndrome with polyarthritis. These risks explain why dose escalation beyond the supported regimen should not be improvised merely because episodes persist.

Follow-up should return to the original formulation. Ask whether bursts are less frequent, less severe, more controllable or less disruptive; obtain collateral observation when feasible; and repeat the mood assessment separately. If there is no benefit, confirm exposure, reconsider the

diagnosis and choose another supported monotherapy rather than stacking drugs reflexively. If episodes improve but sustained sadness remains, treat the depressive syndrome on its own evidence base; general antidepressant pharmacology and comparative drug selection are covered in the Mood disorders: pharmacotherapy notes.

An integrated examination answer is concise but layered: define the mismatch between display and feeling; describe the brief, stereotyped and uncontrollable episode; distinguish it from sustained mood change; examine the corticobulbar syndrome; state the classical bilateral release model and its unilateral-lesion exception; then outline supported monotherapies and the quinidine-driven safety checks. That structure turns an easily recognised symptom into a defensible neuropsychiatric formulation.

> Pseudobulbar affect is a brief, stereotyped and uncontrollable disorder of emotional expression: the display exceeds the felt mood, bilaterality is the classic lesion rule but not universal, and treatment must target episodes while depression is assessed separately.

Structural lesions and the seizure overlap

27 · Chronic subdural haematoma as reversible decline in the elderly

A declining older adult may be carrying a removable lesion, not an irreversible diagnosis. **Chronic subdural haematoma** earns marks because it joins neurology, old-age psychiatry and emergency judgement. It can present through headache, confusion, altered personality and cognitive impairment while producing surprisingly little focal neurology. The clinician who waits for a dramatic hemiparesis, a witnessed major injury or a tidy neurological history may therefore miss it.

The central examination proposition is simple: this is a structural mimic of psychiatric illness and progressive cognitive disorder whose timely recognition can restore cerebral function. Structural imaging is not an ornamental investigation in such a case. It is the step that converts a vague syndrome into a potentially correctable diagnosis. The full dementia syndrome and its general diagnostic work-up belong in *the Dementias and neurocognitive disorders notes*; the present section teaches the subdural lesion that must not be overlooked within that work-up.

Venous	Insidious	Subtle	Treatable
ORIGIN	TEMPO	FOCAL SIGNS	PRINCIPLE

27.1 What the lesion is

The **subdural space** lies between dura and arachnoid. A subdural haematoma is therefore **extra-axial**: blood collects outside the brain rather than within cerebral tissue. The usual source is torn **bridging veins**. Because these veins bleed at relatively low pressure, blood may ooze through an extensive potential space before the expanding collection meets sufficient resistance from the underlying brain. The collection is commonly spread over a cerebral hemisphere and may be bilateral.

This vascular origin explains the tempo. A low-pressure venous collection can enlarge without the immediately catastrophic presentation expected from high-pressure arterial bleeding. Epidural haemorrhage is classically arterial, often involving the middle meningeal artery, and subarachnoid haemorrhage usually follows arterial bleeding from a ruptured aneurysm. The contrasts matter because “intracranial bleed” is not a single physiological event. Site, vessel and pressure determine how quickly symptoms appear and which clinical signals dominate.

Chronicity also changes what the clinician sees. A collection that develops and persists over weeks may spread widely in the subdural compartment. Generalised cerebral dysfunction then outweighs clean lateralising signs. Headache, behaviour and cognition may carry more diagnostic weight than the expectation of a dense motor deficit.

MNEMONIC

SLOW

Subtle focal signs; **L**ucent aged blood on CT; **O**lder person with falls, bleeding-risk medicines or atrophy; **W**orsening headache, personality and cognition. Each letter points back to the lesion's quiet venous expansion rather than to a separate syndrome.

27.2 Why the elderly are vulnerable

Susceptibility rises in people **older than 65 years** because several risks converge. Falls increase the opportunity for head movement and venous tearing. Aspirin, anticoagulants and other medicines that increase bleeding tendency make a small vascular injury harder to contain. Most importantly, **age-related cerebral atrophy** places greater tension on the bridging veins and reduces the brain's capacity to compress a bleeding vessel once bleeding has begun.

That mechanism corrects a common misconception: the severity of the initiating trauma need not match the later disability. In an atrophied brain, even minimal trauma may tear delicate meningeal bridging veins. A remembered fall may be absent, dismissed as trivial or never observed. The history “no head injury” therefore lowers neither suspicion nor urgency enough to exclude the lesion. The relevant question is not only whether a dramatic injury occurred, but whether the biological setting permits a small injury to continue bleeding.

Medication history must be exact in purpose even when the psychiatric presentation appears dominant. Ask what is taken, why it is taken, who supervises it and whether recent dosing has changed. This is not an instruction to stop essential antithrombotic treatment blindly. It is a prompt to recognise bleeding risk and coordinate urgent decisions with the treating medical and neurosurgical teams. The same history should include falls that relatives regard as inconsequential.

GOOD TO REMEMBER

A reliable collateral history is often more diagnostic than the patient's account. Ask separately about minor falls, new headache, functional slippage, altered social conduct, reduced self-care and all medicines that impede clotting. If the story is inconsistent with the injuries or the care environment seems unsafe, consider elder abuse as a possible source of head trauma and activate safeguarding procedures.

27.3 The psychiatric and cognitive masquerade

The usual syndrome is insidious rather than spectacular. Headache is most often the first symptom of chronic subdural haematoma. As cerebral dysfunction develops, confusion, personality change and cognitive impairment may emerge. These are nonspecific manifestations, which is precisely why the patient may first reach psychiatry, a memory clinic or a general physician rather than a neurosurgical service.

The diagnostic clue is the mismatch between broad behavioural or cognitive change and only subtle focal physical findings. Families may describe altered conduct, reduced organisation or inability to manage familiar routines. Such descriptions should not be prematurely translated into a primary psychiatric or degenerative disorder. They identify a change in brain function; they do not identify its cause. The clinician must preserve the structural differential until imaging has addressed it.

The syndrome can resemble dementia because decline is sustained and functionally important, yet it can also be confused with delirium when confusion dominates. Those syndromic diagnoses have their own criteria and examinations elsewhere in this chapter and in the dedicated neurocognitive notes. Here, the useful move is aetiological: ask whether an extra-axial collection can explain the observed decline. Do not allow a psychiatric label to become a reason not to image.

Diagnostic closure often occurs through an apparently coherent narrative. An older person becomes forgetful, stops managing money, neglects household tasks and appears emotionally altered; the family then supplies the word “dementia”, and every later observation is interpreted through it. Chronic subdural haematoma breaks that narrative because one lesion can generate the whole cluster. The better formulation is provisional and layered: describe the cognitive and behavioural syndrome, identify its tempo, record the headache and risk context, and keep the structural cause open until imaging has answered it.

The reverse error is also possible. A patient may already have cognitive impairment or a psychiatric disorder, and new deterioration is attributed to the established diagnosis. Baseline vulnerability does not protect against a superimposed subdural collection. The question is whether there has been a meaningful change from that person's own baseline. A recent shift in conduct, self-care, communication or mobility deserves fresh causal assessment even when the case file already contains a persuasive label.

TRAP **No major trauma and no obvious lateralising deficit do not exclude chronic subdural haematoma.** The lesion often follows little or unremembered trauma and produces generalised headache, confusion, personality change and cognitive impairment more prominently than focal signs.

27.4 Bedside diagnostic reasoning

Assessment should reconstruct change, not merely record symptoms. Establish the previous level of cognition, personality and everyday functioning, then ask how the present state departed from it. The temporal sequence matters: headache preceding behavioural and cognitive decline supports a mass-lesion frame more strongly than a timeless list of complaints. A complete neurological examination remains necessary, but a quiet examination does not cancel the history.

A focused bedside enquiry should cover:

- new or evolving headache, including whether it was the earliest change noticed;
- confusion, personality alteration and cognitive or functional decline, preferably corroborated by someone who knew the baseline;
- falls, antiplatelet or anticoagulant exposure, and the context of cerebral atrophy as converging vulnerabilities;
- minor or absent recalled trauma and possible inflicted injury, without using a negative trauma history as a rule-out test.

Several differentials may coexist at the point of presentation: a primary neurocognitive or psychiatric disorder, delirium, medication effects, brain tumour, cerebrovascular disease and hydrocephalus. Listing them is not enough. The psychiatrist's responsibility is to rank the reversible and dangerous possibilities early. A chronic subdural haematoma deserves priority because clinical phenomenology alone cannot safely remove it from consideration and structural imaging can reveal the cause.

Collateral information should be anchored to observable change. “More confused” is less useful than examples of missed meals, unfamiliar errors, altered judgement or a new inability to complete a previously routine activity. Ask whether headache appeared before, with or after the functional decline. Reconstruct falls from witnesses, bruising, broken objects and changes in walking confidence rather than relying on the patient's spontaneous recall. None of these observations diagnoses the lesion, but together they determine whether a bland neurological examination is falsely reassuring.

Examination findings should likewise be interpreted as a pattern. Generalised cerebral dysfunction with only slight asymmetry fits the established presentation; severe focal findings are not required. At the same time, any new focal abnormality increases urgency rather than changing the case into a purely stroke-shaped problem. Record consciousness, behaviour, cognition and the neurological examination in language that can be compared across assessments. Serial change is often more informative than an isolated adjective such as “stable”.

Interpret cognitive test performance as evidence of impairment, not evidence of aetiology. The standardised instruments and their scoring are covered in *the Psychotherapies, clinical assessment, MSE and nosology notes*. In this setting, a low score may document the consequence of cerebral dysfunction, but it cannot distinguish a subdural collection from other structural or medical causes.

27.5 CT: density changes with the age of blood

Structural neuroimaging is the decisive investigation. CT is generally sufficient to screen for subdural haematoma in the dementia work-up. The image must be read in relation to blood age: fresh blood is denser than brain, whereas aged blood in a chronic collection is less dense. Density falls as an acute collection evolves, creating a transitional period in which the lesion may resemble the adjacent brain.

IMAGING STATE	CT RELATION TO BRAIN	INTERPRETIVE MEANING	PRINCIPAL ERROR
Acute subdural	Radiodense, appearing white	Fresh blood	Failing to distinguish an acute expanding lesion from the quieter chronic presentation
Isodense phase	Similar density to brain	Density has fallen during evolution	Calling the scan normal because collection and brain are difficult to separate
Chronic subdural	Radiolucent, appearing darker than brain	Aged blood; a contrast-enhancing membrane may border the collection	Ignoring a broad low-density extra-axial collection
Acute-on-chronic bleeding	Dense areas within a lucent region	Fresh blood within an older collection	Forcing a mixed-density lesion into a purely acute or purely chronic category

PITFALL

The isodense chronic subdural can be indistinguishable from brain tissue on density alone. A reassuring first glance must not replace a deliberate review of the extra-axial spaces, asymmetry, mass effect and any enhancing membrane, especially when the clinical story remains persuasive.

IN INDIA

Do not postpone an available CT while waiting for a theoretically preferable investigation. For the structural dementia differential, CT is generally sufficient to detect a subdural haematoma. Escalate further imaging when the initial study and the clinical picture do not agree, using the locally available radiology and neurosurgical pathway.

27.6 Why imaging is worthwhile

The yield of reversible structural disease is modest but clinically disproportionate. Structural CT or MRI detects treatable causes such as normal-pressure hydrocephalus and subdural haematoma in about **1 to 2% of demented patients**. This proportion is not the incidence of chronic subdural haematoma and must not be presented as such. It describes the group in whom imaging discovers a treatable structural explanation.

The ethical and clinical reasoning is stronger than the percentage alone. Missing a common irreversible disorder is regrettable; missing a correctable compressive lesion also forfeits recovery. Imaging therefore has a case-finding function, not merely a classificatory function. It identifies conditions in which management can change the patient's cognition, functioning, safety and future care needs.

Normal-pressure hydrocephalus, tumour, metastasis and cerebrovascular events also belong in the structural differential, but their full teaching sits in their respective sections. Their presence on the list should sharpen, not blur, the immediate question: has a subdural collection been excluded in an older person with a new headache-linked decline, subtle focal findings or relevant bleeding vulnerability?

Imaging decisions should therefore be tied to consequence as well as probability. The purpose is not to prove that every late-life cognitive complaint has a structural cause. It is to avoid declaring irreversibility before a treatable extra-axial lesion has been considered. When the history is atypical for the working psychiatric diagnosis, the decline is newly accelerated, headache is prominent, bleeding vulnerability is present or examination and history disagree, the value of CT lies in settling a question that bedside phenomenology cannot.

A report should also be reconciled with the patient. If CT demonstrates a collection, relate its side, extent, density and mass effect to the clinical syndrome with radiology and neurosurgery. If the scan is reported as unrevealing but suspicion remains high, revisit the images and the possibility of an isodense lesion rather than treating the report as infallible. Further imaging is an escalation decision, not a substitute for careful review of the initial study.

RULE **New cognitive or personality decline in an older adult demands a reversible-cause lens.** When chronic subdural haematoma is plausible, obtain structural imaging even if trauma is denied and focal neurology is slight.

27.7 Reversibility, deterioration and urgency

Correctable dementia mimic is the phrase to retain. A chronic subdural collection may resolve without an operation, and a conservative approach can be sufficient in selected cases. Other patients require surgical evacuation. Prompt diagnosis and appropriate treatment usually restore cerebral function, which distinguishes this lesion from diagnoses in which management can only slow decline or support adaptation.

Reversibility must not be mistaken for harmlessness. A small chronic extra-axial collection may exert little mass effect and cause relatively few symptoms. A large, acute or rapidly expanding

subdural haematoma can displace the brainstem and oculomotor nerve through the tentorial notch. Continued expansion may culminate in **transtentorial or foramen-magnum herniation**, an immediately life-threatening state. The full neuropsychiatric differential and management of raised intracranial pressure and hydrocephalus are covered in the dedicated section of this chapter.

Clinical deterioration changes the locus of care. Any acute decline or evidence of increasing mass effect should move the patient out of a routine psychiatric pathway and into emergency medical and neurosurgical assessment. Exact intervention thresholds cannot be improvised from phenomenology. They require current imaging, serial clinical judgement and the treating neurosurgical protocol.

> In an older patient, headache plus insidious personality or cognitive decline with few focal signs is chronic subdural haematoma until structural imaging has made the lesion implausible.

27.8 Management: LOCUS, FOCUS and MODUS

Management follows the patient's physiological risk, not the clinic in which the symptoms were first noticed. LOCUS: a stable patient with an incidentally recognised or mildly symptomatic chronic collection may enter a closely coordinated medical and neurosurgical pathway. A symptomatic, enlarging or acutely deteriorating patient requires emergency or inpatient care. Psychiatric admission alone is inappropriate when structural compression or deterioration remains active.

FOCUS: in the acute phase, protect life, recognise expansion and secure neurosurgical review. In the short term, follow headache, consciousness, behaviour, cognition, neurological findings and functional ability against the pre-illness baseline. After definitive or conservative treatment, confirm that improvement is occurring and reassess any residual psychiatric or cognitive complaint rather than assuming the original label was correct.

Recovery assessment is part of diagnosis. Improvement after the collection resolves or is evacuated supports the conclusion that it contributed materially to the decline. Incomplete recovery does not prove that treatment failed: the lesion may have coexisted with another neurological or psychiatric disorder, or the original baseline may have been inaccurately estimated. Repeat collateral history and functional assessment are therefore as important after treatment as before it. The aim is to separate recovered functions, persistent deficits and newly visible comorbidity.

MODUS: procedural treatment is surgical evacuation when the collection requires it; conservative management may suffice when the treating team judges observation appropriate, and spontaneous resolution can occur. Drug decisions focus on the medical context rather than on treating the collection with a psychotropic. Review medicines that increase bleeding tendency, but alter or reverse them only through an urgent, indication-aware medical plan. Psychological care is supportive: explain the organic basis of the symptoms, reduce frightening misattributions

and help the patient and family understand why serial observation matters. Social care addresses supervision, falls, medication administration, rehabilitation needs and safeguarding.

Care is multidisciplinary by necessity. Radiology establishes the structural evidence; neurosurgery decides whether evacuation or observation is appropriate; physicians manage comorbidity and bleeding-risk treatment; psychiatry clarifies behaviour, capacity for participation, distress and the trajectory of cognition; nursing and family observations make fluctuation or deterioration visible. At discharge, the plan should state who watches for renewed decline, who manages antithrombotic decisions and where follow-up occurs. Vague shared care is not shared care at all.

Use current institutional neurosurgical, imaging and antithrombotic guidance for operative criteria, reversal decisions and follow-up. The psychiatrist's enduring role is to recognise the mimic, avoid diagnostic closure, document change from baseline, support behaviour safely and verify cognitive recovery after the structural lesion has been treated.

28 · Brain tumours and psychiatric presentations by location

Why this matters clinically. A brain tumour may first reach psychiatry as depression, disordered thinking, personality change or cognitive impairment, even when the patient has no accompanying physical symptom. That **psychiatric-first presentation** makes structural disease easy to miss: absence of weakness, seizures or another obvious neurological complaint does not by itself establish a primary psychiatric disorder. The marks lie in recognising the possibility, interpreting location without overclaiming localisation, and separating a causal lesion from an incidental scan finding.

IN INDIA

Investigate a new and persistent behavioural or cognitive change in later life with structural imaging, and keep a low threshold for referral to neurosurgery or neuro-oncology.

The useful framework is anatomical rather than a memorised list of syndromes. Ask where the lesion lies, whether it compresses or infiltrates, which networks it disrupts, and whether its behavioural effects are focal or mediated by mass effect. The accompanying figure places brain tumour within the structural-lesion differential that can present to a psychiatrist.

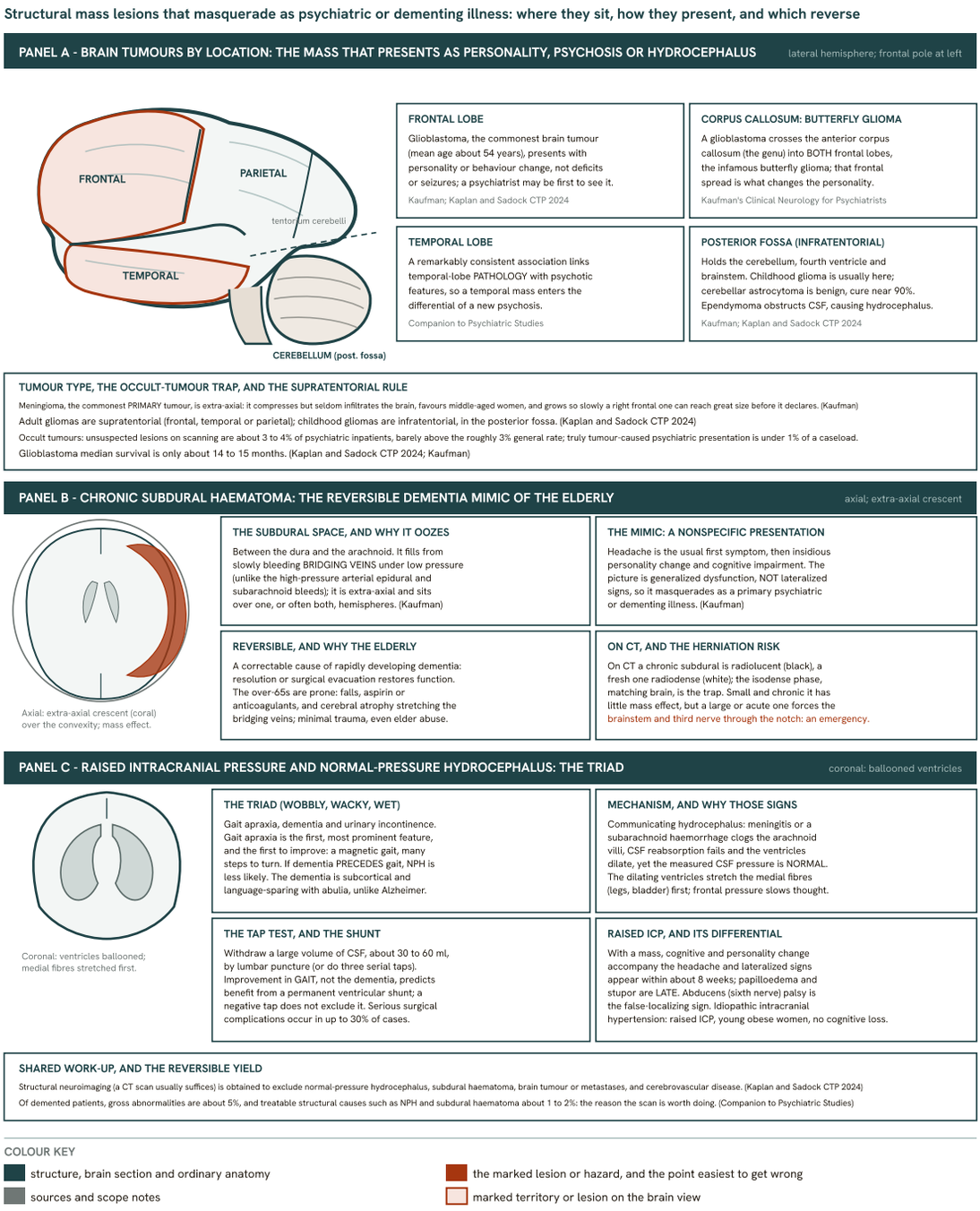


Fig 34.10 **The structural-lesion differential: masses that present as psychiatric or dementing illness.** A brain tumour is read by location: a frontal or callosal butterfly glioma changes personality, temporal-lobe pathology carries a consistent link to psychosis, and the posterior fossa is the childhood and hydrocephalus site; a chronic subdural haematoma is an extra-axial crescent from low-pressure bridging veins that masquerades, nonspecifically, as dementia in the elderly and is reversible; normal-pressure hydrocephalus is the triad of gait apraxia, dementia and urinary incontinence with ballooned ventricles at normal pressure. All three are looked for on a CT scan, which usually detects them but cannot categorically exclude an isodense subdural, a small tumour or normal-pressure hydrocephalus. (Kaufman's Clinical Neurology for Psychiatrists; Kaplan and Sadock's Comprehensive Textbook of Psychiatry 2024; Companion to Psychiatric Studies.)

RULE **A psychiatric presentation does not make the lesion psychiatrically primary.** New behavioural, affective, thought or cognitive change must be read together with tempo, examination and structural context.

28.1 The diagnostic idea: psychiatric symptoms may precede neurology

Brain tumours can mimic psychiatric illness because disturbance of cerebral tissue need not announce itself with a neatly localising deficit. Depression, thought disturbance and cognitive impairment may be the presenting problems, and the physical examination may initially appear unrevealing. The psychiatrist therefore needs a structural differential whenever the clinical story is atypical for a primary disorder. “Atypical” here is a reasoning judgment, not a single screening criterion: it emerges from the combination of change from baseline, progressive functional disruption, cognitive or personality change, and discordance between the apparent diagnosis and the course.

The causal pathways are conceptually distinct. A tumour may directly disturb tissue serving behaviour, interrupt connections between regions, compress adjacent brain, or produce more diffuse dysfunction through mass effect. These routes explain why location is informative but not deterministic. The same broad psychiatric phenotype can arise through different structural routes, while a lesion at a given site may remain clinically quiet until its effect on surrounding tissue becomes substantial.

A referral label must therefore be unpacked into phenomenology. “Depression” and “psychosis” are starting labels, not substitutes for describing affective, cognitive, behavioural, perceptual and belief phenomena. The purpose is not to relabel every atypical symptom as organic. It is to identify whether the syndrome has internal features that make a simple primary psychiatric formulation incomplete. Collateral history is particularly valuable because relatives can describe a departure from the person's established style, occupational functioning and everyday decisions when the patient experiences little change.

The review then joins phenotype to course and context. Define the change precisely, ask whether it evolves like the presumed primary disorder, seek cognitive change, headache, seizures or focal findings, and test any discovered lesion for anatomical and chronological coherence. This sequence keeps both errors in view: prematurely closing on a psychiatric diagnosis and prematurely closing on an imaging abnormality.

GOOD TO REMEMBER

When a new psychiatric syndrome is accompanied by progressive personality or cognitive change, do not allow a normal-looking brief neurological encounter to end the structural enquiry. Brain tumours may produce psychiatric disturbance without accompanying physical symptoms.

28.2 Location, compartment and biological behaviour

Location answers only part of the clinical question. In adults, most gliomas are **supratentorial**, particularly in the frontal, temporal or parietal lobes; in children, glioma is usually infratentorial in the posterior fossa. The incidence of most histological classes of primary brain tumour rises with advancing age. These observations shape the prior anatomical expectation, but they do not permit age alone to determine diagnosis.

Compartment is equally important. An intra-axial tumour arises within brain tissue and may infiltrate the networks it occupies. An **extra-axial** tumour arises outside the parenchyma and commonly acts by compression or irritation. Biological tempo then modifies the picture: a rapidly infiltrating process can disturb behaviour while physical deficits remain unobtrusive, whereas a slowly expanding compressive lesion may become large before it is recognised. The location label must therefore be interpreted alongside tissue relationship and growth pattern.

STRUCTURAL SETTING	GROUNDED ANATOMICAL POINT	PSYCHIATRIC READING
Adult glioma	Usually supratentorial, in frontal, temporal or parietal lobes	Begin above the tentorium, then localise from the full syndrome.
Childhood glioma	Usually infratentorial in the posterior fossa	Think of compartment and obstruction rather than importing an adult psychiatric localisation.
Glioblastoma	Cerebral, infiltrating, and liable to present with personality or behavioural change	Psychiatry may be the first point of medical contact.
Callosal spread	Crosses the genu into both frontal lobes	Bilateral frontal network involvement explains a behavioural presentation.
Meningioma	Extra-axial, slow-growing and compressive	Symptoms reflect the underlying brain being compressed or irritated.
Posterior-fossa tumour	May obstruct cerebrospinal-fluid flow around the fourth-ventricle compartment	Interpret psychiatric change through the hydrocephalus and raised-pressure route.

MNEMONIC

Site, Side, Structure, Symptom route

Read every tumour through its **site**, laterality or **side**, relationship to brain **structure**, and the route by which these produce the observed **symptoms**. This prevents a lobe name from becoming a diagnosis by reflex.

28.3 Frontal and callosal presentations

The strongest tumour-specific location-to-behaviour link in the available evidence is frontal involvement. Glioblastoma often presents with personality or behavioural change rather than a physical deficit or seizure, so a psychiatrist may encounter the patient before the tumour is recognised. This is not permission to reproduce the full frontal syndrome taxonomy here. Frontal lobe syndromes: dorsolateral, orbitofrontal and medial subtypes owns that localisation. The tumour question is narrower: could a structural lesion affecting frontal networks explain a new change in conduct, motivation, judgment or personality?

The classic structural pattern is the **butterfly glioma**. A glioblastoma may cross the anterior corpus callosum through the genu and infiltrate both frontal lobes. The image resembles bilateral

wings, but its clinical importance is connectional: callosal passage permits bilateral frontal involvement. Personality and behavioural change therefore follow from the frontal tissue affected, not from the visual metaphor itself.

Laterality also needs disciplined interpretation. A right frontal meningioma is a grounded example of a lesion that may become exceptionally large before causing problems. Slow expansion and the capacity of frontal regions to tolerate gradual compression can delay recognition. By the time relatives seek help, the complaint may be framed as altered character rather than neurological illness. The correct response is not to diagnose a particular frontal subtype from that history alone, but to recognise that a structural frontal process is plausible and to complete the neurological and cognitive assessment.

The interview should establish whether the change is genuinely new, and an informant account should test it against the person's previous behaviour and everyday function. A coherent cluster across personality, cognition and conduct carries more localising value than one dramatic symptom. Bilateral callosal spread should be read as a connectional and infiltrative process, not merely a midline radiological curiosity. This approach also protects against retrospective overfitting, in which every longstanding personality feature is reinterpreted after the scan.

28.4 Temporal and parietal sites: what may and may not be concluded

There is a consistent association between **temporal-lobe pathology** and psychotic features. That general neuropsychiatric association is clinically useful because it reminds the examiner that psychosis can accompany cerebral disease. It does not, however, establish that a temporal-lobe tumour characteristically produces a schizophrenia-like syndrome. The available claim is about temporal pathology in general, not tumours specifically. A candidate should preserve that scope instead of converting an association into a tumour-localisation rule.

The section on temporal-lobe syndromes provides the full focal-neuropsychiatric localisation. In this tumour fragment, temporal symptoms should prompt a structural and seizure-aware differential, but seizure classification and antiseizure-drug selection belong to the Epilepsy and psychiatry notes. A paroxysmal history may change the interpretation of unusual experiences, yet this section should not infer a seizure type or teach its pharmacology.

Parietal location must be handled with the same restraint. Adult gliomas may be situated in the parietal lobe, but the evidence does not define a distinctive psychiatric presentation for that tumour site. The section on parietal-lobe syndromes owns the focal examination. The clinically sound move is to examine for parietal dysfunction and test whether any finding aligns with the lesion, not to attach an unsupported psychiatric phenotype to the scan.

TRAP **Do not write “temporal-lobe tumours cause schizophrenia-like psychosis” from the general temporal-pathology association.** The direction from pathology to psychotic features is grounded; tumour-specific preference, symptom list and ranking are not.

28.5 Meningioma versus glioma: compression and infiltration

Meningioma arises from meningeal cells and therefore occupies an extra-axial, extraparenchymal position. Its usual effect is compression and irritation rather than infiltration of the underlying central nervous system. Meningiomas predominate in middle-aged women and often expand slowly enough to reach a large size before symptoms become evident. These features make them an excellent model for understanding why psychiatric change can be gradual, nonspecific and deceptively detached from the mass causing it.

Glioma provides the structural contrast. It is intra-axial and arises in brain tissue; glioblastoma in particular grows rapidly and infiltrates widely. The distinction matters because the scan and the syndrome must be read through different mechanisms. With meningioma, ask which cortex or network is being compressed. With an infiltrating glioma, ask which tissue and connections are being invaded, including whether spread across the corpus callosum has made the process bilateral.

A large right frontal meningioma may remain relatively silent until behavioural or functional change becomes conspicuous. This does not mean that right frontal location invariably produces one psychiatric syndrome. It means that slow extra-axial compression can conceal the biological seriousness of the lesion behind an apparently psychiatric story. Conversely, the malignant label of glioblastoma should not be inferred from behaviour alone. Personality change is a presentation clue, not a histological diagnosis.

The comparison also explains why size alone is an unreliable proxy for symptom severity. A slowly compressive lesion can permit functional adaptation until reserve is exceeded, whereas an infiltrating lesion may disrupt critical networks without producing an equally impressive external contour. Clinical interpretation therefore requires the relationship between lesion and brain, not simply a measurement of the mass. For psychiatry, the practical question is whether the structural process offers a better account of the new syndrome than a coincidental scan finding does.

> **PITFALL**
>
> Do not treat every lesion on imaging as causal merely because the patient has psychiatric symptoms. Match the timing, anatomical effect and clinical course. A slow extra-axial mass, an infiltrating intra-axial tumour and an incidental abnormality carry different causal arguments.

28.6 Posterior fossa and the obstructive route

The **posterior fossa** contains the cerebellum, pons, medulla, fourth ventricle, and vertebral and basilar arteries. Childhood gliomas are usually infratentorial, and childhood cerebellar astrocytomas tend to be benign, cystic and noninvasive. Complete removal can be achieved with a cure rate approaching **90%**. This paediatric anatomical pattern should not be extrapolated into a distinct adult psychiatric syndrome without evidence.

The grounded psychiatric route is obstruction. A tumour arising near the ventricular cerebrospinal-fluid pathway may impede flow and produce hydrocephalus; ependymoma is a

supported example. Mental or behavioural change in this setting is therefore interpreted as a possible consequence of hydrocephalus or raised intracranial pressure, not as proof of an independent cerebellar cognitive-affective syndrome. Raised intracranial pressure, hydrocephalus, and the psychiatric implications of post-injury seizures is taught separately and owns the clinical syndrome, differential and seizure-overlap details.

This boundary is important in examination answers. “Posterior fossa” is an anatomical compartment, not a psychiatric diagnosis. A strong answer identifies its contents, recognises the childhood infratentorial distribution, explains the obstruction route, and stops before supplying an unsupported adult symptom complex. In practice, the same discipline prevents overinterpretation of emotional or cognitive symptoms when the decisive mechanism may be diffuse pressure-related cerebral dysfunction.

28.7 Occult lesions, incidental findings and causal attribution

Structural disease deserves vigilance, but its base rate must be interpreted accurately. The accompanying strip shows that clinically unsuspected lesions in psychiatric inpatients are only slightly more frequent than incidental scan abnormalities in the general nonpsychiatric population. Patients whose psychiatric symptoms are actually caused by a hidden brain tumour remain a vanishing minority across a general psychiatrist's career. The comparison warns against assuming that every unexpected lesion explains the psychiatric presentation.

3%-4%	~3%	<1%
UNSUSPECTED LESIONS IN PSYCHIATRIC INPATIENTS	INCIDENTAL SCAN ABNORMALITIES IN THE GENERAL POPULATION	TRUE HIDDEN-TUMOUR PRESENTATIONS IN A PSYCHIATRIST'S CAREER CASELOAD

The diagnostic problem is therefore asymmetric. Missing a causal structural lesion can have grave consequences, but labelling an incidental lesion as causal can also distort care. The solution is neither indiscriminate scanning nor reassurance based only on rarity. It is structured attribution: determine whether the clinical course is compatible with the lesion, whether the anatomical site plausibly relates to the observed change, whether the imaging effect is substantial, and whether competing psychiatric or medical explanations remain stronger.

Base rates are especially useful after, not instead of, clinical assessment. Before imaging, they prevent the rare hidden tumour from becoming the default explanation for every late or unusual psychiatric presentation. After imaging, they prevent the mere presence of an abnormality from being treated as proof of cause. The posterior probability becomes persuasive only when the lesion and the syndrome converge anatomically, temporally and functionally. This is why an incidental lesion in a well-characterised primary psychiatric illness and an infiltrative frontal mass accompanying progressive personality change demand different interpretations even though both scans are “abnormal”.

- **Concordance:** does the behavioural or cognitive change fit the tissue affected without requiring an extravagant localisation claim?

- **Chronology:** did the syndrome and functional decline evolve in a way compatible with the lesion?
- **Burden:** is there compression, infiltration, bilateral spread or obstruction that could plausibly disturb brain function?
- **Alternatives:** could the scan finding be incidental while another disorder better explains the presentation?

The practical balance. Maintain a low threshold for reconsidering structure when the course is progressive or the formulation is unstable, but do not turn imaging into a substitute for phenomenology, collateral history and examination. The bedside cognitive examination as a general method is taught elsewhere in this chapter, while standardised instruments and their scoring belong to the Psychotherapies, clinical assessment, MSE and nosology notes.

28.8 Glioblastoma as the high-stakes psychiatric presentation

Glioblastoma is described in the cited neurology source as the most malignant astrocytoma. It develops almost exclusively in the cerebrum, grows rapidly and infiltrates widely. Crucially for psychiatry, personality or behavioural change may precede physical deficits or seizures, placing the psychiatrist at the front of the diagnostic pathway.

Kaufman's Clinical Neurology for Psychiatrists gives a mean age at diagnosis of **54 years**. That source-specific value should be recognised as such rather than silently replaced by a remembered epidemiological figure. Prognosis is poor: a field-leading trial reported median survival around **14 months**, with about one-quarter alive at 2 years and only 10% alive at 5 years. Kaufman's rounded textbook estimate is about 15 months; the close figures should remain separately attributed rather than falsely harmonised.

The examination answer should finish by linking biology to presentation. Cerebral infiltration can accompany psychiatric-first illness; frontal involvement explains prominent personality and behaviour change; and callosal spread may create the bilateral frontal butterfly pattern. None of these features permits psychiatry alone to determine histology. They identify when a structural explanation deserves urgent investigation and multidisciplinary neurological care.

A concise synthesis should retain uncertainty where the source does. Brain tumour belongs in the differential of an unexplained psychiatric change, but most psychiatric patients with an unexpected structural finding do not thereby become hidden-tumour cases. Conversely, rarity must not neutralise a coherent progressive syndrome. The mature answer holds both propositions together: localisation guides suspicion, and causal attribution requires concordance.

> Memorise the logic, not an unsupported localisation table: psychiatric-first presentation is possible, frontal and callosal glioblastoma has a grounded behavioural link, the general temporal-pathology association does not establish temporal-tumour psychosis, and posterior-fossa psychiatric change is taught through obstruction and pressure.

29 · Raised intracranial pressure, hydrocephalus, and the psychiatric implications of post-injury seizures

The psychiatric presentation may precede the obvious neurological emergency. Raised intracranial pressure, hydrocephalus and post-injury seizures belong together because each can first appear as altered behaviour, slowed cognition, confusion or apparent psychiatric relapse. The scoring points lie in recognising the structural pattern, distinguishing pressure syndromes from normal-pressure hydrocephalus, and interpreting an episodic post-injury mental-state change as potentially epileptic rather than automatically psychogenic or psychiatric.

IN INDIA

When a mass or raised pressure is suspected, obtain structural imaging before attributing a new presentation to a primary psychiatric cause; phenytoin and levetiracetam are reasonable choices for post-injury seizures.

This section therefore follows a psychiatrist's route through the problem: identify pressure-related danger, recognise the treatable hydrocephalus phenotype, classify post-traumatic events by their relationship to injury, and prescribe psychotropics without casually worsening seizure vulnerability. The full classification of seizures and antiseizure-drug pharmacology belong to *the Epilepsy and psychiatry notes*. The dementia syndrome and its general diagnostic work-up belong to *the Dementias and neurocognitive disorders notes*.

Late PAPILLEDEMA AND STUPOR	**30-60 mL** HIGH-VOLUME TAP	**>7 days** PTE WINDOW	**Up to 50%** MAJOR-TBI PTE BURDEN

29.1 Raised intracranial pressure: the psychiatric warning pattern

Raised intracranial pressure from a mass lesion need not announce itself with dramatic neurological signs. Headache may be accompanied by subtle cognitive and personality change, while lateralised findings usually emerge within **8 weeks**. The clinically dangerous misconception is that a normal-looking fundus or preserved alertness early in the course removes a mass lesion from consideration. Papilloedema and stupor are overt signs that generally appear late, if they appear at all.

Once enough blood or mass has accumulated, headache, confusion, nausea, vomiting and focal neurological signs may accompany the pressure rise. For the psychiatrist, the sequence matters more than any isolated complaint. A new headache linked to progressive cognitive or personality change, followed by vomiting or focal findings, is a structural story until investigated. The absence of a fully developed pressure syndrome should not be mistaken for evidence against intracranial disease.

Structural imaging is used to exclude normal-pressure hydrocephalus, subdural haematoma, tumour or metastasis, and cerebrovascular lesions as contributors to cognitive or behavioural change; CT is generally sufficient for this screening purpose. This is especially important when the history has been framed as depression, dementia, medication non-adherence or personality

change. Imaging does not replace neurological examination, but it prevents psychiatric phenomenology from being asked to settle an anatomical question it cannot settle.

GOOD TO REMEMBER

Cognitive and personality change can accompany headache before papilloedema or stupor appears. A late overt sign is not a sensible prerequisite for early imaging and referral.

29.2 False localisation and the raised-pressure differential

Pressure can distort structures distant from the causative lesion. A unilateral or bilateral **abducens nerve palsy** may result when raised pressure stretches and damages the sixth cranial nerve. The affected eye turns inward because medial rectus action supplied by the intact third cranial nerve is unopposed. This is a false-localising sign: it signals global pressure mechanics and does not by itself prove a pontine lesion at the side of the ocular deviation.

PITFALL

Do not localise every sixth-nerve palsy directly to the pons. Raised intracranial pressure can stretch either or both abducens nerves, so the ocular sign must be interpreted with headache, cognition, vomiting, fundus findings and imaging.

Idiopathic intracranial hypertension provides a crucial contrast because pressure is raised without the cognitive and seizure pattern expected from many structural lesions. It occurs predominantly in young obese women with menstrual irregularity; elevated venous-sinus pressure, often related to sinus occlusion or stenosis, is implicated in many cases. The headache is dull and generalised and may accompany pulsatile tinnitus or transient visual obscurations. Papilloedema is the distinctive finding and can progress through an enlarged blind spot to blindness from optic atrophy if untreated.

CLINICAL SETTING	PSYCHIATRIC OR COGNITIVE CLUE	NEUROLOGICAL DISCRIMINATOR	CLINICAL IMPLICATION
Mass-related raised pressure	Subtle cognitive or personality change may accompany headache	Papilloedema and stupor are usually late or absent; focal signs may emerge	Do not wait for the overt syndrome before imaging.
Idiopathic intracranial hypertension	Cognitive capacity is not affected and seizures are not produced	Papilloedema with visual obscurations or pulsatile tinnitus	Protect vision and investigate the pressure disorder rather than attributing symptoms to a mass.
Normal-pressure hydrocephalus	Cognitive decline occurs with gait apraxia and urinary incontinence	Ventricular enlargement occurs despite normal measured CSF pressure	Recognise a potentially correctable cause of cognitive decline.

29.3 Normal-pressure hydrocephalus: syndrome and mechanism

Normal-pressure hydrocephalus is defined clinically by dementia, urinary incontinence and gait apraxia and is important because it is a correctable cause of cognitive decline. The triad should be stated by content. An unsupported eponym adds no diagnostic value and is best omitted.

The cognitive pattern is **subcortical**: thought and gait slow, language is relatively spared, and abulia is common. The patient may therefore appear apathetic, poorly motivated or depressed, but the accompanying motor and bladder phenotype changes the diagnostic frame. The physical features help separate this syndrome from cortical dementias, although formal dementia criteria and the complete general work-up remain outside the present section.

Most cases are idiopathic, while meningitis or subarachnoid haemorrhage may precede secondary cases. In the latter setting, inflammatory material or blood can obstruct cerebrospinal-fluid reabsorption at the arachnoid villi. Production continues, fluid accumulates and the ventricles expand. Measured CSF pressure and CSF protein and glucose concentrations remain normal. The label therefore describes the pressure measured during evaluation, not the absence of a pathophysiological disturbance in CSF circulation.

Anatomy explains the clinical triad. Ventricular expansion compresses brain parenchyma and stretches corticospinal and other internal-capsule tracts. The most medial fibres supply the legs and voluntary bladder musculature, making gait and urinary symptoms prominent. Pressure on frontal lobes contributes to cognitive impairment and psychomotor slowing. The syndrome is thus a unified periventricular and frontal network disorder, not a collection of unrelated complaints.

MNEMONIC

Walk, think, void

Walk: gait apraxia is usually earliest and most prominent. **Think:** cognition slows with language relatively spared. **Void:** urgency and frequency may progress to incontinence. The order keeps gait at the front of diagnostic reasoning.

29.4 Gait-first recognition, tap testing and shunting

The **magnetic gait** is the hallmark. Gait apraxia is generally the initial, most consistent and most prominent feature, and it is the first feature to improve with treatment. Patients may require multiple small steps to turn, yet can often step over a stick because the stepping reflex is relatively preserved. If dementia clearly precedes gait dysfunction, normal-pressure hydrocephalus becomes less likely. Bladder symptoms often evolve from urgency and frequency to incontinence and may also improve after treatment.

The high-volume tap test asks a practical question: does temporary CSF removal improve the component most likely to respond? Withdrawal of **30 to 60 mL** by lumbar puncture, or serial lumbar punctures, is followed by reassessment of gait. Improvement in gait, not necessarily cognition, supports the diagnosis and predicts benefit from permanent drainage. A negative test

does not exclude the diagnosis. This asymmetry is worth stating clearly: a positive gait response is informative, whereas absence of response is not a definitive rule-out.

Permanent drainage uses a shunt from a lateral ventricle to the chest or abdominal cavity. Benefit remains difficult to predict, and serious surgical complications occur in up to 30% of cases. The decision therefore requires neurological and neurosurgical assessment rather than an automatic transition from triad to operation. The psychiatrist contributes reliable baseline and post-tap descriptions of gait, cognition, motivation and function, while the procedural team weighs likely gain against harm.

RULE **In suspected normal-pressure hydrocephalus, follow the gait.** It is usually the first feature to appear and the first to improve; gait improvement after CSF removal predicts shunt benefit more usefully than immediate cognitive change.

29.5 Post-traumatic seizures: substrate, timing and risk

Post-traumatic epilepsy arises because a cortical scar at the injury site, and sometimes retained foreign material, forms an epileptogenic focus. The onset is focal and localises ipsilaterally to the lesion, with possible secondary generalisation; after traumatic brain injury the usual description is complex partial seizures with secondary generalisation. This anatomical logic matters in psychiatry because a stereotyped behavioural spell may be the expression of a focal cortical discharge rather than a new primary psychiatric syndrome.

Timing separates provoked post-traumatic seizures from epilepsy. **Immediate and early post-traumatic seizures** occur within the first 24 hours and within the first 7 days respectively and are classified as provoked, not as post-traumatic epilepsy. Only recurrent seizures **more than 7 days** after injury meet the stated temporal definition of post-traumatic epilepsy. These trauma-specific boundaries must not be copied into stroke without a separate source.

Burden follows injury biology. After major traumatic brain injury, prevalence rises with time and may eventually reach **50%**; minor head trauma rarely produces post-traumatic epilepsy. Risk is greater after penetrating than after blunt or blast injury, greater with alcohol abuse, and increases with traumatic-brain-injury severity. It may account for 5% to 6% of all epilepsy, and remission occurs in only 25% to 50%. These figures describe different denominators and should never be collapsed into one prevalence statement.

- **Substrate:** a cortical scar at the lesion site generates focal-onset seizures.
- **Timing:** events in the immediate and early windows are provoked; recurrent events after the early window define post-traumatic epilepsy.
- **Risk:** penetration, alcohol abuse and greater injury severity raise the likelihood.

29.6 Psychiatric implications after traumatic brain injury

Post-traumatic epilepsy adds more than recurrent convulsions to an already injured brain. It causes disability and creates a risk of further head injury, while antiseizure drugs may worsen trauma-related cognitive and personality change. Treatment review must therefore distinguish injury effects, seizure effects, medicine effects and a comorbid psychiatric disorder. A new

complaint of slowing, irritability or altered behaviour after treatment begins should not be assigned to “the TBI” without examining this layered causation.

Psychogenic nonepileptic seizures also enter the differential because some studies report increased PNES among people with milder traumatic brain injury. This does not justify diagnosing PNES merely because the injury was mild or investigations are unrevealing. It means that recurrent post-injury events need careful semiology and appropriate neurological assessment, while psychological formulation remains available when supported. The distinction is consequential: mislabelling epilepsy as psychogenic withholds seizure care, while mislabelling PNES as epilepsy exposes the patient to ineffective medication and its cognitive burden.

Seizures also interact with the broader psychiatric aftermath. Post-traumatic depression occurs in 25% to 50% of patients with traumatic brain injury, correlates only weakly with injury severity, and is associated with poor quality of life; post-traumatic epilepsy is one of the trauma-related factors that further increases its incidence. The depression syndrome itself belongs in the dedicated section on psychiatric sequelae of traumatic brain injury. Here the point is causal layering: seizure burden can amplify disability, occupational loss and social restriction, all of which alter presentation and recovery.

GOOD TO REMEMBER

A one-week course of phenytoin or levetiracetam after severe traumatic brain injury reduces early seizures only during that period; no antiseizure drug clearly prevents later post-traumatic epilepsy. Prophylaxis for the early window is not disease modification.

29.7 Post-stroke seizures and behavioural presentations

The epileptogenic substrate after stroke is likewise a cortical scar, producing focal-onset seizures that may secondarily generalise. In adults older than 65 years, approximately 50% of newly developing seizures originate from stroke scars. This is the proportion of later-life new seizures attributable to stroke scars, not the proportion of all stroke survivors who develop seizures.

A first seizure after 60 years may herald a cerebral tumour, but stroke is approximately equally likely; in either setting seizures typically begin focally and then generalise. Structural imaging and neurological assessment therefore matter even when the event has resolved and the mental state has normalised. Tumour presentations by location are covered elsewhere in this chapter, and seizure classification remains with *the Epilepsy and psychiatry notes*.

A cortical-stroke survivor who develops confusion, unresponsiveness, abnormal movements or unusual behaviour requires seizure in the differential. This is the safety bridge to psychiatry: episodic or unexplained behavioural change can be ictal or postictal, including when a major convulsion is not witnessed. The working formulation should stay neurological until the temporal pattern, examination and appropriate investigations have been reconciled.

Seizures may also participate in secondary psychosis after stroke. In one small lesion-matched comparison, seizure disorder was present in three of five patients with post-stroke psychosis and none of five stroke controls without psychosis. Together with seizures and subcortical atrophy,

right-hemisphere lesions, especially right lateral prefrontal involvement or disrupted connectivity to that area, appear important in pathogenesis. The tiny comparison supports an association, not a diagnostic rule or causal certainty.

29.8 Seizure-aware psychiatric prescribing: locus, focus and modus

Locus. A patient with an acute seizure, impaired recovery, new focal sign or pressure-related deterioration belongs in emergency or inpatient neurological care, not routine psychiatric follow-up. Stable longer-term psychiatric care can proceed collaboratively as an outpatient when the seizure disorder and structural lesion are being monitored. **Focus.** In the acute phase, preserve neurological safety and avoid obscuring evolving mental-state change. Over subsequent care, target disabling mood, psychotic or behavioural symptoms while repeatedly reviewing seizure control, cognition, personality and adverse effects. **Modus.** Combine appropriate neurological treatment, cautious psychotropic use, psychological work, injury prevention and social rehabilitation rather than treating medication selection as the whole plan.

Antipsychotics require caution in post-stroke psychosis because stroke increases seizure vulnerability and antipsychotics can lower the seizure threshold. Risk is agent-specific and is magnified by rapid introduction and high doses. Haloperidol, risperidone, paliperidone and aripiprazole are among the least threshold-lowering agents, whereas clozapine, olanzapine, quetiapine, chlorpromazine, thioridazine and perphenazine are among the more concerning agents. Clozapine-associated seizures occur in **1% to 4.4%** of treated patients, particularly with rapid dose escalation.

TRAP **"Atypical antipsychotics are safer for seizures" is not a reliable rule.** The epilepsy-focused table places clozapine, olanzapine and quetiapine in the high-potential group alongside chlorpromazine, thioridazine and perphenazine, while haloperidol, risperidone and aripiprazole are low-potential choices. Another chapter offers a broader class-level reassurance, so retain the conflict and answer with agent, dose and titration rate rather than generation.

PRESCRIBING QUESTION	LOWER-CONCERN POSITION	HIGHER-CONCERN POSITION	PRACTICAL READING
Antipsychotic choice	Haloperidol, risperidone, paliperidone, aripiprazole	Clozapine, olanzapine, quetiapine, chlorpromazine, thioridazine, perphenazine	Avoid rapid introduction and high doses.
Antidepressants at therapeutic use	Therapeutic doses usually do not promote seizures; SSRIs and SNRIs are tabulated as low potential	Overdose or intoxication with tricyclic, tetracyclic, SSRI or SNRI agents can cause seizures	Separate ordinary treatment from overdose risk.
Particular antidepressants	Choose according to the whole psychiatric and neurological formulation.	Amoxapine, bupropion, clomipramine and maprotiline are usually avoided in epilepsy	Do not generalise from antidepressant class alone.
Drug interactions	Some newer antiseizure drugs have relatively little enzyme induction or inhibition	Antiseizure drugs may reduce psychotropic efficacy; their withdrawal may raise psychotropic levels; psychotropics may raise antiseizure-drug levels to toxicity	Review each direction whenever either regimen changes.

When a psychotropic is necessary, start at a low dose, titrate slowly, and monitor antiseizure-drug levels and EEGs where clinically indicated. Current neurological guidance should be consulted for the underlying seizure disorder because the allowed evidence does not supply a named guideline. Full antidepressant selection belongs to *the Mood disorders: pharmacotherapy notes*, while detailed antiseizure-drug interactions and drug choice belong to *the Epilepsy and psychiatry notes*.

- **Before prescribing:** clarify whether recent events are controlled epilepsy, provoked seizures or an unresolved episodic-behavioural syndrome.
- **During titration:** avoid rapid escalation and unnecessarily high exposure, and track cognition and personality as well as symptom response.
- **After any regimen change:** reconsider bidirectional metabolic interactions and the possibility of toxic or ineffective levels.

The must-memorise line: gait usually comes first and improves first in normal-pressure hydrocephalus; early post-traumatic seizures are provoked, whereas recurrent seizures after 7 days define post-traumatic epilepsy; and psychotropic seizure risk is agent-, dose- and titration-dependent.

Consolidate and apply

30 · Worked vignettes

Vignettes reward controlled inference, not instant recognition. The examiner gives a compressed story in which psychiatric symptoms, cognitive change, neurological findings and medical context compete for attention. Marks come from showing how the clues alter urgency, syndrome formulation, localisation, differential diagnosis and disposition. A disease label without that chain looks guessed, even when it happens to be correct.

These cases are deliberately qualitative. Their purpose is to demonstrate how knowledge from the disease-specific sections is used without repeating diagnostic thresholds, lesion tables, instrument scores or drug regimens. In every vignette, preserve uncertainty long enough to identify the dangerous alternative, the reversible contributor and the observation that would most efficiently change the formulation.

30.1 Read the stem as a changing clinical state

Vignette compression means that every included clue has a job, but not every clue has equal weight. Begin by converting the narrative into a brief problem representation: previous function, nature of change, tempo, setting, dominant psychiatric or cognitive feature, relevant neurological context and present safety concern. Do not repeat the stem. Reorganise it into information that supports a decision.

A useful reading separates observations from interpretations. “Family reports that the patient no longer manages familiar routines” is an observation about changed function. “The patient has dementia” is an interpretation requiring a broader syndrome assessment. “The patient laughs during serious conversation” is an observation. Depression, disinhibition, emotional incontinence and socially incongruent coping are competing interpretations. This distinction protects against making the opening adjective in the stem carry the whole diagnosis.

State	Tempo	Pattern	Risk
ESTABLISH	ORDER	TEST	ACT

Next, mark clues that change action rather than merely increase diagnostic confidence. A deteriorating level of engagement, new focal finding, recent injury, seizure-like event or pressure-related concern may require urgent medical escalation before refined psychiatric classification. Then identify the negative information that is conspicuously absent. Missing collateral history, an untested level of arousal or an unexplored medication change often represents the next task rather than evidence that nothing is wrong.

Read the command in the question as carefully as the stem. “Most likely diagnosis” requires a concise choice with discriminating support. “Discuss assessment” requires a sequence that moves from safety and state to focused examination and investigation. “Outline management” requires setting, targets, modes of care and monitoring. Do not answer the disease you hoped to see. Answer the decision the vignette actually asks you to make.

RULE **Translate every important clue into a clinical consequence.** State whether it changes urgency, syndrome, localisation, cause, investigation or management. A clue that changes none of these should not dominate the answer.

30.2 The quiet inpatient who is "just depressed"

A patient receiving medical care becomes withdrawn, eats poorly, speaks little and seems intermittently disengaged. Staff describe sadness, while relatives insist that the behaviour is new and variable. The opening task is not to choose between depression and delirium from surface appearance. It is to establish **state**: arousal, ability to sustain engagement, reliability of the interview and departure from the patient's usual functioning.

The answer should explicitly resist equating low activity with a primary mood syndrome. Reconstruct the course from nursing observations and family collateral, review the medical trajectory and treatment exposures, and perform a bedside assessment that the patient can actually understand and complete. If engagement varies, serial observations are more informative than a polished snapshot. A quiet patient may create less disruption while carrying greater medical risk than an agitated patient.

The case may ultimately fit delirium, depression, medication effect, physiological compromise or a mixed picture. The dedicated sections on delirium provide its criteria, screening operations, causes, prevention and treatment. The vignette skill is to show why the syndrome must be considered and what must happen before a psychiatric conclusion is safe. If substance withdrawal becomes plausible, name it and cross-refer to the Substance use disorders notes rather than reproducing its timeline or regimen.

PITFALL

Do not let ward labels substitute for examination. "Confused," "uncooperative," "depressed" and "sleepy" are summaries made by observers. Convert each label back into behaviour, trajectory and testable mental-state findings.

A complete response also states disposition. Physiological instability, worsening cognition, unreliable supervision or inability to participate in essential care supports a medical locus rather than routine psychiatric follow-up. Symptom control is subordinate to identifying and treating the underlying process.

State what would make you revise the formulation after initial care. Improvement with correction of the medical disturbance may support the working account, but persistence should trigger reassessment rather than retrospective certainty. A mixed presentation remains possible, so continuing mood symptoms can be evaluated more reliably after attention, arousal and physiological status have stabilised.

30.3 Emotional change after a vascular event

A patient recovering from a vascular event is described as tearful, disengaged and difficult to motivate. Family members ask whether this is depression, while staff interpret the behaviour as

poor cooperation. This is a **syndrome competition** vignette. The candidate should not collapse tearfulness, reduced initiation, fatigue, subjective distress and loss of function into a common label.

Clarify what the episodes look like, what triggers them, whether the expressed emotion matches the sustained internal mood, and whether reduced activity reflects desire, initiation, physical limitation, cognitive burden or fear. Ask how the patient understands the disability and whether awareness of deficit is intact. Examine attention and communication before interpreting apparent indifference. Language impairment can hide distress, while executive dysfunction can impair initiation despite preserved concern.

The differential may name post-stroke depression, apathy, fatigue, emotional incontinence, anxiety, psychosis and denial of deficit, but each belongs to its disease-specific section. In the vignette answer, use them as hypotheses and state the discriminating question or observation rather than teaching their epidemiology, lesion correlates or treatment evidence. Antidepressant pharmacology and comparative drug selection belong to the Mood disorders: pharmacotherapy notes.

The formulation should remain layered. Direct effects of brain injury, psychological response to disability, pain, sleep disruption, medication effects and pre-existing psychiatric vulnerability may coexist. Explain which account currently leads, what competing account remains clinically important, and what collateral or examination finding would change the ranking. Avoid claiming that emotional phenomenology uniquely identifies lesion location.

In an examination answer, pair each hypothesis with its next discriminator. Sustained mood change calls for a full mood assessment; episodic emotional expression calls for careful phenomenology; reduced goal-directed behaviour calls for assessment of initiation, cognition and environmental demand. This format demonstrates comparison without stealing the detailed criteria or treatment material from the owning sections.

GOOD TO REMEMBER

When relatives say “personality has changed,” ask for examples from comparable situations before and after the event. Concrete changes in initiation, inhibition, empathy, judgement or emotional expression are more useful than a global character judgement.

30.4 Behavioural disturbance after head injury

After a head injury, a patient becomes irritable, impulsive and forgetful. The family requests medication because the behaviour is disrupting care. The tempting answer is a list of drugs. The stronger answer begins with **baseline shift**: document the pre-injury pattern, the injury course, current cognitive state, environmental triggers, sleep and pain, substance exposure, family interaction and the functional consequences of the change.

Separate the original injury from active complications and later psychiatric sequelae. Current agitation may reflect confusion, fear, communication difficulty, overstimulation, frustration, disinhibition, a mood or psychotic syndrome, substance-related factors, or a new medical

problem. Memory complaints require clarification of attention, acquisition, retrieval, awareness and everyday function. Formal injury classification and post-traumatic amnesia belong to their dedicated sections; use those constructs in the formulation without restating thresholds.

The immediate plan follows locus, target and mode. Decide whether behaviour can be managed safely in the present setting or requires higher medical supervision. Define the target behaviour precisely, identify antecedents and consequences, modify the environment, support communication, involve rehabilitation and caregivers, and consider medication only after the reason for using it is clear. Pharmacological management in brain injury has its own section because vulnerability to adverse cognitive, behavioural and neurological effects changes prescribing judgement.

A good answer includes measurable clinical outcomes without inventing a scale: fewer dangerous episodes, improved participation in care, more stable sleep, safer mobility, better communication and reduced caregiver strain. Reassess whether apparent improvement reflects genuine recovery or merely sedation. If seizure classification or anticonvulsant choice becomes relevant, cross-refer to the Epilepsy and psychiatry notes.

Causal language should remain proportionate. Temporal association with injury supports relevance but does not prove that every later symptom is a direct lesion effect. A strong formulation distinguishes direct neurological consequences, treatment and environmental contributors, psychological responses to disability, and independent psychiatric comorbidity. It then assigns each contributor a corresponding intervention rather than seeking a universal explanation.

30.5 The confident but inaccurate history

A patient gives fluent, confident accounts that conflict with collateral history, appears unaware of the discrepancies and cannot reliably retain recent information. The error is to call the patient psychotic or deceptive from the inaccuracy alone. Begin with **memory monitoring**: determine whether the problem lies in attention, learning, retention, retrieval, temporal placement, source attribution or checking the accuracy of what is recalled.

Observe how the account changes with open questions, focused prompts and correction. Ask whether the patient is filling gaps, repeating familiar narratives, misplacing genuine events or defending a fixed belief despite contrary evidence. Evaluate language comprehension, executive control and awareness, because each can shape the narrative. Collateral history is not merely corroboration here. It is part of the examination of memory and function.

The differential can name an amnestic syndrome, confabulation, delirium, a focal neurological process, a seizure-related episode and a broader neurocognitive disorder. The dedicated amnestic sections provide the pathology and distinctions. Emergency nutritional disease and repletion belong to the Endocrine and metabolic psychiatry notes. The full dementia syndrome and its diagnostic workup belong to the Dementias and neurocognitive disorders notes.

Management must account for the practical consequences of unreliable memory: consent discussions, treatment adherence, wandering, vulnerability, financial decisions and caregiver burden. Do not confront inaccuracies as moral failures. Provide orientation and external memory support, simplify communication, treat the underlying cause and reassess capacity for the decision at hand. Standardised cognitive instruments may assist assessment and follow-up, but their content and scoring belong to the Psychotherapies, clinical assessment, MSE and nosology notes.

Capacity should be framed around the actual decision, not inferred globally from poor recall. Present information in an accessible form, check understanding and retention relevant to that decision, and seek support where impairment prevents safe independent action. The same patient may participate meaningfully in some choices while requiring protection or assistance for more complex consequences.

30.6 A focal error hidden inside a psychiatric complaint

A patient is referred for odd behaviour after repeatedly missing objects, mishandling familiar actions or becoming unable to complete previously routine tasks. Conversation remains socially fluent, encouraging a purely psychiatric explanation. The correct pivot is **convergent localisation**: ask whether several observations point toward a coherent cognitive network while controlling for vision, hearing, language, motor ability, attention and comprehension.

Describe the failed operation before naming a lobe syndrome. Determine whether the patient detected the stimulus, understood the command, recognised the object, planned the action and could execute the required movement. Compare spontaneous behaviour with formal testing and use another sensory or response modality when possible. A task failure is not anatomically pure; it reflects every process required between instruction and response.

VIGNETTE PATTERN	REASONING PIVOT	UNSAFE SHORTCUT
Fluent conversation with failed daily tasks	Test specific cognitive operations and function	Assuming social fluency means intact cognition
Apparent inattention to part of space	Separate spatial attention from sensory loss and unawareness	Calling every omission poor effort
Inability to perform a familiar action	Control for comprehension, weakness and coordination	Naming a praxis disorder from a contaminated task
Failure to identify a familiar stimulus	Confirm adequate sensation and language access	Equating recognition failure with memory loss
Disinhibited or apathetic behaviour	Seek executive, social and motivational convergence	Localising from personality description alone
Episodic unusual behaviour	Reconstruct onset, offset, awareness and recovery	Assuming psychiatric causation because examination later looks normal

TRAP **A memorable sign is not a complete localisation.** The examination answer must show convergence, exclude task contamination and acknowledge that distributed networks can produce mixed findings.

After establishing the pattern, name the relevant frontal, temporal, parietal, visual-association or disconnection syndrome and direct the reader to its dedicated section. The vignette marks lie in demonstrating why the label fits and what competing explanation has been tested, not in reproducing the owner section's feature list.

Keep psychiatric phenomenology in the formulation even when localisation appears convincing. Distress, suspiciousness, demoralisation, impulsivity or altered emotional expression may arise through several pathways and can shape risk independently of the focal deficit. Conversely, a psychiatric history does not invalidate a reproducible neurological pattern. The task is integration, not choosing which specialty owns the patient.

30.7 Slowly evolving psychiatric change with neurological risk

A patient develops progressive slowing, irritability, reduced initiative or impaired judgement. The referral asks for treatment of a primary psychiatric disorder, but collateral history suggests a clear departure from baseline and emerging neurological or functional change. This requires **structural vigilance**: preserve structural, pressure-related, vascular and other neurological explanations until tempo, examination and appropriate investigation make them less likely.

Look for a trajectory that does not fit the opening formulation. Ask about headache pattern, vomiting, gait, falls, injury, seizure-like events, focal symptoms, continence, medication exposure and progressive loss of function. Examine cognition and neurological status rather than relying on the mental-state examination alone. Reassessment matters because an evolving process may reveal itself through change rather than through a dramatic finding at the initial encounter.

The differential can name chronic subdural collection, brain tumour, raised intracranial pressure, hydrocephalus, vascular cognitive impairment and seizure-related presentations without reproducing their lesion associations or diagnostic details. Rank by urgency and plausibility. An immediately dangerous possibility may lead the action plan even when another diagnosis leads the probability list.

Investigation should be question led. State what must be detected, what modality is realistically available, and what escalation is needed if local capability is insufficient. An abnormal result must still be reconciled with the clinical pattern, while an unrevealing early result does not cancel a worsening trajectory. In Indian services, pragmatic sequencing may be necessary, but cost or access should not be allowed to convert a neurological warning pattern into routine psychiatric follow-up.

Where a broader neurocognitive syndrome is suspected, cross-refer the general diagnostic workup to the Dementias and neurocognitive disorders notes. Where episodic phenomena raise seizure questions, classification and anticonvulsant pharmacology remain with the Epilepsy and psychiatry notes.

Serial assessment is part of investigation. Document the baseline against which change will be judged, repeat the relevant mental-state and neurological observations, and communicate explicit triggers for escalation. A patient whose trajectory worsens despite an initially plausible psychiatric formulation needs the formulation reopened, not merely a stronger version of the same symptomatic treatment.

30.8 Convert the solution into an examination answer

A defensible answer has visible architecture. Open with a problem representation and provisional syndrome, then state the urgent alternative. Explain which observations support the formulation, which findings are missing, and how bedside examination and investigation will discriminate among the leading possibilities. End with management and reassessment rather than with the diagnostic label.

For management, specify **locus**, **focus** and **modus**. Locus identifies whether outpatient care, admission or emergency escalation is appropriate. Focus identifies the immediate target, the near-term functional goals and the continuing risks. Modus integrates cause-directed medical care, cautious symptom treatment, environmental and nursing measures, psychological support, rehabilitation, family work and social planning. Refer to current guidance for disease-specific treatment rather than naming an unverified guideline.

- State the leading formulation in qualified language.
- Name the dangerous alternative and the reversible contributor.
- Link examination and investigation to explicit clinical questions.
- Describe disposition, immediate safety and multidisciplinary care.
- Define what will be monitored and what would trigger reformulation.

MNEMONIC

TRACE the vignette

Tempo and trigger frame the change; **R**isk decides urgency; **A**rousal and attention test whether the interview is interpretable; **C**ognitive and neurological convergence supports localisation; **E**ffect on function, environment and care determines the plan.

The mnemonic is a reasoning spine, not a substitute for disease knowledge. It prevents premature closure while allowing a concise answer. If evidence conflicts, say so and specify the next observation that would resolve the conflict. If more than one process is plausible, distinguish the primary formulation from contributors instead of forcing a false choice.

In every neuropsychiatric vignette, establish state and safety before converting behaviour into diagnosis or anatomy.

31 · Consolidation and quick review

The marks lie in disciplined synthesis. A good answer does not recite every neuropsychiatric syndrome. It converts an apparently psychiatric presentation into a defensible clinical sequence: describe the change, establish its tempo, identify danger, examine the cognitive and neurological pattern, localise cautiously, construct the aetiological differential, and plan care. This approach also prevents the opposite error, in which every unusual behaviour is treated as proof of structural disease.

Neurological psychiatry is difficult because the same complaint can arise from network dysfunction, a systemic disturbance, medication or substance effects, the psychological response to illness, or a primary psychiatric disorder. The candidate must therefore hold psychiatric phenomenology and neurological reasoning together. The aim of consolidation is not diagnostic bravado. It is to show how uncertainty becomes narrower, safer and more clinically useful as history, collateral information, examination and investigation are integrated.

31.1 Begin with tempo, trigger and baseline

Problem representation is the shortest accurate statement of what changed, in whom, over what kind of time course, and in what clinical setting. It should include the dominant syndrome without prematurely naming a disease. “New behavioural change with impaired attention after a medical event” is more useful than “psychosis,” because it preserves the temporal and cognitive information that guides the next question.

Tempo is the opening discriminator. Abrupt change raises a different group of possibilities from fluctuation, a stepwise course, a gradual progression, or a stable deficit following a defined injury. The sequence of symptoms matters as much as their presence. A psychiatric symptom that follows altered alertness, a focal neurological change or a seizure-like event is framed differently from a longstanding psychiatric syndrome later complicated by neurological illness. Always establish the previous level of cognition, personality, function and independence through collateral history.

Define the last reliably known baseline rather than accepting “normal before” as sufficient history. Place psychiatric, cognitive, neurological and systemic changes on the same timeline. Ask what immediately preceded the change, including illness, injury, procedure, medication alteration, intoxication, withdrawal and psychosocial stress. Separate persistent deficits from episodic phenomena and from symptoms that vary with setting or physiological state.

The timeline should expose competing causal stories. A symptom may be a direct expression of brain dysfunction, an indirect consequence of disability, a treatment effect, or an independent comorbidity. More than one pathway may be active. A concise answer acknowledges this without becoming vague: state the leading formulation, the dangerous alternative, and the observation that would distinguish them.

Baseline is multidimensional. Ask separately about occupational and domestic function, self-care, navigation, social judgement, emotional regulation, communication and use of medicines or finances. A patient may have preserved routine conversation while family members have quietly

taken over complex tasks. Conversely, longstanding dependence should not be mislabelled as recent decline. The relevant comparison is the patient with their own prior function, not with an idealised population norm.

31.2 Build parallel syndrome, site, cause and consequence formulations

A robust case formulation runs on parallel tracks. The **syndrome formulation** describes the clinical pattern: disturbance of alertness and attention, an amnestic presentation, executive-behavioural change, focal higher-function loss, affective symptoms, psychotic symptoms, or a mixed picture. The **anatomical formulation** asks whether the pattern suggests diffuse dysfunction, a lateralised deficit, a network disconnection or pressure-related compromise. The **aetiological formulation** orders plausible causes by urgency, likelihood and reversibility. The consequence formulation covers risk, disability, decision-making ability, caregiver burden and rehabilitation needs.

Syndrome	Site	Cause	Impact
DESCRIBE	LOCALISE	EXPLAIN	PLAN

These formulations constrain each other. A proposed site must explain the observed pattern rather than merely match one dramatic sign. A proposed cause must fit the tempo and context. A treatment plan must address the actual consequence, not only the diagnostic label. When the tracks disagree, do not force agreement. Recheck the history, the level of arousal, sensory and motor limitations, language, medication exposure and collateral information.

RULE **Describe before you localise, and localise before you explain.** Premature disease naming discards the very observations that should test the diagnosis.

This parallel method is especially useful in long answers. It allows the candidate to move from phenomenology to neuroanatomy without claiming that a psychiatric symptom has a unique lesion correlate. It also leaves room for systemic illness and psychological adaptation, which may shape presentation even when a neurological lesion is established.

31.3 Place safety before diagnostic elegance

The early clinical task is not to produce a refined localisation. It is to decide whether the patient may have an evolving neurological or systemic emergency. Reduced or fluctuating alertness, rapid deterioration, a new focal deficit, a severe new headache pattern, repeated vomiting, seizure-like events, recent head injury, fever, marked physiological disturbance or signs suggesting pressure effects should move the assessment toward urgent medical care. These findings are signals for escalation, not diagnoses by themselves.

Diagnostic overshadowing occurs when a psychiatric label causes clinicians to discount new neurological or medical information. The reverse form is also common: an identified lesion is made responsible for every symptom, obscuring medication effects, pain, sleep disruption, demoralisation or an independent psychiatric disorder. Safety improves when the assessor asks paired questions explicitly: “What cannot be missed?” and “What else could be contributing?”

Clarify airway, breathing, circulation, physiological stability and level of consciousness before an elaborate psychiatric interview. Assess immediate risk arising from confusion, impulsivity, aggression, self-neglect, falls, wandering or inability to cooperate with essential care. Seek collateral information when the history may be unreliable because of impaired attention, memory, language, awareness or judgement. Escalate when the trajectory is worsening even if an earlier examination or investigation was reassuring.

PITFALL

A normal-looking conversation can conceal major cognitive or focal dysfunction. Social fluency, humour and confident answers do not establish intact attention, memory, executive control, awareness or neurological status. Test the relevant domains and verify the history.

Urgency depends on trajectory and vulnerability as well as symptom intensity. Quiet withdrawal may be more medically concerning than conspicuous agitation. Similarly, a subtle change noticed by family may carry more weight than a polished interview when it represents a clear departure from baseline. The safe answer explains why a patient can look psychiatrically settled yet still require urgent reassessment.

31.4 Use the bedside examination to test hypotheses

The bedside assessment should be hypothesis driven but ordered. Begin by establishing arousal and capacity to engage, then examine attention, orientation, language, memory, executive control, visuospatial function, praxis, recognition, neglect and relevant neurological signs. The purpose is not to accumulate abnormal findings. It is to determine whether the deficits form a coherent pattern and whether that pattern remains stable when task demands change.

State dependence means that performance may reflect fatigue, pain, intoxication, withdrawal, anxiety, sensory impairment, poor comprehension or fluctuating alertness rather than a fixed cognitive deficit. Before interpreting an error, confirm that the patient heard, understood and could physically perform the task. Repeat or simplify instructions without coaching the answer. Compare free conversation with structured testing and compare current performance with reliable collateral history.

A localising hypothesis becomes credible when several converging observations support it. A single bedside error is rarely sufficient. Language disturbance may contaminate memory and executive tasks; motor weakness may invalidate praxis testing; visual loss may mimic neglect or recognition failure. The examination therefore needs internal controls: use another modality, reduce motor demands, clarify comprehension, and observe spontaneous behaviour outside the formal task.

GOOD TO REMEMBER

When a patient “fails” a cognitive task, ask what the task actually required. Attention, language, vision, motor output and motivation may each sit between the target ability and the observed answer.

Record behaviour descriptively. “Did not search the affected side despite cueing” is more useful than an unsupported lobe label. Standardised cognitive instruments can support communication and follow-up, but their content, scoring and interpretation belong to the Psychotherapies, clinical assessment, MSE and nosology notes. The full dementia syndrome and its diagnostic workup belong to the Dementias and neurocognitive disorders notes.

31.5 Organise the differential by pattern rather than by memorised list

A neurological psychiatric differential becomes manageable when it is built from the observed pattern. Begin with tempo and consciousness, add focality and dominant cognitive domain, then incorporate the precipitating context. Finally, ask whether medication, substance exposure, systemic illness or psychosocial response modifies the picture. This produces a ranked differential rather than a catalogue.

PATTERN FRAME	QUESTION IT RAISES	COMMON REASONING ERROR
Acute or fluctuating global change	Is a diffuse medical, toxic or physiological disturbance active?	Calling it a primary psychiatric syndrome before establishing attention and arousal
Stable focal higher-function deficit	Do language, spatial, praxis, recognition or executive findings converge anatomically?	Localising from an isolated failed task
Predominantly amnestic presentation	Is encoding, storage, retrieval, temporal context or monitoring most affected?	Treating every inaccurate account as deliberate or psychotic
Behavioural or personality change	Is there executive-network dysfunction, an adaptive response, medication effect or psychiatric comorbidity?	Equating disinhibition or apathy with a single lesion
Progressive psychiatric-cognitive change	Could a structural, vascular or degenerative process be evolving?	Waiting for an obvious neurological deficit before reconsidering the formulation
Symptoms after injury or vascular event	Which features reflect direct injury, secondary complications, disability or independent illness?	Attributing the entire course to the original event

The table is a reasoning aid, not a diagnostic rule. Mixed presentations are expected because brain disorders affect networks, and because the person’s prior vulnerabilities, social context and treatment exposures shape expression. A ranked differential should explain the leading possibility, identify a dangerous alternative, name a reversible contributor, and state what information would change the ranking.

A useful ranking also separates probability from priority. A common explanation may lead the probability list, while a less likely but rapidly harmful condition leads the action list. State each explicitly. This prevents “most likely” from becoming “only possibility,” and it shows why urgent investigation can be justified without overstating diagnostic certainty. Re-ranking should follow

new collateral evidence, serial examination and treatment response, not attachment to the opening impression.

Specific syndrome criteria, lesion associations and management evidence belong in their dedicated sections. Substance-withdrawal syndromes are covered in the Substance use disorders notes. Seizure classification and anticonvulsant pharmacology are covered in the Epilepsy and psychiatry notes. The purpose here is to preserve the logic linking those bodies of knowledge.

31.6 Investigate to answer questions, not to display breadth

Question-led investigation begins by stating what must be detected or excluded. The urgent layer looks for instability and conditions in which delay could cause harm. The core layer searches for common medical, toxic, medication-related and structural explanations suggested by the history and examination. The focused layer follows the leading hypothesis with tests chosen for a specific discriminating purpose. A test should enter the answer because its result could change diagnosis, urgency, treatment or disposition.

Investigation never substitutes for bedside reassessment. A changing patient may need the formulation revised even when an earlier test was unrevealing. Conversely, an abnormal result may be incidental and should not displace a better clinical explanation without concordance of tempo, pattern and anatomy. State what each investigation is expected to clarify and how discordant findings will be handled.

Review prescribed, over-the-counter and traditional medicines, recent additions, dose changes, adherence and access. Ask directly about alcohol and other substances, including intoxication, withdrawal and interactions. Use collateral records to reconstruct prior cognition, function, injuries, vascular events, seizures and previous imaging or laboratory abnormalities. Reconcile each test result with the clinical pattern before assigning causality.

Pragmatism matters in Indian services, but it should be expressed as sequencing rather than lowered standards. Use the fastest locally available route that safely answers the immediate question, arrange transfer when the required capability is unavailable, and document why a deferred investigation is safe. Cost and access influence order, not the obligation to recognise danger.

Detailed imaging patterns, screening operations, treatment regimens and disease-specific investigations remain with their owning sections. Emergency nutritional syndromes and repletion protocols are covered in the Endocrine and metabolic psychiatry notes. The consolidating skill is to make every requested test traceable to a clinical question.

31.7 Manage by locus, focus and modus

Management begins with **locus**: decide whether care is safe in the outpatient setting, requires admission, or needs emergency or higher-dependency support. The decision follows physiological stability, trajectory, behavioural risk, supervision, capacity to cooperate, caregiver reliability and access to reassessment. A diagnostic label alone does not determine setting.

Focus identifies what must change now and what can wait. Acute priorities are stabilisation, treatment of the underlying cause, prevention of secondary harm and control of behaviour only when it threatens safety or essential care. Short-term work includes sleep, pain, communication, mobilisation, environmental support and early rehabilitation. Longer-term care addresses residual cognitive, emotional and behavioural problems, recurrence prevention, disability, family education, vocational goals and caregiver strain.

Modus ensures that treatment is not reduced to prescribing. Cause-directed medical care, cautious symptom treatment, psychological support, rehabilitation, environmental modification, nursing strategies, family work and social intervention should be considered together. Choose the least restrictive effective approach and review frequently because brain-injured or medically unwell patients may be unusually vulnerable to sedation, cognitive worsening, falls, interaction effects and lowered participation in rehabilitation.

TRAP **Do not present a drug list as a management plan.** Examiners look for setting, target, cause-directed care, non-pharmacological measures, monitoring, rehabilitation and follow-up as well as symptom control.

Drug pharmacology should be cross-referred rather than duplicated. Antidepressant selection belongs to the Mood disorders: pharmacotherapy notes. Seizure drug choice belongs to the Epilepsy and psychiatry notes. Withdrawal regimens belong to the Substance use disorders notes. When current guidance is needed, consult the relevant up-to-date guideline and local protocol; do not convert a remembered regimen into a universal rule.

Monitoring should be tied to the anticipated benefit and harm. Define the target behaviour or function in observable language, establish who will review it, and decide what deterioration triggers escalation. Involve family without transferring clinical responsibility to them. Explain expected uncertainty, warning changes, environmental strategies and the purpose of follow-up. Rehabilitation begins during acute care through attention to communication, mobility, sleep-wake organisation and participation, then evolves with the person's recovery and social role.

31.8 The TIERED master method for cases and essays

Use one reusable spine under pressure. The master mnemonic is **TIERED**. It does not replace syndrome knowledge. It tells the candidate in what order to deploy that knowledge, whether the stem concerns a vascular event, head injury, acute cognitive change, amnesia, a focal higher-function disorder, a structural lesion or a seizure-related presentation.

MNEMONIC

TIERED

Tempo and trigger: define baseline, onset, sequence and course. **I**mmediate threat: identify instability, deterioration and risks that change the care setting. **E**xamination pattern: describe arousal, cognition, behaviour and neurological findings. **R**egional hypothesis: localise only when findings converge. **E**tiology and effects: rank causes and state functional, behavioural and caregiver consequences. **D**isposition and domains of care: apply locus, focus and modus, then specify monitoring and follow-up.

For a short case, compress the spine into a problem representation, leading diagnosis, dangerous alternative, discriminating findings and immediate plan. For a long essay, expand each letter into a paragraph and insert disease-specific evidence from the relevant section. In either format, keep observation separate from inference. State “the pattern suggests” when localisation is probabilistic, and reserve definitive language for findings that genuinely establish the conclusion.

- Name the dominant syndrome and the main competing formulation.
- Show why tempo, trigger and examination pattern favour one over the other.
- State the urgent risk and the reversible contributor that require active exclusion.
- Close with setting, cause-directed treatment, symptom targets, rehabilitation and follow-up.

The enduring habit is calibrated reasoning. Psychiatric symptoms can be neurologically meaningful without being anatomically unique. Neurological disease can be present without explaining the whole person. Collateral history can outweigh a fluent interview, and a changing trajectory can outweigh a reassuring earlier snapshot. The best answer makes these tensions explicit and resolves them through structured reassessment rather than assertion.

TIERED: establish tempo, detect immediate threat, define the examination pattern, localise cautiously, rank aetiology and effects, then decide disposition and the full domains of care.

Sources and further reading

The clinical specifics in this chapter are grounded in the standard texts below; where two sources set different thresholds, both are named in the text as a conflict rather than reconciled. Instrument content (the cognitive screens) is described and cross-referred, never reproduced.

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PART VI

VI

Neuropsychiatry of Systemic and Neurological Disease

The systemic and neurological diseases that reach psychiatry through inflammation, infection and degeneration, and how each announces itself.

01 HIV and its neuropsychiatric syndromes

02 Parkinson disease and its neuropsychiatry

03 Huntington disease and other movement disorders

04 Autoimmune and infective encephalitides

05 Neurosyphilis and CNS infections

06 Multiple sclerosis and psychoneuroimmunology

07 Degenerative, neuromuscular and functional neurology

08 Consolidate and apply

09 Sources and further reading

VISUAL 6.1

HIV neuropsychiatry is a layered differential



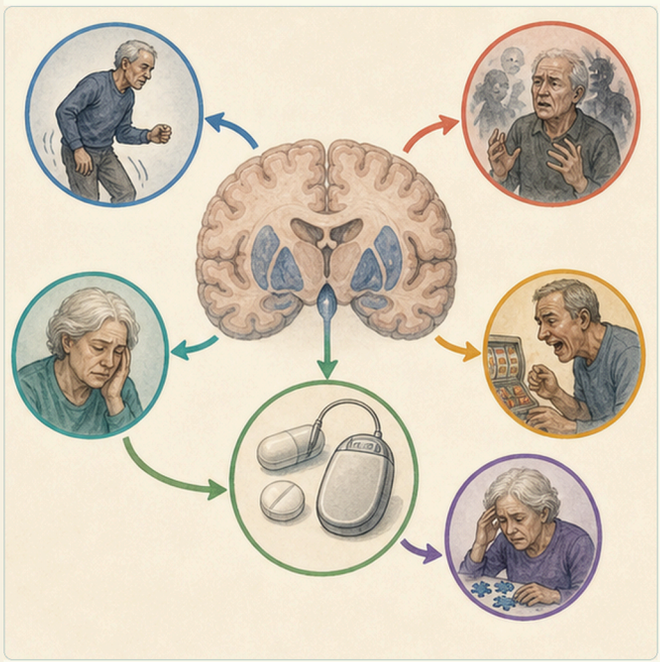
- HAND
- Opportunistic infection
- ART and viral control
- Mood and psychosis
- Drug interactions
- Continuity of care

Neuropsychiatric symptoms in HIV require separation of HAND, infection, treatment effects, primary psychiatric illness and drug interactions.

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VISUAL 6.2

Parkinson treatment changes psychiatric risk

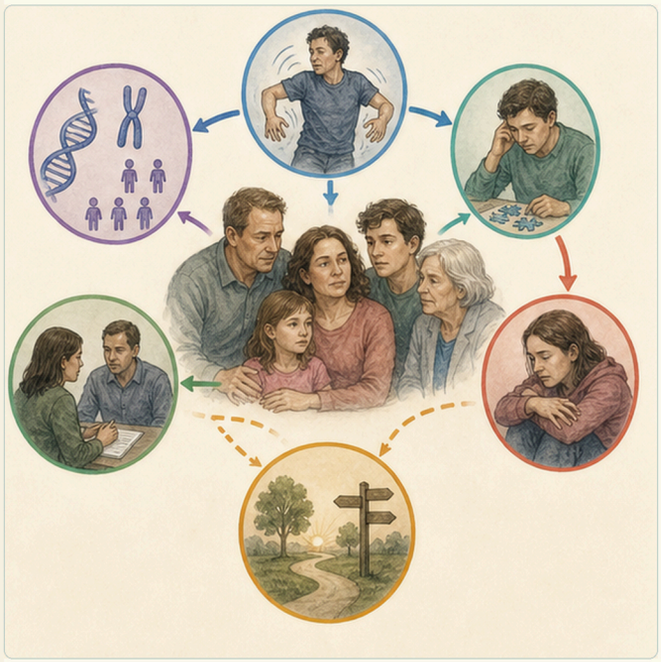


- Motor state
- Psychosis
- Mood and anxiety
- Impulse control
- Cognition
- Treatment review

Parkinson neuropsychiatry is shaped by disease, cognition and dopaminergic or device treatment, so every intervention is reviewed across motor and psychiatric outcomes.

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VISUAL 6.3



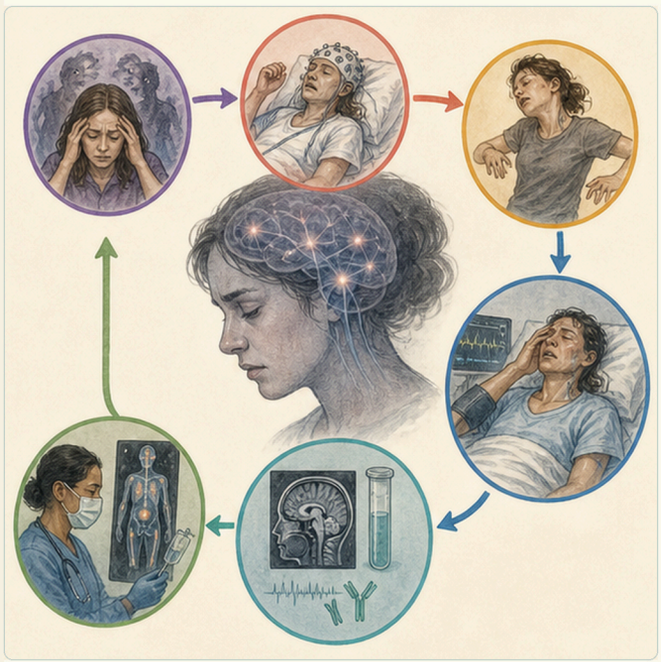
Huntington disease joins genetics to lived decisions

- HTT inheritance
- Movement
- Cognition
- Psychiatric change
- Predictive counselling
- Future planning

Huntington disease links movement, cognition and psychiatric change to an autosomal-dominant diagnosis whose predictive testing requires counselling.

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VISUAL 6.4



Autoimmune encephalitis crosses psychiatric boundaries

- Psychiatric change
- Seizures and catatonia
- Abnormal movements
- Autonomic instability
- CSF EEG MRI antibodies
- Tumour search and immunotherapy

Autoimmune encephalitis is suspected when psychiatric presentation is joined by neurological, autonomic or investigation red flags.

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PAPER IV

Neuropsychiatry of systemic and neurological disease

Seven bands . one complete notes document

HIV and its neuropsychiatric syndromes

1 · Systemic and neurological disease for the psychiatrist: what this chapter owns, and what it points to

A psychiatric presentation is sometimes the first visible sign of a disease that lives in the body or the nervous system rather than in the mind alone. A patient may reach the clinic with depression, mania, psychosis, anxiety, apathy, personality change or failing memory while the process driving the presentation is an infection, an autoimmune attack, a degenerative disorder, a demyelinating disease or the treatment given for one of these. The mental state names what the patient shows. It does not, on its own, name the disease that produced it.

This orientation supplies the **shared method** for the chapter. The dedicated sections teach each disease, its neuropsychiatric features, its investigations and its treatment in full. The task here is different and more portable: to learn how to recognise when a psychiatric syndrome is secondary to a systemic or neurological illness, how to reason from surface to mechanism, how far to pursue the underlying disease, and how to treat the illness and the mind together. This is where the marks sit, because a memorised list of disease-and-symptom associations is not yet a formulation.

1.1 Define the territory before naming the disorder

The **neuropsychiatry of systemic and neurological disease** concerns changes in mood, thought, perception, behaviour, motivation and cognition that arise as manifestations of a definable bodily or brain disease. The unifying idea is that the psychiatric syndrome is the surface and a diagnosable process, infective, immune, degenerative, structural, metabolic or iatrogenic, is the depth. The central difficulty is that the surface looks like ordinary psychiatry. Low mood, elation, delusions, hallucinations, obsessional phenomena, apathy and forgetfulness can each be produced by disease of the brain or the body just as they are produced by primary psychiatric illness.

The opening question is therefore not only which psychiatric diagnosis this is, but what could be producing this presentation, and whether the story behaves like a primary disorder or a secondary one. A **secondary neuropsychiatric syndrome** earns its label from context: an atypical age at onset, an atypical mixture of symptoms, accompanying physical or neurological signs, a course that does not run as the primary illness runs, or a systemic disease already known. Holding the presentation as new psychiatric change in the setting of a medical or neurological illness preserves the sequence and the uncertainty that a premature primary label would throw away.

The same discipline guards against **diagnostic overshadowing** in both directions. A known psychiatric history should not make a new organic change invisible, and a demonstrable disease should not be made to explain every symptom merely because it is concrete. Fear, pain, insomnia, loss, family strain, the effects of treatment and premorbid vulnerability all remain clinically active even when a systemic or neurological disease is established.

RULE **A new or atypical psychiatric syndrome arising in the setting of systemic or neurological disease should be treated as potentially secondary until the disease has been assessed.** Describe the mental state first, ask what disease could produce it, then treat the disease and the syndrome together rather than choosing between them.

1.2 Read the chapter as a map of diseases

The chapter is arranged by the kind of disease confronting the psychiatrist. These are not sealed compartments: an immune process may follow an infection, a degenerative disease may open with a mood disorder, and the treatment of one disease may itself disturb the mind. The value of the map is to show which lens leads and where the detailed teaching lives, so that an answer stays centred on the disease actually in front of the patient. The accompanying figure lays the same territories out as a single reference frame.

DISEASE TERRITORY	OPENING QUESTION	DEPTH SUPPLIED BY THE CHAPTER
HIV and its neuropsychiatric burden	Is this cognitive, affective or psychotic change a direct effect of the virus, an opportunistic complication or a drug effect?	The cognitive spectrum, the neuro-injury and its response to antiretroviral therapy, psychiatric comorbidity, opportunistic infections and drug interactions
Parkinson disease and the parkinsonian disorders	Are these symptoms the disease, its treatment or an independent illness?	Psychosis and antipsychotic choice, depression and anxiety, impulse and dopaminergic behaviour, cognition, stimulation effects and the atypical parkinsonian mimics
Huntington disease and the hyperkinetic disorders	How does an inherited or acquired movement disorder shape mind and behaviour?	The genetics and its counselling, the psychiatric and cognitive course, and the chorea of the other movement disorders
Autoimmune, limbic and viral encephalitides	Could an antibody or a virus be producing this subacute psychiatric change?	The antibody-mediated encephalitides, the red flags for an autoimmune psychosis and the viral encephalitides with psychiatric sequelae
Neurosyphilis and the chronic CNS infections	Is a treatable chronic infection presenting as a psychiatric or cognitive disorder?	Neurosyphilis and general paresis, the endemic neuroinfections and the subacute and rare chronic infections
Multiple sclerosis, demyelination and immunity	How do a relapsing brain disease and the immune system reach the mind?	The psychiatric manifestations of demyelination, the effect of disease-modifying treatment and the immune hypothesis of psychiatric disorders
Degenerative, neuromuscular and functional disorders	Is this a degenerative, neuromuscular or functional process, and can its positive signs be recognised?	Motor neuron disease, the neuromuscular and mitochondrial disorders and the functional neurological disorder spectrum

Disease	**Route**	**Syndrome**	**Care**
WHAT IS WRONG	HOW IT REACHES THE BRAIN	WHAT THE PATIENT SHOWS	WHAT TREATMENT MUST DO

Read the map from either direction. A known systemic or neurological disease directs the clinician toward the psychiatric and cognitive syndromes it can produce. An unexplained psychiatric change directs the clinician back toward the diseases that must not be missed. The sections supply the depth; the orientation preserves integration, so that disease, mechanism, syndrome and care remain part of one formulation rather than four disconnected recollections.

TRAP **Reciting disease-and-symptom associations instead of reasoning through the case.** Candidates lose marks by producing a catalogue of which disease causes which symptom. The examiner is testing a method: recognise the features that mark a syndrome as secondary, identify the disease, investigate it and treat both fronts. A list demonstrates recall; the method demonstrates a clinician.

1.3 Reason from surface to mechanism

Depth in this chapter means asking how a disease reaches the mind. A handful of **mechanistic routes** recur across every territory, and naming the route that applies both explains the presentation and points toward the treatment. The routes are not mutually exclusive, and more than one may be active in the same patient, but each answers a different question about how the surface syndrome was produced.

Direct involvement is the disease acting on the brain itself, whether by infection of neural tissue, by structural injury or by a genetically driven degeneration of specific circuits. **Immune and inflammatory injury** is antibody-mediated, inflammatory or demyelinating disturbance of neural function, sometimes arising remotely from any active infection. **Infective and post-infective** mechanisms cover the organism itself and the host response to it, producing an acute encephalitic picture or a chronic smouldering one. **Systemic and metabolic** routes are disease elsewhere in the body altering the internal environment on which the brain depends. **Iatrogenic** effects are the neuropsychiatric consequences of the treatment given for the disease, or for the psychiatric syndrome itself.

The **iatrogenic neuropsychiatric syndrome** deserves particular vigilance, because it is common, often reversible and frequently missed. The drug that treats the disease and the drug that treats the mind can each disturb cognition, mood, sleep and behaviour, and they can interact so that the effect is greater than either alone. A careful drug history, including the timing of any change against the timing of the syndrome, is therefore a diagnostic instrument rather than a formality. Reaching for the mechanism early is what converts a description into a plan, because the route named is usually the route that treatment must interrupt.

1.4 Recognise organicity through red flags

Because secondary syndromes imitate primary ones, recognition rests on **red flags** rather than on the psychiatric phenotype alone. No single flag is decisive, but their convergence should redirect the assessment from a primary diagnosis toward a search for disease. The recurring flags are an onset at an age unusual for the apparent primary disorder, a mixture of symptoms that does not fit a familiar syndrome, coincident physical or neurological signs, disturbance or fluctuation of consciousness, cognitive decline out of proportion to the affective picture, seizures or other paroxysmal events, systemic features such as fever or weight loss, and a course that is unusually rapid or resistant to appropriate psychiatric treatment.

Organicity becomes probable when several of these run together, and it becomes more urgent when the tempo is subacute, when consciousness is involved or when the trajectory is worsening despite treatment. The reasoning is probabilistic rather than mechanical: the flags raise the pre-

test probability of a secondary syndrome and lower the threshold for examination and investigation. They do not, by themselves, name the disease, and a patient with none of them may still harbour one, so their absence reassures less than their presence alarms.

PITFALL

Formulating without examining. A psychiatrist who omits fundoscopy, a basic neurological screen and a general physical examination can miss papilloedema, a focal sign or a systemic clue that would have redirected the entire diagnosis. The organic sign is found only by the clinician who looks for it, and the examination that finds it takes minutes while the illness it reveals may take a life.

1.5 Investigate to answer a question, not to reassure

Investigation in this chapter is hypothesis-led, not reflexive. The purpose of **targeted investigation** is to answer the mechanistic question the history and examination have raised, not to order every available test in the hope that one will speak. Structural imaging answers a question about structure and mass. Examination of the cerebrospinal fluid answers questions about infection and inflammation. Serological and specific antibody testing answers immune and infective questions. Electrophysiology answers questions about cortical function and paroxysmal activity. Each modality has a question it settles well and questions it cannot settle at all, and choosing the test means first naming the question.

The workup is protected by discipline in sequence and in interpretation. Sequence means letting the leading hypothesis order the tests, so that the investigation most likely to change management is done first and the staged workup is completed rather than abandoned. Interpretation means remembering that a normal result rarely excludes a disease outright. A single unremarkable investigation early in a subacute illness can mislead, and serial testing, a different modality or a later repeat may be needed when clinical suspicion is strong. A result is evidence to be weighed against the whole picture, not a verdict that overrides it.

GOOD TO REMEMBER

In any first episode of psychosis, mania or severe depression with atypical features, examine the nervous system and take a full drug, infection and systemic history before committing to a primary diagnosis. The examination is quick and repeatable; the secondary disease it protects against is neither.

1.6 Know what this chapter owns and what it hands over

The chapter touches many constructs that are taught in full elsewhere. A disciplined answer names the interface and cross-refers; it does not reproduce another chapter's criteria, scoring table or pharmacology. Knowing the **diagnostic boundary** is itself part of competence, because it keeps the answer on the disease question actually asked rather than drifting into a neighbouring syndrome.

- Pseudobulbar affect, the pathological laughing and crying that appears in multiple sclerosis and in motor neuron disease, is named here in those diseases but taught in full, with its

phenomenology and treatment, in the Stroke, TBI, delirium and focal brain syndromes notes.

- Dementia with Lewy bodies and its temporal distinction from Parkinson disease dementia belong to the Dementias and neurocognitive disorders notes; the chapter teaches the Parkinson-disease side of that boundary and cross-refers for the rest.
- The diagnostic criteria and phenomenology of Tourette syndrome belong to the Child behavioural, emotional and other disorders notes; the chapter names it as the archetypal tic disorder while teaching the acquired choreas itself.
- Catatonia phenomenology, its structured rating and the lorazepam challenge belong to the Other psychotic disorders, delusional syndromes and catatonia notes; the chapter teaches only how an autoimmune encephalitis is distinguished from catatonia.
- The primary nosology and pharmacotherapy of depression and schizophrenia belong to the Mood disorders: pharmacotherapy notes and the Schizophrenia: management, antipsychotics and adverse effects notes; the chapter teaches only the secondary and immune-mediated versions of these syndromes.
- The hepatic and metabolic aspects of Wilson disease belong to the Endocrine and metabolic psychiatry notes, and the standardised cognitive instruments, with their item content and scoring, belong to the Psychotherapies, clinical assessment, MSE and nosology notes.

A useful handover sentence does real work: it names the neighbouring construct, says why it matters to the case in hand, and points to its owning chapter, then returns to the disease question. This is shorter and more accurate than inserting a copied criterion set, a scoring table or a drug-selection essay into every answer that happens to touch them.

1.7 Manage the disease and the mind together

Management follows the shared spine, which keeps an answer complete under pressure. The locus of care asks where treatment can safely happen: outpatient and community care for the stable patient, inpatient care when medical or behavioural need exceeds community capacity, and emergency care when an encephalitic, infective or metabolic crisis threatens life or brain. The focus orders the targets over time: acute work treats the underlying disease and the immediate risk, shorter-term work manages the disturbing psychiatric symptoms, and continuing care addresses residual cognitive, affective and behavioural change, relapse prevention and rehabilitation. The modus ensures every mode is considered: disease-directed medical treatment, cautious psychiatric treatment, psychological support, procedural options where the disease indicates them, and social and family intervention.

The two prescriptions, one for the disease and one for the mind, must be planned together, because each can worsen the other and because the choice and dose of a psychotropic often depend on the specific disease and its own treatment. Where a management decision rests on a formal guideline position, that position should be attributed to the body that issues it and drawn from current disease-specific guidance and local protocol rather than recalled as a rule of thumb. The reasoning is taught here; the reader is pointed to current guidance for each disease in its own section.

IN INDIA

Where neurocysticercosis, Japanese encephalitis, cerebral malaria, central nervous system tuberculosis, HIV and neurosyphilis remain part of everyday practice, keep these treatable diseases in the differential of a new psychiatric or cognitive presentation that carries neurological or systemic signs, and investigate the brain and cerebrospinal fluid as the suspected syndrome directs, weighing the contraindications to lumbar puncture, before settling on a primary psychiatric diagnosis. Treating a curable infection as a functional illness is the costliest error this chapter guards against.

1.8 Carry the ORGANIC scaffold into essays and vivas

Under examination pressure, the method must survive when detail fails. The master mnemonic for this chapter is **ORGANIC**. It is an educational scaffold rather than a diagnostic instrument, and it organises any case in the chapter, a viral or autoimmune encephalitis, a movement disorder, a chronic infection, a demyelinating disease or a treatment effect, without replacing the disease-specific knowledge that lives in the owning section.

MNEMONIC

ORGANIC

Onset and course: is the mental-state change atypical in age, tempo or mixture for a primary disorder? **R**ecognise the disease: examine the nervous system and the body for the illness behind the syndrome. **G**enerate the mechanism: direct, immune, infective, systemic-metabolic or iatrogenic. **A**ssess with targeted tests: image, sample the cerebrospinal fluid, serology and electrophysiology as the hypothesis demands. **N**ame the boundary: teach what this chapter owns and hand over what it does not. **I**ntervene on both fronts: treat the disease and the psychiatric syndrome together. **C**ontinue and coordinate: monitoring, rehabilitation and follow-up across settings and disciplines.

For a short case, compress ORGANIC into a problem representation, the leading disease, the dangerous alternative, the discriminating investigation and the immediate plan. For a long essay, expand each letter and insert the epidemiology, criteria, investigations and treatment from the owning section. In a viva, make the calibration audible: state what is observed, what is inferred, what remains uncertain, and which finding would change the ranking. The enduring habit is integration without overreach, so that a psychiatric syndrome can be recognised as the expression of a disease without the disease being made to explain the whole person.

ORGANIC: read onset and course, recognise the disease, generate the mechanism, assess with targeted tests, name the boundary, intervene on both fronts, then continue and coordinate care.

2 · HIV-associated neurocognitive disorders: the HAND spectrum and its classification

A person living with HIV who begins to slip cognitively has not necessarily acquired a dementia. Cognitive change is one of the commonest neuropsychiatric problems in HIV, but in

the treated era most of it is mild and much of it is silent, and the whole clinical value of the field lies in grading what you find rather than treating every positive test as a catastrophe. The marks concentrate here for two reasons. The first is a nomenclature that examiners love, because the disorders sit on a graded spectrum with a precise dividing line. The second is an epidemiological trap: two respectable sources give materially different category splits, and a candidate who quotes one as canonical has walked into it. This section sets out the three-tier **HIV-associated neurocognitive disorder** (HAND) spectrum, the framework that grades it, the clinical criteria that sit alongside the research nosology, and the prevalence figures with their populations kept firmly attached. The mechanism of the neuro-injury itself, and how antiretroviral therapy alters it, is taken up separately in this chapter and is only named here.

2.1 The three-tier HAND spectrum

Most authors divide HIV-associated neurocognitive impairment by severity into three groups, applied only when the presentation cannot be explained by another condition: **asymptomatic neurocognitive impairment** (ANI), **mild neurocognitive disorder** (MND), and **HIV-associated dementia** (HAD), set out in order of increasing severity. The ordering is the spine of the whole topic: ANI is the least severe and HAD the most, with MND between them. Holding that ladder in mind, and knowing what separates each rung from the next, is worth more in an examination than any single prevalence figure.

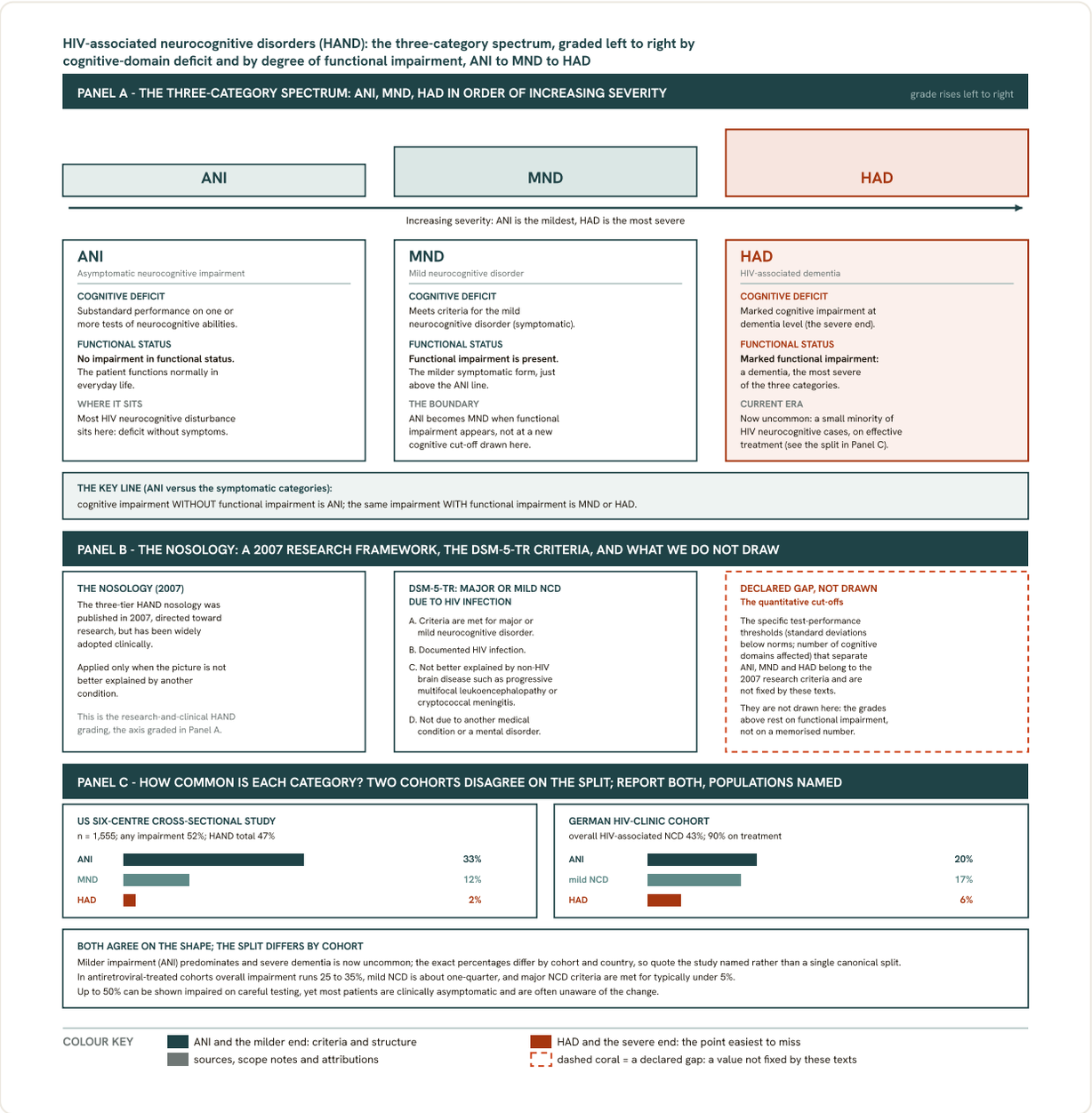


Fig 35.1 **HIV-associated neurocognitive disorders (HAND): the three-category spectrum.** Most authors grade HAND by increasing severity into asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD); the boundary from ANI to the symptomatic categories is the appearance of functional impairment, since ANI shows substandard test performance with intact everyday function. The 2007 research nosology is widely used clinically, but its quantitative test-performance cut-offs are not fixed by these texts and are not drawn here. Category rates differ by cohort: a US six-centre study (n = 1,555) found ANI 33%, MND 12% and HAD 2%, while a German clinic cohort found ANI 20%, mild NCD 17% and HAD 6%. (Kaplan and Sadock, CTP 2024; DSM-5-TR.)

The three tiers are best read as a single axis with two dividing lines rather than as three unrelated diagnoses. The lower line separates measured impairment that leaves the person functioning normally from impairment that has begun to bite into everyday life; the upper line separates that milder symptomatic disorder from frank dementia. The accompanying figure lays the spectrum out this way. What the tiers do not do is describe three different diseases: they are severity categories along a single axis rather than proven sequential stages of one process, which is why a patient can move between them over time and why re-grading at review matters more than the label first applied. Movement in either direction is possible, and this is a point of clinical

substance rather than pedantry: a patient can slip from asymptomatic to symptomatic impairment as function begins to fail, and can equally recover a tier when a reversible contributor is corrected. Because of that mobility, the tier is a snapshot of where the patient sits today, not a permanent classification, and treating it as fixed is one of the ways the grading is misused.

SEVERITY TIER	NEUROPSYCHOLOGICAL TESTING	EVERYDAY FUNCTIONAL STATUS
Asymptomatic neurocognitive impairment (ANI)	Substandard performance on one or more tests	No impairment in functional status
Mild neurocognitive disorder (MND)	Measured impairment present	Functional impairment present
HIV-associated dementia (HAD)	Most severe impairment of the three	Functional impairment present, at the level of dementia

2.2 The 2007 research nosology and the cut-offs it rests on

The currently used nosology was published in **2007** and was directed toward research, but it has been widely adopted clinically and has been the basis of significant discussion. That dual life, born as a research instrument and pressed into clinical service, explains much of the debate around it: a framework built to standardise study populations is being asked to label individual patients, and the fit is imperfect. Understanding that it is a **research nosology** first is the single most useful thing to know about where the categories come from.

The tiers are defined by the degree of measured neuropsychological impairment together with the presence or absence of functional decline. The precise psychometric thresholds, how many standard deviations below normative performance a patient must fall, and in how many cognitive domains, belong to the primary research criteria and are not reproduced here, because a standard reference that names the three categories and dates the nosology does not itself print those cut-offs. This is a real gap rather than an oversight: quoting a remembered standard-deviation rule as though it were grounded is exactly how a plausible but unverified number reaches a candidate. The safe teaching is that the cut-offs exist, that they are demographically anchored, and that they must be read from the primary criteria before being drawn as a grid.

RULE **HAND is a graded diagnosis of exclusion, and the first cut is functional, not psychometric.** The three tiers ascend ANI to MND to HAD, are applied only when the impairment cannot be explained by another condition, and the lowest tier is separated from the rest by whether everyday function is affected, not by the raw test score alone.

2.3 The functional-status hinge: ANI versus the symptomatic disorders

The distinction that carries the most weight, and the one most often tested, is the line between the asymptomatic tier and everything above it. Most neurocognitive disturbances in HIV do not meet the criteria for mild neurocognitive disorder and instead represent asymptomatic neurocognitive impairment: patients who show substandard performance on one or more tests of neurocognitive abilities but do not have any impairment in functional status. The pivot is **functional status**. Below the line, the deficit is detectable only on formal testing and the person

continues to work, manage medication and run a household unimpeded; at and above the line, the deficit has started to cost the patient something in daily life.

MNEMONIC

Impaired but intact, impaired and impaired, demented

The three HAND tiers in ascending severity. ANI: cognition impaired on testing but everyday function intact. MND: cognition impaired and everyday function now affected. HAD: HIV-associated dementia. The hinge between the first tier and the other two is functional status, not the test score.

Getting this hinge right changes both counting and management. It is why ANI, despite being defined by measured impairment, is called asymptomatic: the person does not experience or report a functional problem. It is also why ANI dominates the epidemiology, since the great majority of HIV-related cognitive impairment sits at this sub-threshold level. Whether ANI in an otherwise well patient is a benign finding or an early marker of trajectory remains genuinely contested, which is one more reason to grade rather than to dismiss.

2.4 The DSM-5-TR clinical criteria and what must be excluded

Running alongside the research nosology is the clinical diagnosis, **Major or Mild Neurocognitive Disorder Due to HIV Infection**, set out in DSM-5-TR. It is not a competitor to the ANI/MND/HAD scheme so much as its clinical counterpart: it fixes the diagnosis to a documented infection and, above all, insists that the deficit is not the footprint of something else. Its criteria run as follows:

- The criteria are met for major or mild neurocognitive disorder in the first place, establishing the level of the deficit.
- There is documented infection with human immunodeficiency virus.
- The disorder is not better explained by non-HIV conditions, including secondary brain diseases such as progressive multifocal leukoencephalopathy or cryptococcal meningitis.
- It is not attributable to another medical condition and is not better explained by a mental disorder.

The third criterion is where most clinical errors live. The CNS opportunistic infections it names are the classic secondary causes that mimic HAND, and they are taught in their own right elsewhere in this chapter; here they matter only as the conditions that must be off the table before the label is applied. HAND is, in the end, a diagnosis of exclusion resting on a documented infection.

The clinical diagnosis and the research tiers overlap but do not map cleanly onto one another, and it is worth holding that caution in mind rather than forcing a cell-for-cell translation. The major neurocognitive disorder end of the clinical diagnosis corresponds broadly to the dementia pole of the research spectrum. The milder end is where the two schemes diverge: DSM-5-TR mild neurocognitive disorder does not itself require a loss of independence, so it does not line up one-

to-one with the functional cut that separates asymptomatic impairment from the symptomatic research tiers. Seen this way, the DSM-5-TR diagnosis and the ANI/MND/HAD ladder are overlapping but non-equivalent views of one graded process, and the shared vocabulary of impairment and function is what keeps the two frameworks talking to each other.

PITFALL

Labelling new cognitive decline in a patient with HIV as HAND without first excluding the secondary brain diseases. An opportunistic CNS infection can present as subacute cognitive change, and DSM-5-TR makes the exclusion an explicit criterion precisely because the treatable mimic is easy to miss when the HIV diagnosis is already known and anchors the clinician's thinking.

2.5 How common HAND is, and why most of it is quiet

Cognitive disturbance in HIV is common by any measure. Between about one-third and over one-half of HIV-infected individuals have at least some evidence of a neurocognitive disturbance, and on formal assessment the figure reaches the upper end of that range: **up to 50%** of HIV-infected individuals can be shown to have cognitive impairment on careful testing. The catch, and it is the clinically decisive one, is that most of these patients are clinically asymptomatic. The impairment may improve on retesting, and patients are often unaware of the changes, which is the opposite of the relentless pre-antiretroviral picture in which cognition tracked steadily downhill.

up to 50%	52%	43%	25-35%
IMPAIRED ON CAREFUL NEUROPSYCHOLOGICAL TESTING	OVERALL IMPAIRMENT, US SIX-CENTRE COHORT	OVERALL PREVALENCE, GERMAN HIV-CLINIC COHORT	IMPAIRMENT IN ART-TREATED COHORTS

GOOD TO REMEMBER

A single positive cognitive screen in a person with HIV is not a diagnosis of dementia. Because up to half test positive on careful assessment yet most are asymptomatic and unaware, and because performance may improve on retesting, a low score is a prompt to grade the deficit and to repeat the assessment, not a verdict. Most of what you detect will be at the asymptomatic or mild end of the spectrum.

2.6 The cohort trap: two distributions, two populations

This is the single most examinable pitfall in the topic, and it is a lesson about reading sources rather than about HIV. Two clean sources give materially different category splits for HAND, and both are correct for the population each describes. A clinically diverse cross-sectional study of 1,555 patients at six academic centers showed an overall rate of neuropsychological impairment of 52%, of which the HAND categories accounted for 47%: 33% ANI, 12% MND and only 2% HAD. A German HIV-clinic cohort gave a different picture: an overall HIV-associated neurocognitive disorder prevalence of 43%, of whom 90% were in treatment, distributed as 20% ANI, 17% mild NCD and 6% HAD.

COHORT AND POPULATION	OVERALL IMPAIRMENT	ANI	MND / MILD NCD	HAD
US six-centre cross-sectional study (n=1,555)	52%	33%	12%	2%
German HIV-clinic cohort (90% on treatment)	43%	20%	17%	6%

TRAP **There is no single canonical HAND distribution to memorise.** The two cohorts agree qualitatively, that milder impairment predominates and frank dementia is now uncommon, but their exact percentages differ by country and case-mix. A stem that asks for "the" proportion in each category is either quoting one specific study or testing whether you will invent an average. Name the population before you quote a figure, and never harmonise the two into a single set of numbers.

2.7 The shift in the treated era

Read together, the figures tell a consistent story about what effective treatment has done to the shape of the disease. In cohorts mostly on effective antiretroviral treatment and assessed with comprehensive batteries, overall rates of cognitive impairment run around 25% to 35%. Within that impaired group the weight has shifted downward: mild neurocognitive disorder accounts for approximately one-quarter, while the criteria for major neurocognitive disorder are met for typically **fewer than 5%** of individuals with HIV-related neurocognitive disturbance. Severe HIV-associated dementia, once the defining neurological complication of advanced disease, is now the exception.

That shift is why the classification matters more now than it did in the past, not less. When almost everyone with cognitive impairment was heading toward dementia, a grading scheme added little; when most impairment is asymptomatic or mild and may not progress, the tier a patient occupies genuinely guides how closely to watch and how hard to look for a reversible contributor. The persistence of impairment despite effective treatment is itself the point of interest: cognition no longer collapses as it once did, but a substantial minority of well-treated patients still test below par, which tells you that suppression of the virus in the blood does not automatically clear the problem in the brain. That residue is what keeps the milder tiers clinically alive and what makes the sub-threshold category worth defining at all. The reasons the treated brain fares better, the biology of the neuro-injury and the role of antiretroviral penetration into the central nervous system, belong to the account of HIV neuro-injury given elsewhere in this chapter and are named here only as the mechanism behind the change.

In the treated era most HIV-related neurocognitive impairment is asymptomatic or mild and frank HIV-associated dementia is uncommon, but the exact category split differs by cohort, so name the population before you quote a figure.

2.8 Assessing and following the patient

The practical corollary of an epidemiology dominated by quiet impairment is that the diagnosis rests on deliberate assessment rather than on spontaneous complaint. Patients are often unaware of the changes, so waiting for a subjective cognitive complaint will miss most cases; screening the at-risk patient, and repeating it, is the only reliable way to catch and stage the deficit. The standardised cognitive instruments used to do this, the bedside and office batteries, are covered in the Psychotherapies, clinical assessment, MSE and nosology notes and are not reproduced here; what this topic adds is the discipline of grading the result against the functional-status hinge rather than reading a single cut-off score as a diagnosis.

Following the patient over time is as important as the first assessment, because the tiers are not fixed. Impairment may improve on retesting, a stable ANI can be an early signal rather than an endpoint, and an intercurrent illness or a new secondary cause can push a patient across a line. The psychiatric consequences of the disease, the depression, and the other comorbidities that so often accompany HIV, are addressed separately in this chapter; the cognitive spectrum described here is one strand of a larger neuropsychiatric picture, not the whole of it. In practice the two strands interact at the bedside, because low mood, poor sleep and anxiety all depress test performance in their own right, and a patient assessed in the middle of a depressive episode can look more impaired than they are. That is one more argument for repeating the assessment rather than fixing a tier on a single sitting, and for treating the reversible before concluding that what remains is HAND.

IN INDIA

Where HIV remains a live clinical entity, keep HAND on the differential for any person living with HIV who reports or shows cognitive change, and treat the diagnosis as one of exclusion: document the infection, then actively rule out the secondary brain diseases before applying the label. Because up to half of patients test positive on careful assessment and most are unaware of it, formal screening of the at-risk patient will pick up impairment that the history alone would miss, and grading it correctly keeps a treatable mimic from being written off as dementia.

3 · The pathophysiology of HIV neuro-injury and the effect of antiretroviral therapy

The single fact that unlocks this whole topic is that HIV does not kill the neurons it damages by living inside them. The brain is injured while the virus sits, for the most part, in other cells altogether. Get that relationship right and the neuropathology, the cognitive profile, the risk markers and the response to treatment all fall into place; get it wrong and every downstream question becomes a memory test you will fail. The marks here reward mechanism rather than lists: how the virus reaches the central nervous system, why the damage it does is indirect, where in the brain that damage concentrates, and what antiretroviral therapy does and does not achieve. The clinical syndromes that this injury produces, the HIV-associated neurocognitive disorders and their formal classification, are set out separately in these notes; here the concern is the pathophysiology that sits underneath them and the effect of treatment on that pathophysiology.

Keep one discipline throughout: the specifics that matter are few, and everything else is reasoning from them.

3.1 How HIV reaches the brain: the Trojan-horse route and the viral reservoir

The virus reaches the central nervous system early, and it does so by hitching a ride inside cells it has already infected. HIV infects several cell types, chiefly the CD4 T-helper lymphocytes and monocytes, and it is the infected monocyte, crossing the blood-brain barrier and maturing into a perivascular macrophage, that carries the virus across. This is the **Trojan-horse** model of central nervous system entry, described in Kaplan and Sadock's Comprehensive Textbook of Psychiatry: infected monocyte-derived macrophages and lymphocytes seed the brain during early infection. Once inside, the virus infects macrophages and microglia, and a small subset of astrocytes may harbour productive infection, as set out in the DSM-5-TR.

What follows is the feature that makes HIV brain disease so hard to eradicate. The virus establishes a locally productive infection that can run relatively independently of viral activity elsewhere in the body, so the brain becomes a **viral reservoir** in its own right. Dulcan's Textbook of Child and Adolescent Psychiatry records how fast this happens: the brain is a repository for HIV, and the virus may penetrate brain tissue as early as **2 weeks** after infection. A compartment that is seeded within a fortnight and thereafter sustains its own replication is a compartment that systemic control alone may never fully reach.

Indirect	**CD4 and monocytes**	**Basal ganglia**	**Aggressive ART**
HOW HIV INJURES NEURONS, NOT BY INFECTING THEM	THE CELLS HIV CHIEFLY INFECTS	HIT EARLY; FRONTOTEMPORAL LOSS COMES LATE	THE BEST AND ESSENTIALLY ONLY TREATMENT FOR HAND

3.2 The central principle: neurons are bystanders, not hosts

The neuron is not the host cell. The effects of HIV on neural functioning are, as Kaplan and Sadock's Comprehensive Textbook of Psychiatry puts it, largely indirect: they arise through exposure to viral proteins, through the proinflammatory cytokines produced by infected or activated monocytes and other cells, and through alteration of the blood-brain barrier, rather than through direct infection of neurons. This is the point on which the whole subject turns, and it is worth stating the comparison explicitly because examiners test exactly this discrimination. The injury is indirect, mediated by proteins, cytokines and a leaking barrier, and it is not the consequence of the virus replicating inside neurons.

The blood-brain barrier belongs in the same account rather than as an afterthought. Its disruption is one of the three routes of indirect injury, and it is also self-amplifying: a leaking barrier admits more infected monocytes, which mature into more perivascular macrophages, which release more of the products that both injure tissue and loosen the barrier further. The same logic extends to the other cells that are damaged. According to Tasman's Psychiatry, neither the oligodendrocytes nor the neurons are themselves infected; both are damaged through indirect routes, by the surrounding macrophages and by the toxicity of viral proteins. This dissociation, between where the virus lives and where the damage shows, is the single organising

idea of HIV neuropathogenesis, and it explains why a patient can carry a heavy brain burden of injury with almost no virus demonstrable in the injured cells at post-mortem.

RULE **HIV injures the brain indirectly; it does not directly infect neurons.** The productively infected cells are macrophages, microglia and a small subset of astrocytes, as recorded in the DSM-5-TR. Neurons and oligodendrocytes are damaged by viral proteins, by macrophage-derived cytokines and by blood-brain-barrier disruption, never by the virus setting up house inside them.

MNEMONIC

Proteins, Cytokines, Barrier

The three arms of indirect neuronal injury in HIV: toxic viral **P**roteins, macrophage-derived proinflammatory **C**ytokines, and disruption of the blood-brain **B**arrier. None of the three requires the neuron itself to be infected.

3.3 The neurotoxic cascade: viral proteins and macrophage-activation products

Unpacking the indirect mechanism is where the mechanistic marks are won. Dulcan's Textbook of Child and Adolescent Psychiatry lists the implicated routes: direct neuronal injury by viral proteins, of which **Tat** and gp120 are the named culprits; the products of macrophage activation, a suite of proinflammatory cytokines and chemokines including interleukin 1, interleukin 6, tumour necrosis factor alpha, interferon gamma, monocyte chemoattractant protein 1, and macrophage inflammatory proteins 1alpha and 1beta; neuroreceptor blockade; autoimmunity; and antibody-mediated cellular toxicity. The through-line is that macrophage and microglial activation, not neuronal infection, drives the chemical injury.

Tasman's Psychiatry sharpens the picture of one protein in particular. The **gp120** glycoprotein, carried on the surface of the virus, is toxic to cells it never infects. Its consequences map onto two compartments of tissue. When oligodendrocytes are lost, a **leukoencephalopathy** emerges, the white-matter injury that gives HIV brain disease much of its imaging signature; and when neurons are touched, they undergo both apoptosis and dendritic simplification, a pruning back of the synaptic tree rather than outright cell death alone. The accompanying figure sets the Trojan-horse entry, the microglial activation and this protein-driven cascade in a single sequence.

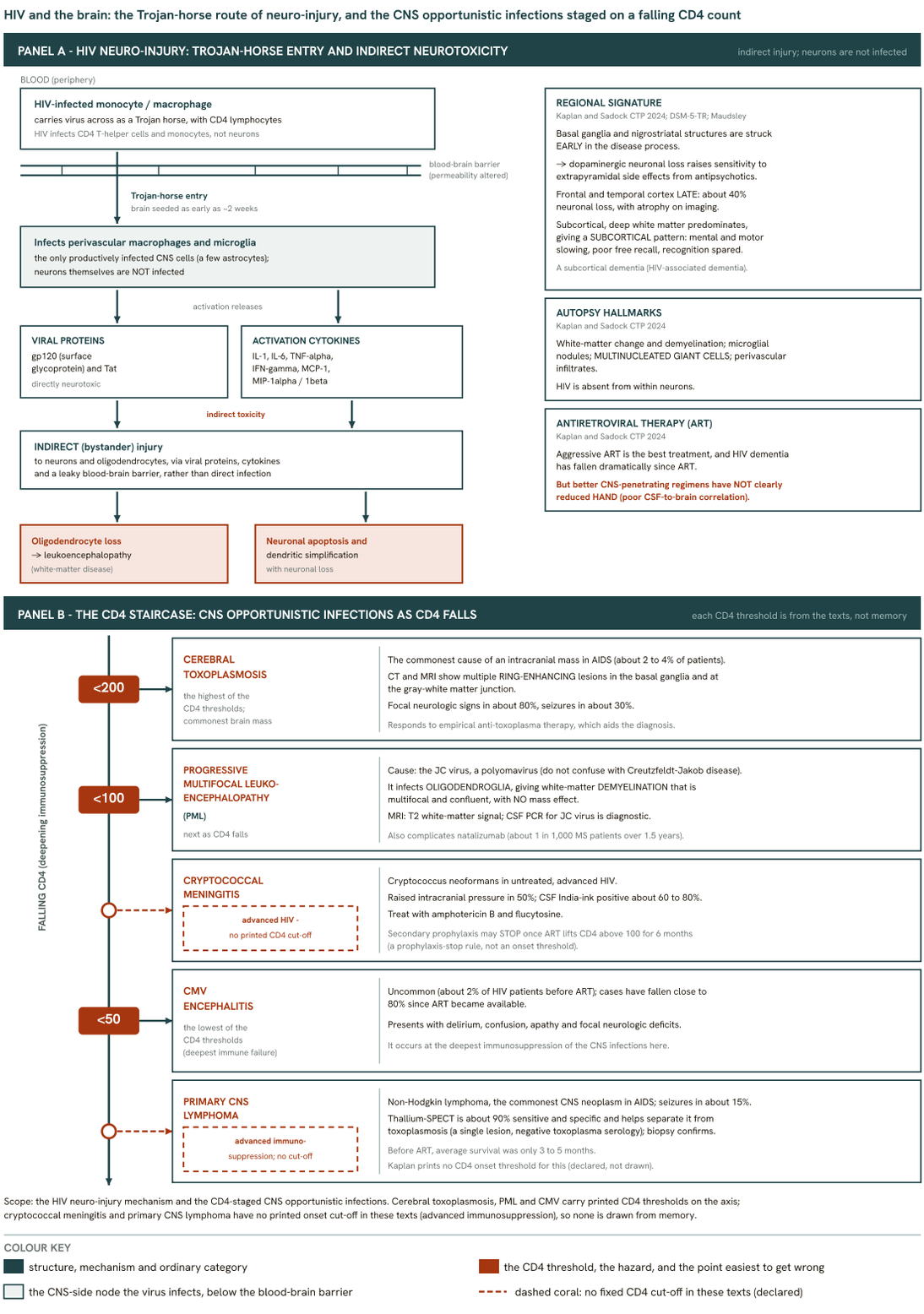


Fig 35.2 HIV neuro-injury and the CD4-staged CNS opportunistic infections. Panel A: the Trojan-horse route into the brain and indirect neurotoxicity that injures neurons without productively infecting them, with the regional and treatment signatures. Panel B stages toxoplasmosis, PML and CMV encephalitis by their printed CD4 thresholds, while cryptococcal meningitis and primary CNS lymphoma carry no printed onset cut-off in these texts. (Kaplan and Sadock CTP 2024; DSM-5-TR; Maudsley 15th edition; Dulcan; Tasman Psychiatry; Kaufman's Clinical Neurology for Psychiatrists.)

CELL TYPE	PRODUCTIVELY INFECTED BY HIV?	ROLE IN THE NEURO-INJURY
Monocyte-derived macrophages	Yes, and the Trojan-horse carrier into the brain	Deliver virus across the barrier; release neurotoxic cytokines
Microglia	Yes	Sustain the central nervous system reservoir; activation drives injury
Astrocytes	A small subset only	Contribute to barrier dysfunction and the inflammatory milieu
Oligodendrocytes	No	Damaged indirectly; their loss yields the leukoencephalopathy
Neurons	No, HIV is markedly absent within neurons	Injured indirectly; apoptosis and dendritic simplification

3.4 The anatomy: a subcortical disease that begins in the basal ganglia

Where the injury concentrates determines what the patient looks like. Kaplan and Sadock's Comprehensive Textbook of Psychiatry describes an early predilection: the basal ganglia and the nigrostriatal structures are affected early in the dementing process, with more diffuse neuronal losses following. The late picture is quantified as an approximate **40%** reduction in frontal and temporal neurons, with atrophy that becomes visible on imaging. The temporal order matters and must not be reversed: deep grey matter first, cortical loss later.

This regional bias produces a recognisable cognitive signature. The DSM-5-TR notes that because HIV preferentially affects subcortical regions over the course of the illness, including the deep white matter, the disorder progresses in a subcortical pattern: mental slowing coupled with motor dysfunction, deficits in procedural learning and in free recall, and relative sparing of recognition memory, verbal abstraction and naming. That profile, slowed and effortful rather than amnestic and aphasic, is the fingerprint of a disease that lives in white matter and deep nuclei. The memory dissociation is worth dwelling on because it is diagnostically useful and frequently examined. A subcortical disorder impairs the effortful, self-generated retrieval that free recall demands, while leaving the stored trace itself relatively intact, so performance recovers markedly when the patient is offered cues or a recognition format. That is the opposite of a cortical amnestic dementia, in which the trace is not laid down and cueing does not help. When the deficit is retrieval rather than encoding, and when motor slowing and procedural difficulty travel alongside it, the anatomy is pointing downward, into the white matter and deep grey, and away from the cortex. The broader distinction between subcortical and cortical dementia is developed in the Dementias and neurocognitive disorders notes, and the standardised instruments used to measure the deficit belong to the Psychotherapies, clinical assessment, MSE and nosology notes; here the point is simply that the anatomy predicts the phenotype.

3.5 The neuropathology at autopsy: a signature you can recognise

The post-mortem findings close the loop between mechanism and syndrome. Autopsy studies of patients who died with AIDS dementia, reported in Kaplan and Sadock's Comprehensive

Textbook of Psychiatry, show a characteristic constellation: white-matter changes and demyelination, **microglial nodules**, **multinucleated giant cells**, and perivascular infiltrates, set against a marked absence of HIV within the neurons themselves. The multinucleated giant cell, formed by the fusion of infected macrophages and microglia, is the histopathological hallmark, and its presence alongside a scarcity of virus in neurons is the tissue-level restatement of the indirect-injury principle.

The same source names the clinical counterpart of these findings. The disorder is a **subcortical dementia**, dominated by loss of attention and concentration and by marked motor slowing. This is the description a candidate should be able to give without hesitation: not a cortical amnestic dementia but a slowed, dysexecutive, motorically retarded picture that follows directly from the deep-structure and white-matter pathology described above.

PITFALL

Reading the psychomotor slowing, poor concentration and flattened output of early HIV brain disease as a depressive episode and stopping there. The subcortical profile of slowed thinking with motor slowing overlaps heavily with the appearance of depression, and the two can coexist; anchoring the assessment to the neurocognitive pattern, and to serostatus, rather than to surface affect keeps a reversible neurological disorder from being managed as a mood disorder alone.

3.6 Dopaminergic vulnerability and its bedside consequence

The early basal-ganglia involvement is not a purely academic point; it changes how you prescribe. The Maudsley Prescribing Guidelines make the clinical consequence explicit: people living with HIV are more susceptible to **extrapyramidal side effects**, because HIV, a neurotropic virus, enters the brain and replicates in the basal ganglia, producing dopaminergic neuronal loss. A brain already depleted of striatal dopamine has less reserve to absorb the dopamine blockade that antipsychotic drugs impose, so movement side effects appear readily and at exposures a seronegative patient would tolerate.

This dovetails with the anatomy established earlier: the same early nigrostriatal injury that begins the dementing process also strips the motor system of its dopaminergic buffer. The practical corollary belongs at the bedside rather than in a mechanism diagram, and it is one of the few places where this pathophysiology directly dictates a prescribing decision.

GOOD TO REMEMBER

When an antipsychotic is genuinely needed in a person living with HIV, expect extrapyramidal effects sooner and at lower exposures than usual, because the virus has already depleted basal-ganglia dopaminergic neurons. Favour an agent with lower extrapyramidal liability, start low and titrate slowly, and watch the motor examination closely. The management of the psychiatric comorbidities themselves, and the interactions between psychotropics and antiretrovirals, are addressed separately.

3.7 What antiretroviral therapy does, and the penetration paradox

Treatment is the part of this story with a genuinely happy chapter and a genuinely humbling one. The happy chapter is that with the arrival of antiretroviral therapy there has been a dramatic reduction in HIV-induced dementia. Kaplan and Sadock's Comprehensive Textbook of Psychiatry is unambiguous about what to do: the best treatment for any HIV-associated neurocognitive disorder is aggressive antiretroviral therapy in patients who are untreated or inadequately treated, and this may produce dramatic improvement. The corollary is sobering in equal measure: to date no clearly effective treatment for these disorders beyond antiretroviral therapy has emerged, so there is no adjunctive neuroprotective agent to reach for once the virus is suppressed.

The humbling chapter concerns drug penetration into the brain, and it is a classic examination trap. The intuitive expectation, that antiretrovirals which penetrate the central nervous system better would be associated with less neurocognitive disorder, has not materialised. The same source offers the reasons: a poor correlation between drug concentrations in the cerebrospinal fluid and those in the brain itself, direct mitochondrial toxicity of the drugs, the degree of immune reactivation, and subtle ongoing viral replication within the central nervous system. Note the direction carefully, because it is the opposite of what feels right: better central penetration has not been shown to buy less injury. Each reason repays a moment's thought. Cerebrospinal-fluid concentration is a convenient surrogate but a treacherous one, since the drug the neuron actually sees is the brain-parenchymal level, which the fluid measures poorly. The drugs themselves are not inert in the compartment they are meant to protect, carrying a mitochondrial toxicity that can injure the very tissue being defended. And a compartment that was seeded within the first fortnight and thereafter replicates on its own terms may sustain low-grade viral activity that suppression of the blood never quite silences. The paradox, then, is not a failure of logic but a lesson in how imperfect a proxy the cerebrospinal fluid is for the brain.

TRAP **Assuming that the more central-nervous-system-penetrant a regimen is, the less HIV neurocognitive disorder it will cause.** This is the expected finding that, per Kaplan and Sadock's Comprehensive Textbook of Psychiatry, has not materialised, plausibly because cerebrospinal-fluid levels track brain levels poorly, the drugs carry their own mitochondrial toxicity, and low-level viral replication grinds on in the compartment. Candidates who have half-remembered a ranking of drugs by brain penetration reach for it here and answer the wrong question.

HIV never directly infects neurons; the brain is injured indirectly, and aggressive antiretroviral therapy in the untreated or inadequately treated patient is the one treatment that can produce dramatic improvement in the neurocognitive disorder.

3.8 Predicting who is at risk: the biomarker and clinical panel

Because the injury is inflammatory and immune-driven, the markers that predict it are markers of immune activation and neuronal breakdown rather than of the virus alone. The DSM-5-TR sets out the panel: the risk of an HIV-related neurocognitive disorder rises with prior episodes of

immunosuppression, with high viral loads in the cerebrospinal fluid, and with a cluster of raised peripheral markers, alongside several clinical and haematological red flags. The single most illuminating of the newer markers is **neurofilament light chain**, a direct readout of axonal injury that ties the blood test back to the tissue damage described throughout this section.

- Immune-activation and inflammatory markers: tumour necrosis factor alpha, interleukin 6, C-reactive protein, D-dimer, sCD14 and sCD163.
- Neuronal-injury marker: neurofilament light chain, rising with axonal damage.
- Virological and immunological history: high cerebrospinal-fluid viral load, a low CD4 cell nadir, and prior episodes of immunosuppression.
- Systemic red flags: anaemia and hypoalbuminaemia.

Read together, these predictors reinforce the mechanistic argument of the whole topic: cumulative immunosuppression and sustained immune activation, not a snapshot of viral load, are what put the brain at risk, which is also why aggressive antiretroviral therapy started before that damage accumulates is the intervention that matters most.

IN INDIA

With a large population living with HIV, the potentially improvable subcortical neurocognitive disorder described here remains a live clinical entity, not a historical one. In any patient presenting with new mental and motor slowing, particularly a younger adult, keep HIV-associated neurocognitive disorder in the differential and establish serostatus early, because aggressive antiretroviral therapy in the untreated or inadequately treated patient can produce dramatic improvement in exactly this picture. The opportunistic infections that complicate advanced disease, and the immune reconstitution that follows treatment, are addressed separately.

4 · Psychiatric comorbidity in HIV: depression, mania, psychosis, suicide and anxiety

A new mood, psychotic or suicidal presentation in a patient living with HIV is rarely a coincidence sitting on top of the infection. The virus, the brain injury it produces, the opportunistic diseases it permits, the drugs used to control it and the psychosocial weight of a chronic transmissible illness all converge on the same clinical picture, and psychiatric comorbidity in HIV is common, consequential and heavily examined for exactly that reason. Depression is the dominant theme; mania and psychosis emerge as the disease reaches the brain; and suicide risk runs above what the measurable risk factors alone would predict. This section works through each in turn: how much more common depression is and how to read its epidemiology without being tripped by the comparator, how the mood and psychotic syndromes track the falling CD4 count, why suicide deserves separate vigilance, and how to treat mania and psychosis in a brain that has become exquisitely sensitive to the very drugs that would help it. The cognitive syndromes of HIV, the CNS opportunistic infections and the interactions between antiretroviral and psychotropic drugs are each addressed separately and are named here only where they bear directly on the psychiatric picture.

4.1 Depression: the commonest comorbidity, and reading its epidemiology

Depression is the single most frequent psychiatric comorbidity in HIV and the one that most reliably degrades the course of the medical illness. Living with HIV carries a three- to fourfold higher prevalence of **major depression** than is seen in the general population. That figure is the one to hold, but it must be read alongside a second, apparently smaller, number that is not in conflict with it. When the comparison is made not against the general population but against an **at-risk HIV-negative comparator**, a group already loaded with the same social adversity, substance use and disadvantage that so often accompany HIV, a meta-analysis of ten studies found a twofold increase in major depression among those infected. The two multipliers answer two different questions. Against the population at large the excess looks larger, because the comparison group carries little of the surrounding hardship; against a well-matched at-risk group the excess shrinks, because much of that hardship is shared, and what remains, the smaller multiplier, is a less-confounded estimate of the association rather than a clean causal measure of the virus and its consequences themselves.

TRAP **Reading the two- and the three- to fourfold depression figures as a contradiction.** They are not in conflict. The larger multiplier is measured against the general population and the smaller against an at-risk HIV-negative comparator, so the smaller figure is not a weaker version of the larger one but a cleaner estimate of the disease-attributable excess once shared social adversity has been controlled for. A stem that quotes one and asks you to reconcile it with the other is testing whether you noticed that the denominator changed.

3- to 4-fold	2-fold	2.5-fold
MORE DEPRESSION THAN THE GENERAL POPULATION	VERSUS AN AT-RISK HIV-NEGATIVE COMPARATOR	AS CD4 FALLS, NEAR THE AIDS TRANSITION

4.2 Depression tracks the failing immune system

Depression in HIV is not distributed evenly across the course of the illness; it intensifies as immune function collapses. The **Multicenter AIDS Cohort Study** demonstrated a two-and-a-half-fold rise in rates of depression as the CD4 count fell **below 200**, in the window just before patients crossed into AIDS. That gradient is clinically instructive, and the psychiatric burden shifts as immune function declines. A depressive syndrome appearing for the first time in a patient whose counts are dropping is not simply a psychological reaction to bad news. It coincides with advancing immunosuppression and a mounting systemic and central-nervous-system disease burden, the virus having seeded the brain far earlier in the infection, and it should draw as much attention to the state of the infection as to the mood itself.

The gradient also reshapes the differential. Early in the illness, reactive and social factors dominate, and a low mood is most readily understood as an adjustment to diagnosis, stigma and uncertainty. Late in the illness, once the count has fallen and the brain is involved, the same syndrome carries a heavier biological loading and sits closer to the neuropsychiatric complications of advanced disease. A first depressive episode at that stage therefore warrants a wider look than the same complaint would at seroconversion, because the machinery generating it has changed even when the surface presentation has not.

4.3 Why the depression matters: adherence, transmission and outcome

Depression earns its place at the front of this topic because it alters the trajectory of the medical illness, not merely the patient's comfort. It exerts a negative influence on medical care and outcome, and it does so through two channels in particular. Patients who are depressed take their antiretroviral therapy less reliably, so virological control slips; and depression is associated with more **transmission-risk behaviour**, raising the chance of onward spread. The relationship runs in both directions, because advancing infection and its brain involvement in turn deepen the mood disturbance, so that a treatable psychiatric problem and a progressing medical one feed each other if neither is addressed.

Anxiety travels alongside the depression in this population and shapes engagement, sleep and the experience of somatic symptoms, though the strength of that association is not quantified in the source used here and is not asserted as a figure. What can be said with confidence is that recognising and treating the affective burden is inseparable from managing the infection well. The primary nosology and pharmacotherapy of the mood disorder itself belong to the Mood disorders: pharmacotherapy notes and are not reproduced here; what matters in the HIV clinic is that the mood syndrome is actively looked for rather than waited for.

> **GOOD TO REMEMBER**
>
> Screen for depression at every review of a patient on antiretroviral therapy, and treat it as a driver of the medical result rather than as a separate complaint. Because depression worsens adherence and outcome, recognising and treating it is part of protecting the virological response, not an optional extra. In practice the depressed, poorly adherent patient and the patient with rising viral load are frequently the same person.

4.4 AIDS mania: how often, and the two populations it comes from

Mania is far less common than depression but far more striking, and it carries a distinctive relationship to disease stage. In one clinic series, **AIDS mania** was recorded in **8%** of all patients with AIDS seen across seventeen months of attendance. Set against the baseline, that is **more than ten times** the six-month prevalence of mania in the general population, which is why the syndrome is treated as a genuine complication of the disease rather than a chance co-occurrence.

Two populations sat within that group, separated by their CD4 count and by the timing of their first manic episode. One set had its first episode early, while CD4 counts were still above 200; the other had its first episode late, once CD4 counts had fallen below 200. The distinction is not bookkeeping. The early group behaves like people with a pre-existing bipolar diathesis whose illness happens to surface during the infection, whereas the late group is where the mania is being generated by the disease in the brain. The two look superficially alike at the bedside and pull apart sharply once history, family history and cognition are examined, which is the subject of the next section.

4.5 The face of HIV-driven mania

The late-onset group is the one that matters most to the neuropsychiatrist, because its mania behaves like a **secondary mania**, a mood syndrome arising from brain disease rather than from

an inborn mood diathesis. It is largely confined to late HIV infection and appears to be a consequence of advanced HIV-related brain involvement. These patients are less likely to carry a personal or family history of mania or mood disorder, and more likely to show dementia or other cognitive impairment alongside the mood change; the co-occurring cognitive syndromes of HIV are addressed separately and are named here only as company the mania keeps. The mood itself tends to be irritable rather than euphoric, the course chronic rather than episodic, and the illness often severe and malignant in its trajectory, which is a different and more forbidding picture than the classic euphoric mania of primary bipolar disorder.

The clinical importance of naming it as secondary is twofold. First, it reorients the assessment: rather than reaching for a mood-disorder formulation and a longitudinal history of past episodes, the clinician who recognises the pattern goes looking for the state of the brain and the immune system that produced it. Second, it warns about the course. A chronic, irritable, cognitively coloured mania that does not remit in the way an episodic bipolar illness would is both harder to live with and harder to treat, and the malignant trajectory means that undertreatment and overtreatment are both dangerous. The bedside discriminators that matter most are the absence of a prior mood history, the presence of cognitive change, and the timing of onset deep into the infection; taken together they point away from a primary diagnosis and towards the diseased brain.

FEATURE	EARLY-ONSET MANIA	LATE-ONSET, HIV-DRIVEN MANIA
Timing and CD4	Early, CD4 above 200	Late, CD4 below 200
Personal or family history of mood disorder	More likely than in late-onset; suggests a primary bipolar diathesis	Characteristically absent
Cognitive state	Usually less impaired than in late-onset	Dementia or cognitive impairment common
Predominant mood quality	More often euphoric or classic	Irritable more than euphoric
Course	More often episodic	Chronic, often severe and malignant

MNEMONIC

Irritable, Chronic, No family history, Cognitive decline

The signature of HIV-driven late-onset mania: an **I**rritable rather than euphoric mood, a **C**hronic rather than episodic course, **N**o personal or family history of mood disorder, and accompanying **C**ognitive decline, the whole picture appearing only once the infection is advanced.

4.6 New-onset psychosis and mania as late-stage events

Psychosis in HIV, when it appears for the first time in advanced disease, should be read the same way as the late mania: as a signal from the brain rather than the start of an independent psychiatric career. **HIV-associated psychosis** and, as a distinct syndrome, new-onset mania can each emerge in late-stage disease, arising as part of the HIV disease process itself or from

opportunistic infections in the central nervous system, and both may respond to low-dose neuroleptics. The practical consequence is a single reflex: a first psychotic or manic episode in this setting is a secondary syndrome until the workup says otherwise, and the search is for a neurological cause before a psychiatric label.

RULE **A first manic or psychotic episode in advanced HIV is secondary until proven otherwise.** New-onset mania or psychosis late in the illness can be a manifestation of HIV disease or of a CNS opportunistic infection, so it demands a search for a neurological cause before it is treated as a primary psychiatric disorder. The primary nosology and management of psychotic illness belong to the Schizophrenia: management, antipsychotics and adverse effects notes.

Holding that rule means keeping a short differential in view whenever the picture is new:

- The HIV disease process reaching the brain in advanced infection.
- CNS opportunistic infections, which are addressed separately and not detailed here.
- An intercurrent delirium from systemic illness, medication or metabolic disturbance.
- An underlying primary mood or psychotic disorder surfacing more or less independently of the infection.

4.7 Suicide: a risk above the sum of its parts

Suicide in HIV is not fully explained by the depression, the substance use and the social adversity that accompany it. Suicidal ideas, suicidal behaviour and **completed suicide** are all increased in people living with HIV, and the crucial observation is that this excess appears to persist beyond the contribution of the known mediating risk factors. Even after accounting for the measurable drivers, in other words, HIV seems to add risk of its own. That is the point to carry into any assessment: a patient whose depression is mild and whose social situation looks manageable is not thereby low-risk simply because the familiar predictors are quiet.

Treatment has changed the landscape without flattening it. The development and use of antiretroviral therapy has been associated with a fall in suicide risk, a welcome shift that tracks the broader improvement in prognosis, but the risk has not returned to that of the background population. The residual elevation is the part that matters clinically, because it is easy to assume that a patient doing well on treatment has been returned to baseline on this axis too, when the evidence says otherwise.

PITFALL

Assuming that a virologically well-controlled patient on antiretroviral therapy no longer carries an elevated suicide risk. Treatment lowers the risk but does not normalise it, so good viral control is not a reason to relax suicide assessment. The stable, adherent, outwardly-thriving patient still warrants direct and unhurried enquiry about suicidal thinking.

4.8 Treating the mania and psychosis safely

Treatment of the mood and psychotic syndromes of advanced HIV is governed by one overriding fact: the same brain that has turned manic or psychotic has also become intolerant of the drugs

used to treat it. Most care happens in the outpatient setting shared with HIV medicine, with admission reserved for the patient whose mania or psychosis threatens safety or is being driven by an acute intercurrent illness, and the emergency presentation is the acutely disturbed, disinhibited patient who cannot be contained at home. The immediate target is behavioural control and the treatment of any precipitating infection or metabolic disturbance; over the medium term the aim is remission of the syndrome together with protection of cognition and of adherence to the antiretroviral regimen. Across every mode of treatment, drug, psychological and social, the governing instruction is caution with dose. The psychological work is largely supportive and practical, aimed at containment, orientation and the rebuilding of adherence, rather than the insight-oriented approaches that a cognitively impaired and acutely disturbed patient cannot use. The social mode carries real weight here, because housing, income, stigma and the reliability of a caregiver determine whether the antiretroviral regimen survives the episode at all.

Pharmacologically, patients with AIDS mania respond to relatively low doses of antipsychotic medication and are very sensitive to their side effects, even with second-generation agents; new-onset psychotic symptoms similarly respond to low-dose neuroleptics. The sensitivity does not stop at the antipsychotic itself. It extends to the drugs used to manage adverse effects, so that extrapyramidal symptoms treated with even modest doses of anticholinergic agents can precipitate an **anticholinergic delirium** in a brain that is already cognitively vulnerable. The interactions between antiretroviral and psychotropic drugs, which further constrain which agent and which dose are safe, are addressed separately and must be checked before prescribing.

IN INDIA

Where HIV remains a live part of the differential, a first manic or psychotic episode presenting in mid-adult life with cognitive slowing, or with an atypical, irritable and chronic course, should prompt review of serostatus and immune function before it is settled as a primary mood or psychotic disorder. Keeping HIV-driven secondary mania and psychosis on the list changes the workup and the prescribing, because both the treatment approach and the prognosis differ from those of a primary illness.

In advanced HIV, treat new mania and psychosis as secondary syndromes of a diseased brain: use low doses of antipsychotic medication, expect heightened sensitivity to side effects even with second-generation agents, and be wary of anticholinergics, which can tip an already vulnerable patient into delirium.

5 · CNS opportunistic infections and HIV-related secondary psychiatric syndromes

In advanced HIV the brain becomes vulnerable to a defined, ordered set of opportunistic infections and tumours, and the order is dictated by the CD4 count. As cell-mediated immunity fails, each fall in the CD4 count opens a fresh window for a different organism, so the count is the single most useful piece of information at the bedside: it tells you which diseases are plausible before the first image is obtained. These processes matter to the psychiatrist for two

reasons. The first is that several of them present with exactly the symptoms a psychiatrist is asked to assess, apathy, low mood, confusion and personality change, so an opportunistic CNS process is a standing differential for what looks like depression or delirium in an HIV-positive patient. The second is that getting the diagnosis wrong is costly, because the treatments diverge sharply and some of these conditions are rapidly fatal if missed. The marks concentrate here because the topic rewards a clean mental model: pair each condition with its CD4 threshold, its imaging signature and its confirmatory test, and hold firmly to the one differential that trips candidates most, the enhancing mass lesion. This account works through the mass lesions first, then the white-matter and meningeal infections, and closes on the secondary psychiatric syndromes these conditions generate. The pathophysiology of HIV neuro-injury itself, and the direct CNS effects of antiretroviral therapy, are taken up separately in these notes and are only named here.

5.1 The CD4 count as the organising axis

The clinical power of the CD4 count is that it stratifies risk into a staircase. Antiretroviral therapy has flattened that staircase, because restoring the CD4 count above the danger thresholds withdraws the immunological permission these organisms need, and the incidence of every disease in this section has fallen where treatment is available. What remains true, and what the examiners test, is the staging logic: a patient who is virologically controlled with a reconstituted immune system is at low risk, whereas the patient who presents late, defaults from treatment, or does not yet know their status arrives with the profound immunosuppression in which these diseases flourish. The strip below sets out the ladder from the least to the most profound immune failure.

< 200	< 100	< 50	up to 10%
CD4 CELLS/MICROLITRE: CEREBRAL TOXOPLASMOSIS BECOMES LIKELY	CD4 CELLS/MICROLITRE: PML TYPICALLY APPEARS	CD4 CELLS/MICROLITRE: CMV ENCEPHALITIS, THE DEEPEST SUPPRESSION	OF AIDS PATIENTS: PRIMARY CNS LYMPHOMA, THE COMMONEST CNS NEOPLASM

Two of these conditions resist a single fixed number and are best held as diseases of advanced disease rather than of a named threshold. Cryptococcal meningitis is described as occurring in untreated patients with advanced HIV, and primary CNS lymphoma is likewise a disease of profoundly low counts for which a defining onset cut-off is not securely established in this source. Writing a precise number for either from memory is exactly the kind of confidently-held error this field punishes, so they are staged qualitatively.

CONDITION	IMAGING OR LESION	CONFIRMATORY POINTER	DISCRIMINATING FEATURE
Cerebral toxoplasmosis	Multiple ring-enhancing lesions in the basal ganglia and at the gray-white junction	Toxoplasma serology; response to empirical anti-toxoplasma treatment	Commonest intracranial mass; multiple lesions, often febrile
Primary CNS lymphoma	Often a solitary enhancing lesion	Thallium SPECT; brain biopsy for confirmation	Afebrile, toxoplasma IgG negative, single lesion
PML	Multifocal white-matter demyelination without mass effect	CSF JC virus PCR	Subacute, progressive, no fever, no enhancement
CMV encephalitis	Clinical: delirium, confusion, apathy and focal deficits	Marker of the deepest immune failure	The lowest CD4 setting of the group
Cryptococcal meningitis	Meningitis with raised intracranial pressure	India ink stain; fungal culture	Subacute meningism; raised pressure the immediate danger

RULE **In a patient with known or suspected advanced HIV, a new neurological or neuropsychiatric change is an opportunistic CNS process until it is excluded.** Stage by CD4 count, neuroimage, and where safe examine the CSF, before a psychiatric label is applied. Reaching for the psychiatric diagnosis first is the single error the whole approach is built to prevent.

5.2 Cerebral toxoplasmosis: the commonest mass lesion

Cerebral toxoplasmosis is reactivation of latent *Toxoplasma gondii* within the brain, and in AIDS it is the single commonest reason for an intracranial mass. Active disease generally occurs once the patient is immunocompromised, with a CD4 count below **200 cells/microlitre**, and across the AIDS population it affects between 2% and 4% of patients. Because the organism seeds the brain through the bloodstream it tends to lodge at vascular watersheds, which is why the lesions cluster in the basal ganglia and at the gray-white matter junction and why they are characteristically multiple.

On CT and MRI the hallmark is multiple **ring-enhancing lesions**: a necrotic centre, a rim that takes up contrast, and surrounding vasogenic oedema that produces mass effect. The ring reflects the immune response mounting a wall around the infection, so the appearance is essentially that of a group of abscesses. Clinically the picture is that of one or more expanding brain lesions. Focal neurologic signs are present in approximately 80% of cases, reflecting the location of the deposits, and focal or generalized seizures occur in roughly 30%. Headache, fever and a subacute encephalopathy commonly accompany them. The reason toxoplasmosis heads the differential for any enhancing lesion in AIDS is simply arithmetic: it is both the commonest such lesion and the most treatable, so it is the diagnosis to assume and treat while the alternatives are being excluded.

5.3 Primary CNS lymphoma and the enhancing-lesion trap

Primary CNS lymphoma, which is a non-Hodgkin lymphoma of the brain, is the commonest CNS neoplasm seen in AIDS, affecting up to 10% of patients, and seizures are present in about 15%. It is the great mimic of toxoplasmosis, because it too presents as an enhancing mass in an immunosuppressed brain, and distinguishing the two is where candidates most often come unstuck. The imaging and clinical clues run in a consistent direction. Lymphoma tends to produce a single lesion in a patient who is afebrile and whose toxoplasma IgG is negative, whereas toxoplasmosis is typically multiple and febrile with positive serology. **Thallium SPECT** is around **90% sensitive and specific** for lymphoma and helps separate the two, but definitive diagnosis rests on brain biopsy. The stakes are high: before antiretroviral therapy the disease carried an average survival of only 3 to 5 months.

TRAP **Treating every enhancing lesion in AIDS as toxoplasmosis and forgetting the lymphoma hiding behind it.** The reflex to cover toxoplasmosis first is correct, because it is commoner and treatable, but the lesion that is solitary, afebrile and toxoplasma IgG negative is the one that is more likely lymphoma. A lesion that fails to respond to an adequate empirical anti-toxoplasma trial should prompt thallium SPECT and biopsy, not a longer course of the same treatment.

GOOD TO REMEMBER

The clean discriminators to carry into the exam and the ward are number, fever and serology. Multiple lesions, fever and a positive toxoplasma titre point to toxoplasmosis; a single lesion in an afebrile, toxoplasma IgG negative patient points to lymphoma and to the need for biopsy. Note that the source used here does not attach a CD4 threshold or a specific oncogenic virus to primary CNS lymphoma, so neither is asserted.

5.4 Progressive multifocal leukoencephalopathy and the JC virus

Progressive multifocal leukoencephalopathy is a demyelinating disease of the white matter that occurs in immunocompromised patients, and in AIDS it typically affects those with fewer than **100 CD4 cells/microlitre**. Its prevalence before antiretroviral therapy was between 1% and 10% of AIDS patients. The causative agent is a polyomavirus, the **JC virus**, named after the patient in whom it was first identified and not, despite the shared initials, to be confused with Creutzfeldt-Jakob disease. That single point of nomenclature is a favourite examination pitfall, and getting it wrong signals a shaky grasp of the whole topic.

The mechanism is worth holding precisely because it explains the imaging. The JC virus targets **oligodendroglia**, the cells that generate and maintain CNS myelin, and through their destruction the infection produces demyelination in the white matter of the brain and spinal cord, along with death of astrocytes. The result is multiple, widespread, often confluent white-matter lesions with a multifocal distribution. On MRI these show as areas of high signal (hyperintensity) on T2-weighted and FLAIR images, with corresponding low signal on T1, primarily in the white matter, and crucially they carry no mass effect, which is what separates PML from the enhancing, space-occupying lesions of toxoplasmosis and lymphoma. Diagnosis is secured by detecting JC virus DNA in the CSF by PCR, a test that is both sensitive and specific. Clinically the disease advances

over weeks as a progressive accumulation of focal deficits, cognitive decline and, not infrequently, the behavioural and affective change that brings it to psychiatric attention.

5.5 PML beyond HIV: natalizumab and reactivation

PML is not exclusive to HIV, and understanding why it appears in other settings sharpens the concept that it is fundamentally a disease of failed immune surveillance over a latent virus. It complicates a range of immunosuppressive situations, including the treatment of multiple sclerosis and organ transplantation. The most instructive example is the monoclonal antibody natalizumab, used in multiple sclerosis: probably as a result of the immunosuppression it produces, roughly 1 person for every 1000 patients treated for 1.5 years initially developed PML.

What subsequent study of these cases revealed is the key teaching point. The multiple sclerosis patients who went on to develop PML had anti-JC virus antibodies present before natalizumab was started, which indicates that the virus was already there, quiescent, and that the drug permitted reactivation rather than fresh infection. The same principle underlies PML in AIDS: the falling CD4 count lifts the immune restraint that had kept a latent polyomavirus in check. Multiple sclerosis and its disease-modifying therapy are addressed in their own right elsewhere in these notes; here natalizumab is named only to make the reactivation mechanism explicit.

5.6 Cytomegalovirus encephalitis: the deepest immunosuppression

Cytomegalovirus encephalitis sits at the floor of the immunological staircase. CMV infection is an uncommon complication of AIDS overall, affecting about 2% of HIV patients before antiretroviral therapy, and clinically evident encephalitis is rarer still, occurring almost only in patients whose CD4 count has fallen below 50 cells/microlitre. It is therefore a marker of the most profound immune failure in this section, and its presence tells you the patient's defences are essentially exhausted.

The clinical syndrome is one that lands squarely in psychiatric territory. The commonest features are delirium, confusion, apathy and focal neurologic deficits, so a CMV encephalitis can present as an acute confusional state or as a flat, withdrawn patient who is easily mistaken for someone who is depressed. Antiretroviral therapy has had a striking effect on its epidemiology, with close to an 80% reduction in cases since effective treatment became available, so like the rest of this group it is now chiefly a disease of the untreated and the late-presenting. When it does appear, it signals that the immune system has reached the point at which the full range of opportunistic processes must be actively sought.

5.7 Cryptococcal meningitis: raised pressure and the India ink stain

Cryptococcal meningitis, caused by *Cryptococcus neoformans*, is the classic fungal meningitis of advanced HIV and is usually seen in untreated patients with advanced disease. Its incidence is now around five cases per 1,000 people living with HIV. It presents subacutely, with headache, fever and meningism that can be surprisingly muted, and the immediate danger is mechanical rather than infective: intracranial pressure is elevated in 50% of patients, and it is the raised pressure, causing visual loss and herniation, that kills early. Recognising and relieving it, by therapeutic lumbar puncture, is as important as the antifungal treatment itself.

The CSF is diagnostically rich but can mislead, because it is normal in about 20% of cases. When abnormal it typically shows a monocytosis, an elevated protein, a decreased glucose and positive fungal cultures. The bedside test worth memorising is the **India ink stain** of the CSF, which is positive between **60% and 80%** of the time and reveals the encapsulated yeast directly. Treatment requires amphotericin B and flucytosine. Once the patient has received antiretroviral therapy for six months and the CD4 count has risen above 100 cells/microlitre, secondary prophylaxis may be terminated: a figure that belongs to stopping prophylaxis after immune recovery, and not to the count at which the disease begins.

- Elevated opening pressure, raised in half of patients and the immediate threat to sight and life.
- A monocytic (lymphocytic) pleocytosis rather than the neutrophil predominance of bacterial meningitis.
- Elevated CSF protein.
- Decreased CSF glucose.
- Positive fungal cultures, with a positive India ink stain in the majority.

IN INDIA

Where late-presenting HIV remains common, cryptococcal meningitis is a leading cause of subacute meningitis in the immunosuppressed adult, so keep it firmly in the differential for any HIV-positive patient with headache and altered behaviour. Two clinical decisions follow directly from the biology above: measure and actively manage the opening pressure at lumbar puncture, because raised pressure is the early killer, and send CSF for an India ink stain and fungal culture rather than treating the presentation as a primary psychiatric disturbance.

5.8 When the infection wears a psychiatric mask

The reason all of this belongs in a psychiatry chapter is that these conditions imitate the disorders a psychiatrist is trained to treat. Several of the HIV-related CNS conditions can produce depressive symptoms in their own right, including toxoplasmosis, cryptococcal meningitis, lymphoma and syphilis. More insidiously, AIDS dementia and other HIV-related CNS conditions can generate a flat, apathetic state that is often misdiagnosed as depression, and a superimposed delirium can mimic a wide range of psychiatric presentations. The clinical consequence is that low mood, apathy or confusion in an HIV-positive patient is never to be taken at face value as a primary mood disorder until an organic cause has been considered and, where indicated, excluded. The primary nosology and pharmacotherapy of depression itself belong to the Mood disorders: pharmacotherapy notes, and the assessment and phenomenology of delirium to the Stroke, TBI, delirium and focal brain syndromes notes; the point here is only that this population reaches those diagnoses through a longer and more suspicious route.

One infection in this group deserves special mention as a psychiatric imitator. CNS syphilis, a condition that had become quite rare, has been reappearing in medical centres with HIV specialty services, and it remains **the great imitator** it was originally named, capable of presenting with

depression among a broad range of neuropsychiatric pictures. Its full staging, features and penicillin treatment are set out in the dedicated account of neurosyphilis elsewhere in these notes; the reason to name it here is that a resurgent syphilis in an HIV clinic is precisely the sort of treatable cause a psychiatrist must not overlook when the presenting complaint is a change in mood or personality.

MNEMONIC

Toxo, Crypto, Lymphoma, Syphilis

The HIV-related CNS conditions that can masquerade as, or produce, depressive symptoms: **T**oxoplasmosis, **C**ryptococcal meningitis, **L**ymphoma and **S**yphilis, with AIDS dementia adding the flat, apathetic state that most often gets misread. Each is a treatable diagnosis hiding behind a psychiatric one.

PITFALL

Labelling the flat, withdrawn, poorly motivated HIV patient as depressed and starting an antidepressant, when the apathy is the face of an AIDS dementia or another CNS condition misdiagnosed as depression. The error is understandable, because the surface presentations are identical, but it delays the neurological workup that the low CD4 count demands and lets a treatable infection or a dementing process advance unrecognised.

In advanced HIV, treat any new focal deficit, seizure, or apathetic-depressive change as an opportunistic CNS process until CD4 staging, neuroimaging and CSF have excluded one; the enhancing mass is toxoplasmosis until biopsy proves lymphoma, and the flat, apathetic patient may harbour a CNS infection rather than a mood disorder.

6 · Antiretroviral-psychotropic interactions and the neuropsychiatric effects of antiretrovirals

A patient living with HIV who also needs a psychotropic is being asked to take two of the most interaction-prone drug groups in medicine at the same time. That single fact organises the whole topic. The interface between antiretroviral therapy and psychiatric medication generates trouble in two directions at once. In one direction the two drug classes interfere with each other's handling and effects, so that a regimen that is safe alone becomes toxic or ineffective in combination. In the other direction several antiretrovirals are themselves psychoactive, producing depression, disturbed sleep, psychosis and suicidal thinking regardless of any co-prescribed drug. The marks here are safety marks, because getting them wrong harms a patient who came for help with the very symptoms your prescribing may cause or worsen.

The depression, mania, psychosis, suicidality and anxiety that complicate HIV are substantial in their own right and are addressed separately in this chapter. The concern here is narrower and more practical. It is, first, the pharmacology of co-prescribing antiretrovirals with psychotropics,

and second, the direct neuropsychiatric toxicity of the antiretroviral agents themselves, of which efavirenz is the exemplar the examiners return to.

6.1 Why the antiretroviral-psychotropic interface carries marks

The starting principle is that **pharmacokinetic interactions** between antiretroviral drugs and psychotropics occur frequently and can be clinically significant. They are numerous and complex, too many to hold in memory reliably, which is why prescribers are directed to regularly updated resources such as www.hiv-druginteractions.org rather than to a fixed list committed to recall. Alongside these, **pharmacodynamic interactions** may also occur through overlapping adverse effects, where two drugs that each nudge the same physiological parameter combine to push it into dangerous territory even when neither has altered the other's blood level.

Holding those two mechanisms apart is the organising move of the topic. A pharmacokinetic interaction changes how much drug is present: one agent alters the absorption, metabolism or clearance of another, most often through hepatic enzymes, so the measured concentration rises or falls. A pharmacodynamic interaction leaves the concentrations untouched and instead sums the effects of two drugs acting on the same target system, the heart's repolarisation or the seizure threshold being the classic examples. The reason the distinction earns marks is that the two demand different safeguards. A pharmacokinetic problem is anticipated by knowing the metabolic route and, where needed, adjusting the dose or checking a level; a pharmacodynamic problem is anticipated by knowing what each drug does to the end organ and monitoring that organ directly.

2-4 weeks	**30% lower**	**2-fold higher**
UNTIL THE ACUTE EFAVIRENZ NEUROPSYCHIATRIC SYMPTOMS USUALLY SUBSIDE	EFFECT OF THE INDUCER EFAVIRENZ ON A SHARED SUBSTRATE (LEDIPASVIR, A NON-PSYCHOTROPIC EXEMPLAR)	EFFECT OF THE ENHANCER COBICISTAT ON THE SAME SUBSTRATE

6.2 The cytochrome P450 axis: boosters raise, the inducer lowers

Most of the important pharmacokinetic interactions run through hepatic cytochrome P450, and the CYP3A subfamily in particular. Two antiretroviral strategies sit at opposite poles of this enzyme system, and the exam wants you to know which way each one pushes. **Ritonavir** and cobicistat are boosting agents; cobicistat is best understood as a pure **pharmacokinetic enhancer**, a drug added not for antiviral effect but to inhibit CYP3A and thereby raise the level of the agent it accompanies. By that same inhibition they raise the levels of co-administered psychotropics that are CYP3A substrates. At the other pole, efavirenz behaves as a CYP3A **enzyme inducer**, upregulating the enzyme and lowering the concentration of its substrates.

The magnitude and direction are worth anchoring with a concrete, if deliberately non-psychiatric, illustration. Using the hepatitis C drug ledipasvir purely as an exemplar substrate, the inducer efavirenz reduces its concentration by around **30%**, whereas the enhancer cobicistat increases the same drug's concentration roughly **2-fold**. Ledipasvir is not a psychotropic and these figures do not transfer to any particular psychiatric drug; they are quoted only to fix the two directions in the mind. The clinical corollary is what matters: a boosted regimen and an

efavirenz-based regimen pull a shared substrate in opposite directions, so the same psychotropic may need a higher maintenance dose alongside one and a lower one alongside the other.

RULE **Boosters raise the substrate, the inducer lowers it.** The pharmacokinetic enhancers ritonavir and cobicistat inhibit CYP3A and raise the levels of psychotropic substrates, while efavirenz induces CYP3A and lowers them. Because the interactions are individually numerous and complex, do not trust memory: confirm the direction and magnitude against a maintained interactions resource before you co-prescribe.

6.3 A worked example: when inhibition raises a substrate to toxicity

The danger of the boosting strategy is easiest to see in a single worked interaction. Ritonavir can decrease the metabolism of ecstasy (MDMA) and precipitate toxicity: by inhibiting the enzyme that would ordinarily clear the recreational drug, the antiretroviral lets it accumulate to harmful levels. The principle generalises well beyond one recreational substance. Any cytochrome P450 substrate a patient is taking, prescribed or not, becomes a candidate for the same accumulation once a potent inhibitor is added, and the psychotropics most vulnerable are those with a narrow gap between a therapeutic and a toxic concentration.

What makes this counter-intuitive is that the enzyme inhibition is not an accident of the drug but its intended action. Ritonavir earns its place in modern regimens precisely because it inhibits metabolism and so sustains the levels of the antiretrovirals it accompanies; the same inhibition that boosts a partner drug on purpose boosts an unrelated co-substrate by the same route. The pharmacology working as designed for the antiviral is the pharmacology working against the psychiatrist.

Two habits follow from this. The first is to take a full drug history, including recreational and over-the-counter agents, because the inhibitor is silent until the co-substrate reaches toxicity and gives no warning at the point of prescribing. The second is to treat the boosted regimens with particular respect: they are the regimens most likely to turn a previously well-tolerated psychotropic dose into an overdose without a single change to that psychotropic's prescription. Anticipation, not reaction, is the whole game.

TRAP **Assuming that all antiretroviral therapy lowers psychotropic levels.** Candidates who have learned that efavirenz is an inducer generalise the reflex and expect every regimen to reduce a co-prescribed drug, so they instinctively push the psychotropic dose up. The boosted regimens do the opposite: ritonavir and cobicistat raise the substrate, and the same upward dose adjustment then risks the accumulation that lets ritonavir precipitate frank toxicity. Direction depends on the regimen, and the two are exactly opposite.

6.4 Pharmacodynamic overlap: QT prolongation and the seizure threshold

Not every dangerous interaction changes a blood level, and two pharmacodynamic overlaps are worth committing to memory. The first is cardiac. Several antiretrovirals prolong the **QT interval** in their own right, efavirenz, rilpivirine and the saquinavir-ritonavir combination among them, while atazanavir, lopinavir and saquinavir prolong the PR interval instead. Add a QT-prolonging psychotropic to a QT-prolonging antiretroviral and the two contributions to

repolarisation summate, so the arrhythmia risk compounds. This is precisely why ECG monitoring is recommended when citalopram or escitalopram is co-administered with antiretroviral therapy that prolongs the QT interval.

The second overlap is the seizure threshold. A number of antiretrovirals, including darunavir, efavirenz, maraviroc, ritonavir, saquinavir and zidovudine, may increase the seizure risk associated with certain psychotropics, of which clozapine is the obvious example. Neither of these interactions is visible on a plasma-level check; both are predictable only from knowing what the two drugs do to the heart and to the cortex, which is exactly what makes the pharmacodynamic category easy to overlook and important to teach.

GOOD TO REMEMBER

Before adding citalopram or escitalopram to a QT-prolonging antiretroviral regimen, obtain a baseline ECG and monitor, because the two QT contributions add up even when neither drug alters the other's level. In the same spirit, when a seizure-threshold-lowering psychotropic such as clozapine is in the picture, remember that several antiretrovirals independently raise seizure risk, so the combined threshold is lower than either drug alone would suggest.

6.5 Choosing a mood stabiliser in HIV

Treatment of bipolar disorder in a patient with HIV is broadly similar to treatment in the general population, and the general pharmacotherapy belongs to the Mood disorders: pharmacotherapy notes. What changes is that the interaction burden reshapes the choice among the standard agents, so the selection becomes interaction-driven rather than efficacy-driven. Lithium is renally excreted, so cytochrome P450 interactions with antiretrovirals are unlikely; the catch is that its use is problematic in the renal impairment often seen in people living with HIV, where a narrow-index drug cleared by the kidney becomes difficult to hold in range. **Carbamazepine** is best avoided altogether, both because it carries significant drug interactions with antiretroviral therapy and because of its own risk of blood dyscrasias. Valproate is a known teratogen and is best avoided alongside other hepatotoxic drugs and in the presence of hepatic infection, a genuine consideration when viral hepatitis co-travels with HIV.

MOOD STABILISER	INTERACTION ISSUE IN HIV	PRACTICAL POSITION
Lithium	Renally excreted, so cytochrome P450 interactions with antiretrovirals are unlikely	Interaction-favourable, but problematic in the renal impairment often seen in people living with HIV
Carbamazepine	Significant interactions with antiretroviral therapy; risk of blood dyscrasias	Best avoided
Valproate	Known teratogen; hepatotoxicity concern	Best avoided with other hepatotoxic drugs and in hepatic infection

The logic reads cleanly off the table. The agent that interacts least through the liver, lithium, is limited by the organ that clears it rather than by the enzymes; the two anticonvulsant mood stabilisers are each constrained by a different hazard, carbamazepine by its interactions and marrow toxicity, valproate by teratogenicity and hepatic risk. Reasoning from those constraints, rather than from a memorised first-line list, is what the question is really testing.

6.6 The direct neuropsychiatric effects: efavirenz as the exemplar

The second half of the topic leaves interactions behind entirely: some antiretrovirals injure mood and cognition directly. **Efavirenz**, a non-nucleoside reverse transcriptase inhibitor, is the drug that defines the syndrome, and its recognised neuropsychiatric profile is broad: somnolence, insomnia, abnormal and vivid dreams, impaired concentration, depression, psychosis and suicidal ideation. The reassuring part is the time course, because these symptoms usually subside or diminish after **2-4 weeks** of treatment, so a patient warned in advance can often ride the early phase out. The caveats are two: subtler long-term neuropsychiatric effects may still occur once the acute phase settles, and the drug can exacerbate pre-existing psychiatric symptoms, which is why it is best avoided in a patient with a history of psychiatric illness.

The wider prescribing lesson generalises from that one agent. Psychiatric adverse events have been reported with most antiretroviral drugs, although for many the causal relationship remains uncertain and hard to separate from the psychological weight of the diagnosis itself. Efavirenz has been the most commonly implicated of them, and HIV guidelines accordingly suggest avoiding its use in patients with psychiatric comorbidity. The presence of suicidal ideation on the effect list is what lifts this above a tolerability footnote: it is a patient-safety issue, and it is the reason a psychiatric history is relevant to an antiretroviral choice at all.

PITFALL

Attributing new depression, insomnia or suicidal ideation in a patient recently started on efavirenz entirely to the psychological impact of learning an HIV diagnosis, and reaching for an antidepressant while leaving the antiretroviral untouched. The drug is the most commonly implicated agent for exactly these symptoms, and the early, largely self-limiting time course is a clue, not a coincidence. The regimen belongs in the differential for the psychiatric presentation before a primary disorder is assumed.

6.7 Efavirenz depression and psychosis, and the widening list of implicated agents

Looking more closely at efavirenz, of all the antiretroviral agents it is the one most often associated with depressive symptoms. Their course is variable and cannot be assumed: they remit spontaneously in some patients but persist in a few, so a wait-and-see stance does not serve everyone equally. Efavirenz has also been reported to cause frank psychosis in some patients, severe enough to necessitate withdrawal of the drug, and that is the crucial point about severity, because it means substitution rather than mere dose adjustment is sometimes the only safe course. More recently the list of implicated agents has widened beyond efavirenz alone: rilpivirine and efavirenz among the non-nucleoside reverse transcriptase inhibitors, and dolutegravir among the integrase inhibitors, have all been linked to depression.

That widening matters for how the topic is examined. The old teaching that efavirenz is the single neuropsychiatric offender is no longer the whole picture; the safer formulation is that efavirenz remains the principal and most consistently implicated agent, but that a newer non-nucleoside agent and a newer drug class have joined it. Keeping the three names together as a group is more useful than memorising efavirenz in isolation.

MNEMONIC

Efavirenz, Rilpivirine, Dolutegravir

The three antiretrovirals most consistently linked to depression, remembered as **E**favirenz and **R**ilpivirine among the non-nucleoside reverse transcriptase inhibitors, and **D**olutegravir among the integrase inhibitors. Efavirenz remains the principal offender; the other two mark where the concern has since spread.

6.8 Rilpivirine and the integrase inhibitors

Rilpivirine, the other neuropsychiatrically active non-nucleoside agent, produces depression, suicidality and sleep disturbances, a profile that resembles efavirenz's but carries a lower incidence of each event; it too is worth avoiding in a patient with a history of psychiatric illness. The **integrase strand transfer inhibitors** are the newer focus of concern. Dolutegravir, elvitegravir and raltegravir have each been associated with insomnia, depression and suicidal ideation, and the signal is strongest for dolutegravir, in which the symptoms characteristically appear within the first months of treatment.

AGENT OR CLASS	KEY NEUROPSYCHIATRIC EFFECTS	RELATIVE BURDEN AND TIMING	PRESCRIBING CAUTION
Efavirenz (NNRTI)	Somnolence, insomnia, vivid dreams, impaired concentration, depression, psychosis, suicidal ideation	Most commonly implicated; acute symptoms usually self-limit	Avoid in psychiatric comorbidity
Rilpivirine (NNRTI)	Depression, suicidality, sleep disturbance	Similar profile to efavirenz but lower incidence	Consider avoiding in a psychiatric history
Dolutegravir, elvitegravir, raltegravir (INSTI)	Insomnia, depression, suicidal ideation	Signal strongest for dolutegravir, within the first months	Monitor early, especially dolutegravir

The early timing of the integrase-inhibitor signal is a practical gift, because it makes attribution easier: neuropsychiatric symptoms that begin in the first months of a new integrase-based regimen point back to the drug more confidently than symptoms emerging years into stable therapy. Read together with the efavirenz story, the message across the whole class is consistent. Ask what the regimen is, ask when the symptoms started, and treat a close temporal link as a reason to reconsider the antiretroviral rather than simply to add a psychotropic on top of it.

- Before co-prescribing, check a maintained interactions resource, because the antiretroviral-psychotropic interactions are individually numerous and complex.

- Expect a boosted regimen to raise, and efavirenz to lower, the level of a shared substrate, and adjust the dose in the correct direction for the regimen in front of you.
- Take a full drug history: a potent inhibitor such as ritonavir can push a co-substrate, prescribed or recreational, into toxicity.
- Obtain a baseline ECG before adding citalopram or escitalopram to QT-prolonging antiretrovirals, and remember the shared effect on the seizure threshold with clozapine.
- Treat new depression, insomnia or suicidal ideation in a patient on efavirenz, rilpivirine or dolutegravir as possibly drug-related, not simply as a reaction to the illness.

In HIV, boosted regimens (ritonavir, cobicistat) raise psychotropic levels while efavirenz lowers them; efavirenz is also the antiretroviral most likely to cause depression, psychosis and suicidal ideation, so avoid it in anyone with psychiatric comorbidity.

Parkinson disease and its neuropsychiatry

7 · Parkinson disease psychosis: features and antipsychotic choice

A Parkinson patient who begins to see people who are not in the room has not acquired a second, independent psychiatric illness. Psychosis in Parkinson disease is a non-motor feature of the disease and of the drugs used to treat it, and it is common enough, and consequential enough, that recognising it and treating it safely is core neuropsychiatry rather than a footnote. The reason the marks concentrate here is a genuine therapeutic trap. The agents that reliably quieten psychosis in a younger patient are dopamine blockers, and dopamine blockade is precisely what the Parkinson brain cannot tolerate. Treat this psychosis the way you would treat schizophrenia and you will worsen the movement disorder you were asked to protect. This section defines **Parkinson disease psychosis**, works through its phenomenology and what drives it, sets out the anatomy that makes the wrong drug dangerous, and then follows the management logic: reduce the offending drug burden, treat any precipitant, and only then reach for a motor-sparing antipsychotic. The narrower and more dangerous problem of neuroleptic sensitivity in dementia with Lewy bodies is a different entity and belongs to the Dementias and neurocognitive disorders notes; it is named and pointed to here, not taught.

7.1 What Parkinson disease psychosis is, and how common it becomes

Parkinson disease psychosis is a non-motor symptom in which a patient with established Parkinson disease develops at least one of illusions, a **false sense of presence**, hallucinations or delusions, present for **at least 1 month**, once other causes have been excluded. That closing clause carries real clinical weight: a first psychotic episode in a Parkinson patient is a diagnosis of exclusion, and an intercurrent delirium, a metabolic disturbance or a newly added drug must be considered before the label is applied. The false sense of presence, the unshakeable feeling that someone is standing just beyond the edge of vision, together with fleeting illusions, is often the earliest and mildest expression and is easily dismissed by patient and family alike.

It is not a rare complication. Over the course of the illness a large proportion of patients are affected, and its importance is prognostic as much as symptomatic. Parkinson disease psychosis is associated with cognitive decline and, through it, with more frequent hospitalisation, heavier caregiver burden, earlier nursing-home placement and increased mortality. It behaves as a hinge point in the trajectory of the disease rather than as an incidental add-on, which is exactly why it deserves to be treated well and treated cautiously in equal measure.

up to 60%	**25-36 mg/day**	**40 mg/day**	**2016**
OF PD PATIENTS AFFECTED OVER THE DISEASE COURSE	MEAN CLOZAPINE DOSE FOR PSYCHOSIS IN PD	PIMAVANSERIN, PIVOTAL PDP TRIAL	PIMAVANSERIN FDA APPROVAL FOR PDP

7.2 The phenomenology: what the hallucinations look like

The characteristic disturbance is visual. Patients commonly experience **visual hallucinations** that take the form of complex, formed visions of people and animals, which fluctuate through the daytime and characteristically worsen at night when lighting is poor and cues are few. The content is frequently benign at first, familiar figures or small animals passing through the room, and the phenomenology tracks a recognisable arc as the disease advances.

Early in the course, and this is the discriminating point, the patient hallucinates while the sensorium is clear and while **retained insight** is preserved: the person knows the vision is not real even as they see it. That preserved insight, when the hallucinations are benign and non-distressing, is what can allow early psychosis to be managed conservatively, though only after an explicit assessment of safety and function, since insight alone does not establish that the patient is not at risk. As the disease progresses the picture darkens. The majority of patients go on to develop vivid hallucinations, disordered thinking and, often, paranoid ideation that tends to centre on the treating physicians and on family members. The loss of insight, rather than the appearance of hallucinations as such, marks the transition to a psychosis that changes what the clinician must do.

It helps to hold the spectrum in mind rather than a single symptom. The minor phenomena, illusions and the sense of a presence at the edge of vision, sit at one pole and are compatible with full insight and independent living; the formed, insight-poor, paranoid hallucinations sit at the other and drive the outcomes that make the syndrome matter. The nocturnal accentuation is itself a clinical clue, because it points to the contribution of impoverished sensory input and disturbed sleep and suggests correctable ground before any drug is changed. Grading the presentation along this axis, and re-grading it at review, is more useful than recording the mere presence or absence of hallucinations.

7.3 The anatomy that makes the treatment dangerous

The whole therapeutic dilemma is anatomical, so it is worth grounding. The motor syndrome of Parkinson disease, chiefly bradykinesia, rigidity and tremor, arises from the loss of dopaminergic neurons in the **substantia nigra pars compacta**. These nigrostriatal neurons degenerate slowly and lose tyrosine hydroxylase, and once approximately 60% of them are gone the pathway can no longer synthesise adequate dopamine and the clinical signs emerge. At post-mortem there is

depigmentation of the substantia nigra, the locus ceruleus and the vagal motor nuclei, and the surviving neurons contain Lewy bodies built around a core of alpha-synuclein, which is why the disease sits among the **synucleinopathy** group.

The pharmacological corollary follows directly. The projection from the nigra terminates in the **dorsal striatum**, and it is dopamine D2 receptor antagonism at that site that a dopamine-blocking antipsychotic produces. In a brain already dopamine-depleted, adding D2 blockade in the dorsal striatum removes what little motor drive remains. This is not an idiosyncratic adverse effect to be watched for; it is the predictable pharmacology of the drug meeting the pathology of the disease, and it is the single fact from which the entire antipsychotic-choice rule is derived.

7.4 What drives the psychosis and what precipitates it

Understanding the correlates changes management, because several of them are modifiable. Psychosis in Parkinson disease correlates most closely with dementia and with the duration and severity of the illness, and it also tracks with the number and dosage of dopaminergic medications and with the visible signs of excessive medication, particularly **dyskinesias**. A patient who is dyskinetic and hallucinating is, in effect, showing you two faces of the same dopaminergic excess. It is worth being precise about causation here: although Parkinson medications often precipitate the psychosis, they cause neither the comorbid depression nor the dementia that so often accompany the disease. The mood and anxiety complications of Parkinson disease, and the impulse control disorders and dopamine dysregulation syndrome that dopaminergic treatment can drive, are addressed separately and are only named here.

Beyond the disease itself, the additional risk factors are advanced age, sleep disturbance and visual impairment, each of which is worth screening for because each is at least partly correctable. The most actionable point of all is that intercurrent illness readily tips a stable patient into psychosis or frank delirium.

GOOD TO REMEMBER

Before reaching for any antipsychotic in a newly hallucinating Parkinson patient, actively look for a precipitant. An intercurrent pneumonia or urinary tract infection, dehydration, or a recently increased dopaminergic dose commonly triggers the psychosis, and correcting it may be all that is required. Uncorrected sensory impairment and disturbed sleep pull in the same direction.

7.5 First moves: rationalise the drug burden and treat the precipitant

Management is best thought of as a sequence, not a single prescribing decision, and most of it happens in the outpatient setting shared between neurology and psychiatry. Admission is reserved for the patient whose psychosis is driven by an intercurrent illness or delirium, or whose agitation and paranoia have become a safety risk, and the emergency presentation is the acutely agitated, frightened patient who cannot be contained at home. The acute target is not the hallucination itself but the driver behind it: treat the precipitating infection or metabolic upset, correct dehydration and sensory deprivation, and reduce the offending drugs before anything is added.

Drug rationalisation follows a deliberate logic rather than a rigid recipe. Because the antiparkinson agents differ in how much motor benefit they buy for the psychiatric cost they carry, the regimen is rationalised individually, withdrawing the least essential and most psychotogenic agents first, typically anticholinergics, then amantadine, MAO-B inhibitors and dopamine agonists, with COMT inhibitors and levodopa reduced last, before an antipsychotic is introduced at all. Levodopa comes down last precisely because it is the least dispensable for motor control. Only when the psychosis persists despite a rationalised regimen and a treated precipitant does the question become which antipsychotic, and by then a substantial fraction of patients no longer need one.

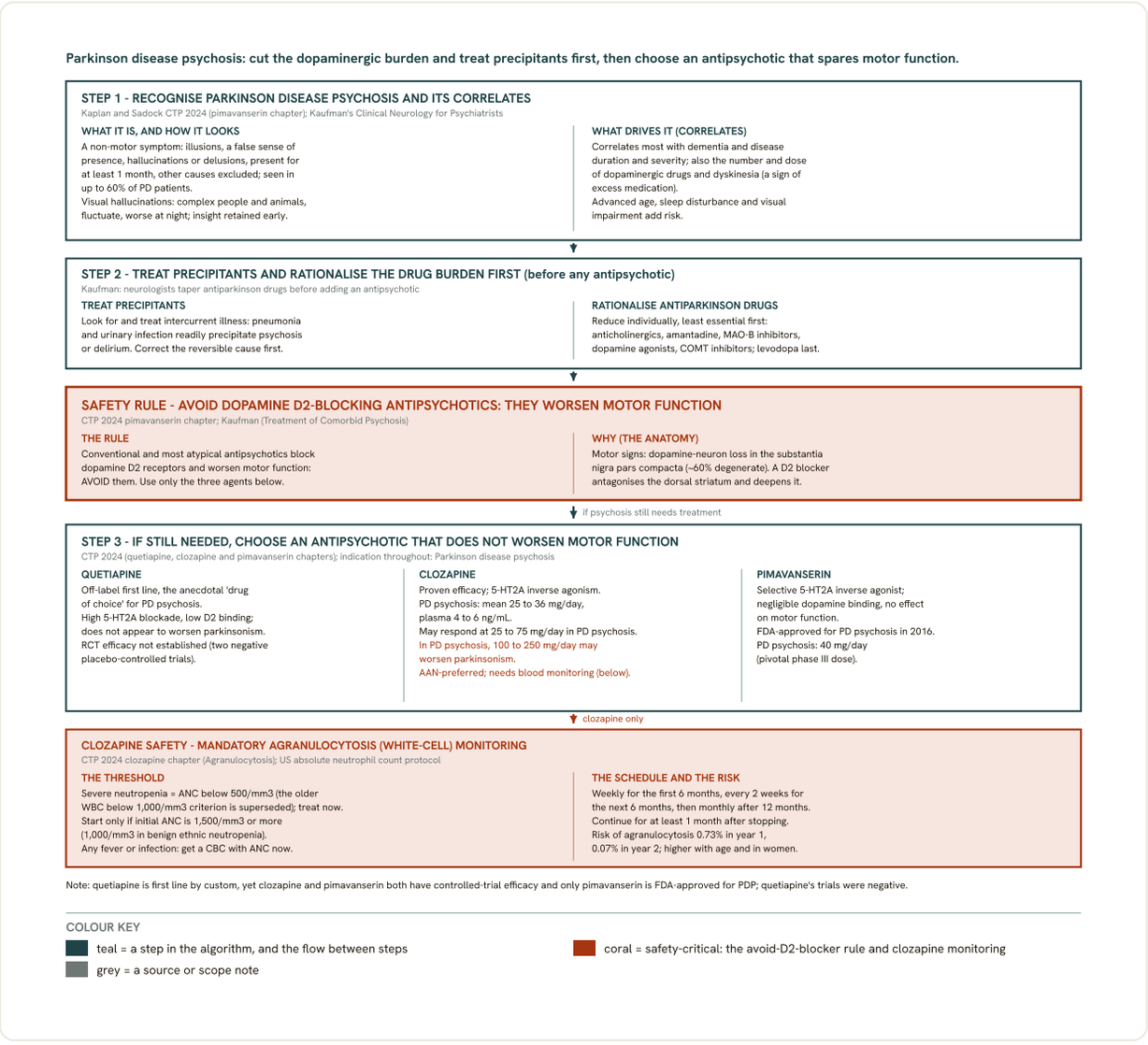


Fig 35.3 **Parkinson disease psychosis: the antipsychotic-choice algorithm.** Because dopaminergic drugs and disease severity drive the psychosis, the path first treats intercurrent precipitants and rationalises the antiparkinson burden, and only then reaches for a drug; the salient rule is that conventional and most atypical D2-blocking antipsychotics worsen motor function through antagonism in the dorsal striatum and are avoided, leaving quetiapine, clozapine with mandatory agranulocytosis monitoring, and the 5-HT2A inverse agonist pimavanserin as the motor-sparing choices. (Kaplan and Sadock 2024; Kaufman's Clinical Neurology for Psychiatrists.)

MNEMONIC

Anticholinergics, Dopamine agonists, Levodopa last

A simplified reminder of the core of an individualised taper before an antipsychotic is added: the least essential agents come down first (**A**nticholinergics, and also amantadine and MAO-B inhibitors), then the **D**opamine agonists, and **L**evodopa is spared till last as the agent the patient can least afford to lose for motor function.

7.6 The antipsychotic-choice rule and its safety boundary

This is the point on which the marks turn, and it is a safety point before it is an examination point. With the exception of low-dose clozapine and low-dose quetiapine, treating Parkinson disease psychosis with drugs that have antipsychotic actions frequently results in intolerable motor impairment, because those drugs act through dopamine D2 receptor antagonism in the dorsal striatum. The instruction that follows is unambiguous: avoid agents that block dopamine receptors, because they exacerbate the parkinsonism, and prefer agents whose antipsychotic action rests on serotonergic rather than dopaminergic blockade. The motor-sparing choices are quetiapine, clozapine and pimavanserin.

The logic of why the safe agents are safe is worth making explicit, because it is what the examiners are really testing. Ordinary antipsychotic effect is bought with dopamine D2 blockade, and in this disease that currency is exactly what the patient cannot spend. The motor-sparing agents instead lean on serotonergic action at the 5-HT2A receptor, which modulates the aberrant salience and perceptual disturbance of psychosis at a cortical level while leaving the already-fragile nigrostriatal dopamine transmission largely untouched. That dissociation, an antipsychotic action that does not depend on striatal dopamine antagonism, is the single pharmacological escape route the class exploits, and it is why a drug can quieten hallucinations without stiffening the patient. The corollary is that the more a candidate agent behaves like a classical D2 blocker, the less place it has here.

RULE **Do not use dopamine D2-blocking antipsychotics in Parkinson disease psychosis.** Conventional agents and most atypicals worsen the movement disorder through D2 antagonism in the dorsal striatum. The three motor-sparing options are quetiapine, clozapine and pimavanserin: pimavanserin is essentially non-dopaminergic, while low-dose clozapine and quetiapine retain some dopamine D2 antagonism but, at the low doses and strong serotonergic action used here, impose far less nigrostriatal motor burden.

AGENT	RECEPTOR BASIS	EFFECT ON PARKINSONISM	EVIDENCE AND REGULATORY STANDING
Quetiapine	High 5-HT2A blockade, relatively low D2 binding	Does not appear to worsen parkinsonism	Off-label first-line by convention; two placebo-controlled trials failed to establish efficacy
Clozapine	Serotonergic action; effective at low dose	Effective without worsening motor function at low dose	Established controlled-trial efficacy and tolerability; needs white-cell monitoring
Pimavanserin	Selective 5-HT2A inverse agonist, negligible dopamine binding	No effect on motor function	FDA-approved specifically for PD psychosis

The boundary of this rule must be drawn deliberately. What is described here is the treatment of Parkinson disease psychosis, which commonly coexists with Parkinson disease dementia; where it does, the antipsychotic risk-benefit balance shifts and the increased-mortality caution that applies to antipsychotics in dementia comes into play. The distinct and more hazardous phenomenon of neuroleptic sensitivity in dementia with Lewy bodies, and the antipsychotic-choice algorithm that follows from it, are owned by the Dementias and neurocognitive disorders notes and are not reproduced here. The two are easily confused and must not be run together.

PITFALL

Reaching for haloperidol or another high-potency typical antipsychotic when a Parkinson patient becomes acutely psychotic in a general ward. It is the intuitive move for agitation, and in this population it predictably precipitates severe motor deterioration through striatal D2 blockade. The safe reflex is the opposite of the general-psychiatry one.

In Parkinson disease psychosis, first rationalise the dopaminergic and anticholinergic burden and treat any precipitant; if an antipsychotic is still needed, choose a motor-sparing agent and never a dopamine D2 blocker.

7.7 Clozapine: low-dose efficacy at a haematological price

Clozapine is the reference agent, the one against which the others are measured, and its behaviour in Parkinson disease is instructive about the whole class. Used to treat the psychotic symptoms that are secondary to the dopaminergic agents themselves, patients with Parkinson disease psychosis may respond to relatively low dosages, in the region of 25 to 75 mg a day; higher dosages of **100 to 250 mg a day** may begin to exacerbate the parkinsonian symptoms. The efficacious range is narrow and low. Its ability to treat the psychosis at mean daily doses of 25 to 36 mg and at minute plasma levels of 4 to 6 ng/mL was historically important, because it pointed to 5-HT2A inverse agonism rather than dopamine blockade as the basis of the antipsychotic effect. A report from the American Academy of Neurology recommends clozapine as a preferred agent for psychosis in Parkinson disease.

The price is haematological and is the reason clozapine is not simply first-line for everyone. **Agranulocytosis**, defined by current monitoring as an absolute neutrophil count below 500 cells per mm3 (the older white-cell-count threshold of 1,000 cells per mm3 has been superseded by the neutrophil criterion), is a potentially fatal complication whose risk rises with age and is higher in women. The risk is front-loaded: it is **0.73%** during the first year of treatment and falls to 0.07% in the second year. Baseline and ongoing neutrophil-count monitoring is obtained according to current prescribing guidance, and although the mandatory United States clozapine registration requirement was withdrawn in 2025, any fever or sign of infection remains an immediate indication for a complete blood count with absolute neutrophil count.

- Initial absolute neutrophil count must be at least 1,500 per mm3, or at least 1,000 per mm3 in benign ethnic neutropenia, before the first dose.
- Count weekly for the first six months of treatment.
- Count every two weeks for the second six months.
- Count monthly thereafter, once the patient has passed twelve months.
- Continue monitoring for as long as the drug is taken and for at least one month after it is stopped.

7.8 Quetiapine, pimavanserin, and the trap of the single best drug

Quetiapine is, anecdotally, the antipsychotic drug of choice in practice for psychosis in Parkinson disease. It does not appear to worsen parkinsonism, and because of its high 5-HT2A blockade and relatively low D2 binding it has been used off-label as a first-line treatment. The awkward fact sitting underneath that popularity is that two placebo-controlled trials failed to show efficacy for quetiapine in treating the psychotic symptoms associated with the dopaminergic treatment of the disease, even though one study comparing it directly with clozapine found comparable levels of efficacy. It is convenient and well tolerated; its evidence base is weaker than its reputation.

Pimavanserin occupies a different position again. It is a selective **5-HT2A inverse agonist** and antagonist, acting at 5-HT2A and 5-HT2C receptors, and it is unique among drugs with antipsychotic actions in having negligible binding at dopamine receptors and no effect on motor function. That property is what took it to regulatory approval for Parkinson disease psychosis. The pivotal phase III trial, reported by Cummings and colleagues in 2014, used a uniform pimavanserin dose of 40 mg daily against placebo, begun after a 2-week lead-in, in 199 patients with Parkinson disease psychosis, and demonstrated significant improvement on the Scale for the Assessment of Positive Symptoms adapted for Parkinson disease compared with placebo. By the end of the sixth week, 37.2% of pimavanserin-treated and 27.8% of placebo-treated patients had responded, defined as a **50%** reduction on that scale.

TRAP **There is no single "best drug for Parkinson disease psychosis"; the right answer depends on which bar the question sets.** Quetiapine is the off-label drug of choice in practice, though its controlled trials were negative. Clozapine has the longest-established controlled-trial efficacy and tolerability, at the price of haematological monitoring. Pimavanserin also has positive controlled-trial efficacy and is the only agent approved by the FDA specifically for the indication. Preferred-in-practice, trial-proven and regulator-approved are different standards, and a stem that does not say which one it means is testing whether you conflate them.

8 · Depression and anxiety in Parkinson disease

Mood is not a bystander in Parkinson disease; depression is one of its defining non-motor features and, for the patient, often more disabling than the tremor. Parkinson disease carries a non-motor burden that is frequently heavier than its movement disorder, and depression sits at the centre of that burden. The marks cluster here for a reason that is clinical before it is academic: this depression is common, easy to overlook against a background of slowness and flat affect, and treated badly if the reflexes carried over from primary mood disorder are applied unchanged. Where the depression arises as a direct physiological consequence of the neurodegenerative process, the presentation is captured by the DSM-5 category of **Depressive Disorder Due to Another Medical Condition**; the broader nosology and staged pharmacotherapy of a primary depressive illness belong to the Mood disorders: pharmacotherapy notes and are not reproduced here. This section works through how common the depression is and why the figure is slippery, the recognition problem created by symptom overlap, the risk factors and the akinetic phenotype that carries them, the effect on cognition and quality of life, the companion problem of anxiety, the suicide risk that must be actively assessed, and finally a management logic that begins with the antiparkinson regimen rather than an antidepressant.

8.1 How common it is, and why the number refuses to settle

Reports of the prevalence of depression in Parkinson disease vary widely, because studies differ in how they define and ascertain a depressive disorder against the somatic background of the illness. That variability is not a footnote; it is the reason no single canonical figure can be quoted with confidence. By any measure, however, the prevalence is substantial. Clean prose sources commit only to a floor: studies typically report that **at least 30%** of patients with Parkinson disease manifest depression. Treat that as a lower bound rather than a headline. Part of the disagreement is methodological: instruments that count somatic items such as fatigue, slowing, and sleep disturbance tend to over-estimate depression in a disease that generates those signs for non-mood reasons, while instruments that discount the somatic items risk under-counting, and different studies sit at different points along that spectrum. The true proportion in any given clinic rises or falls with the diagnostic threshold applied and with whether minor and subsyndromal presentations are counted, which is exactly why apparently authoritative higher percentages should be held loosely unless the criteria behind them are stated. The clinically useful takeaway is not a precise percentage but the expectation itself: in any Parkinson clinic, a large minority of patients are depressed, and the clinician who is not actively looking will miss a treatable illness in a great many of them.

Akinesia	Assess risk	ECT
THE MOTOR SIGN LINKED TO DEPRESSION, NOT TREMOR	PD CARRIES INCREASED SUICIDAL IDEATION AND BEHAVIOUR	EFFECTIVE FOR BOTH MOOD AND MOTOR SYMPTOMS

8.2 The recognition problem: depression hiding inside the motor disorder

The single greatest obstacle to diagnosis is that the somatic vocabulary of depression and the phenotype of Parkinson disease speak over one another. Psychomotor slowing, reduced facial expression, a soft monotonous voice, disturbed sleep, fatigue, and reduced appetite are read by the somatic criteria of a depressive episode as evidence of depression, yet every one of them is also a face of the movement disorder itself. The masked, bradykinetic, hypophonic patient can look depressed while being euthymic, and the genuinely depressed patient can be dismissed as merely parkinsonian. Because the two conditions borrow each other's signs, the diagnosis has to lean on the cognitive and affective content that the motor disorder does not touch: pervasive low mood, anhedonia, hopelessness, excessive guilt, and a loss of interest that is out of proportion to the physical limitation.

A related discrimination is worth making explicit, because it changes treatment. **Apathy**, a flattening of motivation and goal-directed behaviour, occurs in Parkinson disease and is easily read as depression, but it can exist without dysphoria, guilt, or sadness, and it responds poorly to antidepressants that would help a true depressive episode. Separating a depressed patient from an apathetic one, and both from the involuntary flat affect of the disease, is a bedside skill that no rating scale substitutes for.

> **PITFALL**
>
> Attributing a Parkinson patient's slowness, poverty of expression, and disturbed sleep entirely to the movement disorder, and so never asking about mood at all. The overlap runs both ways: the same reflex also over-diagnoses depression in a patient whose flat, hypomimic presentation is purely motor. The corrective is to weigh the cognitive and affective content, low mood, anhedonia, guilt, hopelessness, rather than the somatic signs the two conditions share.

8.3 Risk factors and the akinetic phenotype

The risk factors are worth knowing precisely, because one of them is a classic examination discriminator. The most powerful predictors of depression in Parkinson disease cluster around illness severity and cognitive vulnerability rather than around tremor. Depression tracks the akinetic-rigid presentation, and not the tremor-dominant one, so that **akinesia** is a risk factor while tremor is not. That dissociation is the point examiners reach for, and it fits the wider pattern that the features signalling more diffuse and advanced disease are the ones that carry the mood risk.

- A previous history of depression, the strongest single predictor.
- Cognitive impairment.
- Akinesia, the akinetic-rigid phenotype, but not tremor.
- A young age at onset.

- A longer duration of illness.

Read together, these say that depression is more likely in the patient whose disease is cognitively involved, akinetic, early-onset, and long-standing. None of this is incidental to management: it tells the clinician which patients to screen hardest, and it warns that the appearance of depression may itself be a marker that the illness has moved into a more diffuse phase.

8.4 Why it matters: cognition, sleep, disability, and quality of life

Depression in Parkinson disease is not a parallel misfortune that leaves the neurological course untouched; it actively worsens it. When it occurs, the depression is associated with faster cognitive decline, disturbed sleep, and greater physical disability, so that a depressed Parkinson patient is functionally worse than the movement disorder alone would predict. The mechanism is partly a vicious loop: disrupted sleep worsens daytime motor performance and fatigue, disability erodes the very activity that ordinarily protects mood, and each increment of cognitive loss strips away some of the coping the patient had in reserve, so the depression and the disease amplify one another rather than merely coexisting. The relationship with cognition is bidirectional in practice: cognitive impairment predisposes to depression, and the depression, once present, predicts greater subsequent decline. The dementia of Parkinson disease itself, and its distinction from dementia with Lewy bodies and the one-year rule that separates them, are taught in this chapter's account of Parkinson disease dementia and in the Dementias and neurocognitive disorders notes; here it is enough to register that depression and cognitive deterioration pull each other downward.

The most striking single fact about its impact concerns quality of life. Of all the non-motor symptoms of Parkinson disease, depression is the one that correlates most closely with poor quality of life. That is a stronger claim than it first appears: it places mood, not the visible motor handicap and not the other non-motor complaints, at the head of what determines how a patient experiences the illness. It is also the strongest argument for treating the depression aggressively, because the lever it offers on overall wellbeing is larger than any other non-motor target.

8.5 Anxiety, the companion syndrome

Anxiety commonly travels with the depression, though it may also arise independently or fluctuate with the dopaminergic cycle. Where it accompanies the depression, the **anxiety** may present as another comorbidity in its own right, so that the two are often best thought of as a coupled disturbance rather than as entirely separate diagnoses, even though the anxiety can also stand on its own. Clinically the anxiety takes familiar forms, generalised apprehension, panic, and phobic avoidance, and in many patients it is at least as disabling as the low mood that drives it. It is worth eliciting specifically, because patients volunteer motor complaints far more readily than emotional ones, and an anxiety that is dismissed as understandable worry about a progressive illness is an anxiety that goes untreated.

Two practical points follow. First, because the anxiety is so often yoked to the depression, treating the depressive disorder frequently eases the anxiety alongside it, and anxiety that persists after the mood has lifted deserves its own attention. Second, the clinician should be alert

to anxiety that fluctuates with the patient's motor state through the day, since apprehension that rises and falls with the dopaminergic cycle points toward the timing of medication rather than toward a free-standing anxiety disorder. Where the anxiety is disabling in its own right, it is managed on the same principles as anxiety elsewhere, with the standing caveat that this elderly and frail population tolerates anticholinergic and sedative burden poorly, so agents and doses are chosen with that vulnerability in mind. The precise prevalence and subtype distribution of anxiety in Parkinson disease are not settled by the sources drawn on here, and the honest position is to name anxiety as a frequent, depression-linked comorbidity and to treat it on its clinical merits.

8.6 The suicide question: assess the risk, do not be reassured

Older teaching held that, although a chronic, progressive, disabling illness complicated by depression seems bound to carry a high suicide risk, earlier studies suggested Parkinson disease did not raise it, and that reassuring line was widely taught. Contemporary pooled evidence has overturned it: Parkinson disease is associated with increased suicidal ideation, suicidal behaviour and suicide mortality, and depression remains an important risk factor even though the absolute risk varies between studies. The practical consequence is the opposite of complacency: every patient, and especially every depressed patient, is assessed for suicidal ideation as a matter of course, with particular vigilance around a recent diagnosis, functional decline and changes in treatment.

One specific signal deserves to be held apart, because it is a different construct. Suicidality emerging in the context of deep brain stimulation is a recognised concern with its own literature, and it is addressed with that procedure in this chapter rather than folded into the natural history described here. Keeping the two apart, the raised baseline risk of the disease itself against the specific post-stimulation signal, is what allows the clinician to assess and counsel families accurately without either missing the day-to-day risk or overlooking the perioperative one.

TRAP **Relying on the older teaching that Parkinson disease does not raise the suicide rate.** That reassurance is outdated: contemporary evidence links Parkinson disease with increased suicidal ideation, behaviour and mortality, so a stem that offers "no increased suicide risk" as the expected answer is testing an obsolete fact. Assess suicide risk routinely, and remember that deep brain stimulation carries its own additional, separately recognised suicidality signal.

8.7 Treatment begins with the antiparkinson regimen, not the antidepressant

The first therapeutic move in Parkinson depression is counter-intuitive to a psychiatrist and it is the principle worth carrying away. Because the antiparkinson medicines can themselves improve mood, the antiparkinson regimen should be optimised before an antidepressant is added, so that some patients need no antidepressant once their dopaminergic therapy is adequate. This is not merely a sequencing nicety; it reflects that a component of the low mood is bound up with the state of dopaminergic transmission, and correcting the motor treatment can lift the mood as a by-product.

That dopaminergic logic extends to a specific and examinable agent. **Pramipexole**, a dopamine agonist used for both Parkinson disease and restless legs syndrome, has shown some promise in relieving the depression associated with Parkinson disease, and in a head-to-head comparison it proved superior to sertraline (Barone and colleagues, **2006**; the promise had been signalled earlier by Lemke and colleagues, 2006). The importance of this is conceptual as much as practical: a dopaminergic drug outperforming a standard serotonergic antidepressant reinforces the message that mood in this disease is partly a dopaminergic problem, and that optimising dopaminergic therapy is treatment for the depression and not only for the movement.

RULE **Optimise the antiparkinson regimen before prescribing an antidepressant.** The Parkinson medicines can improve mood in their own right, so an adequate dopaminergic regimen may lift the depression without a second drug, and a dopamine agonist has outperformed an SSRI for this indication. Only once the motor treatment is optimised does the question of a dedicated antidepressant properly arise.

8.8 Antidepressant choice, the serotonin-syndrome caveat, and ECT

When a dedicated antidepressant is needed, the historical and the modern evidence pull in different directions, and both matter. Earlier studies, corroborated in Tasman Psychiatry, found **tricyclic antidepressants** to be more effective than SSRIs for Parkinson-associated depression (Menza and colleagues, 2009). The difficulty is that these patients are generally elderly and therefore especially susceptible to the anticholinergic adverse effects of the tricyclics, and antidepressants as a class carry a greater risk of extrapyramidal side effects in this population. More recent research has demonstrated the efficacy of SSRIs here, which, set against the tolerability problem of the tricyclics in an elderly cohort, is why an SSRI is now a reasonable and often preferred first choice despite the older efficacy signal.

CLASS	EFFICACY SIGNAL	TOLERABILITY IN PARKINSON DISEASE
Tricyclic antidepressants	Older studies found them more effective than SSRIs, corroborated by Menza and colleagues	Elderly patients are susceptible to anticholinergic adverse effects; antidepressants also raise the risk of extrapyramidal side effects
SSRIs	More recent research has demonstrated efficacy in this population	Better tolerated in the elderly; the pragmatic first choice for many

A specific interaction generates more anxiety than it deserves. Prescribing an SSRI together with a **monoamine oxidase inhibitor** used in Parkinson disease, such as selegiline or rasagiline, can in theory precipitate **serotonin syndrome**. In practice the actual incidence is very low, because at the doses used to treat Parkinson disease selegiline selectively inhibits monoamine oxidase-B and largely spares the monoamine oxidase-A activity through which a dangerous serotonergic surge would occur. The clinical corollary is that the theoretical interaction should not by itself deprive a depressed Parkinson patient of an effective antidepressant, provided the usual vigilance for serotonergic toxicity is maintained.

GOOD TO REMEMBER

Do not reflexively withhold an SSRI from a depressed Parkinson patient merely because they take selegiline or rasagiline. At the low doses used in Parkinson disease the MAO-B selectivity keeps the risk of serotonin syndrome very low, so the combination is usually manageable with ordinary monitoring rather than an absolute contraindication.

The most robust option of all is one psychiatrists already know well. **Electroconvulsive therapy** is effective and safe for depression in Parkinson disease, and it has the notable bonus of temporarily improving rigidity and bradykinesia, an effect long recognised in the movement disorder alongside its antidepressant action. In an elderly, physically frail population in whom drug tolerability is the recurring constraint, a treatment that sidesteps the anticholinergic and extrapyramidal liabilities of the oral agents while acting on both mood and movement has an obvious and often under-used place. It is the treatment to remember for the severely or refractorily depressed Parkinson patient, precisely because it addresses mood and motor state together.

Treat the parkinsonism first, because dopaminergic therapy can lift mood on its own; if depression persists, favour an SSRI over the poorly tolerated tricyclic, do not fear the selegiline interaction at Parkinson doses, and reach for ECT when the depression is severe, remembering that the disease itself carries an increased suicide risk that must be actively assessed.

9 · Impulse control disorders and the dopamine dysregulation syndrome in Parkinson disease

The most damaging psychiatric complications of Parkinson disease are often the ones the treating team never thinks to ask about. A patient whose tremor and rigidity have been beautifully controlled may quietly gamble away the family savings, pursue sexual encounters wholly out of character, fill the house with things bought and never used, or spend hours a night dismantling and rebuilding the same small contraption. None of this is a coincidental second illness. Each is a behavioural complication of the dopaminergic drugs that restore movement, which is what makes the group at once dangerous, easy to miss and, encouragingly, often reversible. This section teaches three overlapping medication-driven syndromes: the **impulse control disorders**, the repetitive purposeless behaviour called punding, and the compulsive overuse of medication known as dopamine dysregulation syndrome. The mood and anxiety complications of Parkinson disease, and the psychiatric effects of deep brain stimulation in its own right, are close relatives that are addressed separately in these notes and are only named here.

9.1 The spectrum of impulse control disorders in Parkinson disease

An **impulse control disorder** in this setting is a failure to resist a drive towards a rewarding behaviour that has become excessive, repetitive and harmful. They are among the more dramatic

psychiatric complications of the disease, and they cluster into **four** cardinal appetitive behaviours that a candidate should be able to recite without hesitation:

- Compulsive or pathological gambling, from cards and casinos to online betting.
- Compulsive sexual behaviour, ranging from insistent demands on a partner to the pursuit of pornography or paid sex.
- Compulsive shopping, with impulsive and often ruinous buying.
- Compulsive or binge eating, frequently nocturnal and unrelated to hunger.

The behaviours are not rare curiosities. Taken together, one or more of them affects about **14%** of Parkinson disease patients in cross-sectional surveys, and a single patient may carry more than one at a time. What unites them is their appetitive, reward-seeking quality: the patient is driven towards a source of pleasure or relief and cannot moderate the pursuit, so the damage falls on finances, marriages and reputations long before it reaches the clinic. Recognising the pattern as a coherent syndrome, rather than as four unrelated misfortunes, is the first step towards treating it.

14%	four	3
OF PD PATIENTS DEVELOP ONE OR MORE IMPULSE CONTROL DISORDER	CORE BEHAVIOURS: GAMBLING, SEX, SHOPPING, EATING	FURTHER RISK FACTORS BEYOND THE DOPAMINE AGONIST

MNEMONIC

Bet, Bed, Buy, Binge

The four cardinal impulse control behaviours of Parkinson disease map cleanly onto four appetites: **Bet** for pathological gambling, **Bed** for compulsive sexual behaviour, **Buy** for compulsive shopping, and **Binge** for compulsive eating. All four are reward-driven behaviours, which is the feature that separates them from the aimless repetition of punding.

9.2 Why the dopaminergic drugs drive the behaviour

The mechanism is the reason these behaviours belong to neuropsychiatry rather than to primary addiction medicine. Parkinson disease depletes dopamine most severely in the motor circuits, while the reward-related dopaminergic projections are relatively spared until later, so a dose calibrated to rescue movement inevitably over-drives a reward system that was never as depleted to begin with. The replacement drugs flood the whole dopaminergic system, including the mesolimbic reward pathway that assigns value and salience to appetitive cues. Where the motor system is grateful for the extra transmitter, the reward system is over-stimulated, and behaviours that a healthy brain would weigh and abandon acquire an urgency the patient cannot override. The clinical fingerprint of this is that the offending drug and the disease are pulling in different directions in the same brain at the same moment, so the very act of dosing for good motor control tips a susceptible patient towards the behavioural complication.

The single most important fact for the examination follows directly from this. Treatment with a **dopamine agonist** is the most powerful risk factor for impulse control disorders in Parkinson disease, more so than the total dopaminergic load or levodopa alone. Agonists deliver a smoother,

more continuous stimulation of reward circuitry than the shorter-acting replacement of levodopa, and it is that sustained drive on the reward pathway that appears to matter. The corollary is clinically liberating: because the behaviour is pharmacological, it can usually be undone pharmacologically.

RULE **The impulse control disorders of Parkinson disease are iatrogenic and dopaminergic.** The dopamine agonist is the most powerful risk factor, and the same drug is therefore the treatment lever: reducing the agonist usually eliminates the behaviour, while deep brain stimulation, where appropriate, may help only indirectly by allowing the dopaminergic dose to be lowered. A behaviour you can switch off by adjusting a prescription is not a coincidental character flaw.

9.3 The risk profile: who develops an impulse control disorder

Not every patient exposed to a dopamine agonist develops an impulse control disorder, and the additional risk factors sketch a recognisable profile that is worth eliciting before and during agonist treatment. Beyond the agonist itself, the recognised associations are being unmarried, cigarette smoking, and a personal or family history of gambling. Each of these is easy to ask about and easy to record, and together they let the clinician flag the higher-risk patient before a drug is started rather than after the money has gone.

Two of these deserve a moment's thought because they point at the same underlying vulnerability. A personal or family history of gambling suggests a pre-existing sensitivity of the reward system, onto which the agonist then acts; cigarette smoking is itself a nicotine-reward behaviour and a marker of that same appetitive temperament. The practical message is not that these patients cannot receive agonists, but that the drug should be started with eyes open, with the risk named to the patient and the family, and with a plan to review the behaviour actively at each visit rather than waiting for a crisis to declare itself.

9.4 Recognition: the syndrome hides, so you must ask

The central clinical difficulty is that impulse control disorders are concealed. Gambling and sexual behaviour in particular carry shame, and the behaviour is frequently ego-syntonic, so the patient does not experience it as a symptom to report. The diagnosis is therefore made far more often on collateral history, when a spouse describes vanished savings, a secret credit card or a marriage under strain, than on spontaneous disclosure in the consulting room. A clinician who waits to be told will systematically miss the syndrome, and by the time the harm is loud enough to surface unprompted, the financial and relational damage is frequently irreversible. That asymmetry, a silent early phase followed by a catastrophic disclosure, is exactly why the syndrome rewards a screening habit rather than a reactive one.

The remedy is a low threshold and a direct question. Every patient on dopaminergic treatment, and especially every patient on a dopamine agonist, should be asked specifically and without euphemism about gambling, sexual behaviour, spending and eating, at the point of starting the drug and at every subsequent review, and the same questions should be put to the person who knows them best. A validated screening questionnaire for these behaviours in Parkinson disease

exists and can structure the enquiry, but the instrument is only as good as the willingness to raise the topic in the first place. The absence of a complaint is not the absence of the disorder.

GOOD TO REMEMBER

Ask about the four behaviours directly, and ask the family too. Because impulse control disorders are ego-syntonic and shameful, the single most useful move on a Monday morning is a routine, non-judgemental enquiry into gambling, sexual behaviour, spending and eating at every dopaminergic review, backed by collateral history. Screening tools help, but only after you have decided to ask.

9.5 Punding: repetition without reward

A distinct medication-induced complication is **punding**, defined as mindless, repetitive, purposeless behaviour. It is not appetitive and it is not pleasurable, which is precisely what separates it from the impulse control disorders. The classic vignettes are worth carrying: a patient who spends hours incessantly arranging the peas on a plate into small piles, who dismantles small constructions only to rebuild them, who opens and shuts a door over and over, or who folds and unfolds a newspaper without ever reading it. The acts are stereotyped, absorbing and utterly without product.

Three features define the syndrome and are examined together. Punding captures the patient's entire attention, displaces normal daily activities, and does not seem to yield any pleasure or excitement. That last point is the discriminator: the gambler is chasing a reward, but the punder is simply trapped in a loop. Related medication-driven behaviours sit on the same spectrum: **hobbyism**, which is repetitive activity pursued at a higher and more complex level than punding, and **hoarding**. The same aimless, stereotyped picture is seen outside Parkinson disease in autism and in amphetamine intoxication, a parallel that points squarely at dopaminergic and stimulant overactivity as the shared substrate.

COMPLICATION	CORE PHENOMENOLOGY	USUAL DRUG DRIVER	PLEASURE OR REWARD
Impulse control disorders	Gambling, sexual behaviour, shopping, eating	Dopamine agonist	Reward-seeking and appetitive
Punding	Aimless, stereotyped, purposeless acts	Dopaminergic medication	None; no pleasure or excitement
Hobbyism and hoarding	Higher-level repetition; accumulation	Dopaminergic medication	As for punding
Dopamine dysregulation syndrome	Compulsive overuse of medication	Levodopa	Craving, addiction-like

9.6 Dopamine dysregulation syndrome: addiction to the medication

The third syndrome shifts the compulsion from a behaviour to the drug itself. In **dopamine dysregulation syndrome**, once described as **hedonistic homeostatic dysregulation**, some Parkinson patients begin to overmedicate themselves. They express much greater concern for

their medication, usually levodopa, than their symptoms warrant, and describe their requirements in the language of obsession or addiction rather than of symptom relief. The medication has stopped being a means to move and has become an end in itself.

It is most useful to file this as a substance-addiction phenotype that happens to involve a prescribed antiparkinson drug. The patient escalates the dose beyond motor need, resists reduction, and hoards or hides supplies, and the behaviour tracks the short-acting, quickly rewarding forms of dopaminergic replacement rather than the smoother agonists. The three syndromes are not mutually exclusive, and a single patient can gamble, pund and overmedicate at once, because all three are expressions of the same dopaminergic overshoot read out through different circuits; recognising one should prompt an active search for the others. That distinction is the crux of the topic and the crux of the examination: the impulse control disorders are driven above all by the dopamine agonist, whereas dopamine dysregulation syndrome is a disorder of levodopa overuse. Two dopaminergic syndromes, two different culprits, two different management levers.

TRAP **Blaming the gambling on levodopa and the levodopa craving on the agonist.** Candidates lump all the dopaminergic behavioural complications together and attribute them to a single drug. The discriminator is precise: the impulse control disorders have the dopamine agonist as their most powerful driver, while dopamine dysregulation syndrome is the compulsive overuse of levodopa. Match the syndrome to the culprit and the management writes itself.

9.7 The withdrawal state and the danger of an abrupt taper

Because dopamine dysregulation syndrome is an addiction, it behaves like one when the supply is cut. Rapidly tapering or abruptly stopping dopaminergic medicines can throw the patient into a withdrawal state, with cravings, anxiety and drug-seeking behaviour, akin to an amphetamine user deprived of stimulants. This is not a psychological reluctance to lose a helpful drug; it is a recognisable pharmacological withdrawal, and it can be severe enough to defeat a well-intentioned attempt to bring the dose down.

The clinical consequence is that the drug cannot simply be withdrawn on the ward the way an offending agent might be stopped elsewhere. Reduction has to be gradual and negotiated, the withdrawal symptoms anticipated and managed, and the patient supported through a state that will otherwise drive them straight back to overuse. It is exactly the discipline of tapering any addictive agent, applied to a medication the patient also genuinely needs for movement, which is what makes dopamine dysregulation syndrome one of the harder problems in the whole field to manage well.

PITFALL

Yanking the dopaminergic dose down quickly once dopamine dysregulation syndrome is recognised, in the belief that stopping the misused drug is the obvious fix. An abrupt taper precipitates a withdrawal state of craving, anxiety and drug-seeking that both distresses the patient and undermines the reduction. The correct move is a slow, supported taper, not a sudden stop.

9.8 Management: working the dopaminergic trade-off

Management turns on a single tension that a figure can make vivid. Care is almost always delivered in the shared outpatient setting between neurology and psychiatry, with admission reserved for the rare patient whose behaviour has become an acute safety or financial catastrophe. The acute focus is to protect the patient and family from harm, chiefly by installing financial and relational safeguards and enlisting the family, while the longer-term focus is to bring the behaviour itself under control. In practice that acute containment can mean handing control of accounts and cards to a trusted relative, restricting access to online betting and shopping, and making the family a partner in monitoring, so that the behaviour cannot quietly resume between reviews while the slower work of adjusting the drug regimen proceeds. The definitive lever is pharmacological: reducing the dopamine agonist usually eliminates the impulse control behaviour. Deep brain stimulation, where it is appropriate, helps largely by allowing the dopaminergic drug burden to be lowered rather than by treating the behaviour directly, and it can occasionally leave impulsivity unchanged or worse; its own direct psychiatric effects are a separate matter taken up elsewhere in these notes.

The catch, and the reason this is a judgement rather than a formula, is that the drug you must reduce to stop the behaviour is the same drug that is controlling the movement. Every reduction that quietens the reward system risks re-emergent tremor, rigidity and slowness, so treatment is a deliberate weighing of motor benefit on one side against behavioural cost on the other, tuned to what each individual patient can tolerate.

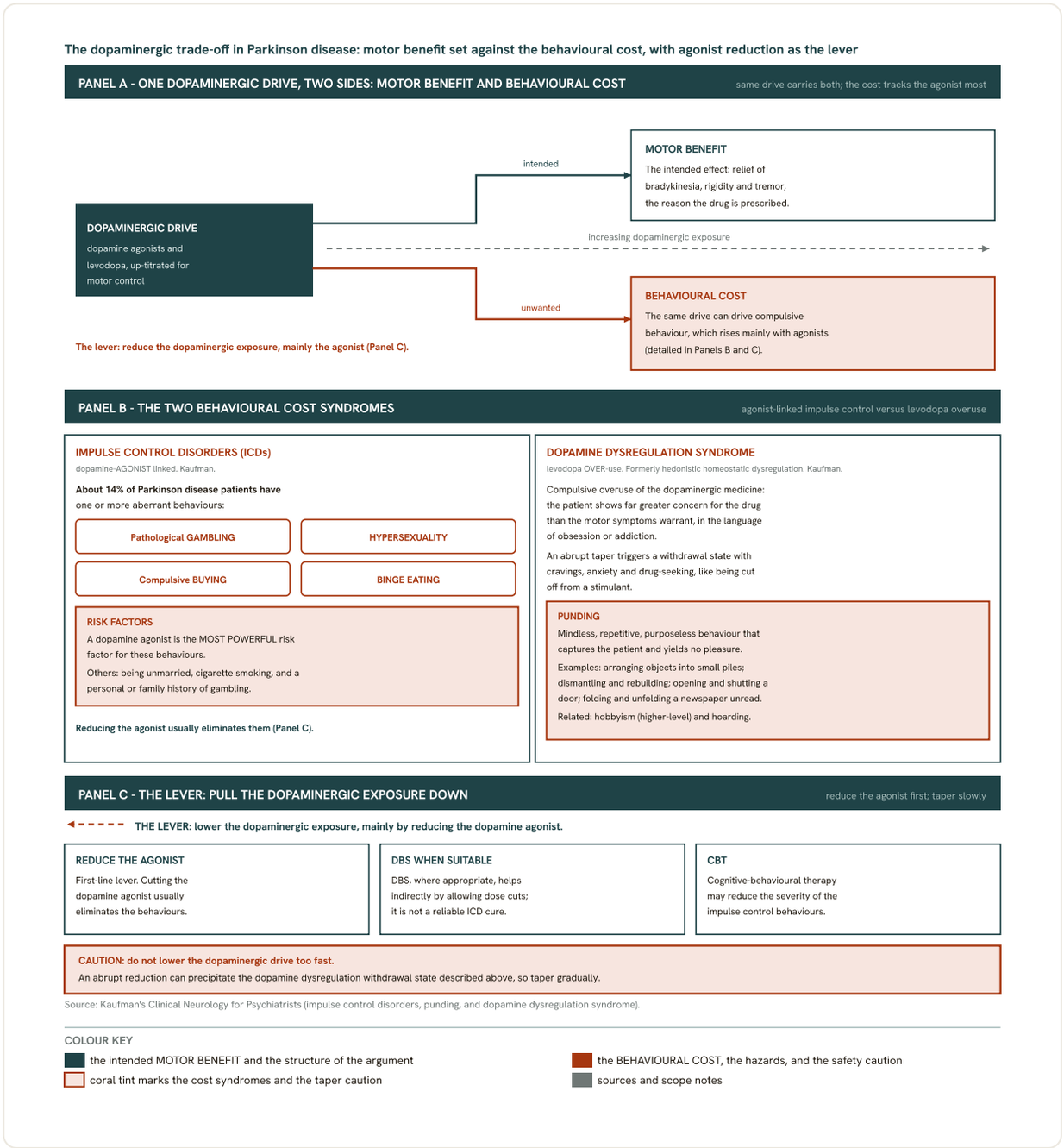


Fig 35.4 The dopaminergic trade-off in Parkinson disease. The same dopaminergic drive that relieves bradykinesia, rigidity and tremor also carries a behavioural cost: dopamine-agonist-linked impulse control disorders (pathological gambling, hypersexuality, compulsive buying and binge eating, affecting about 14% of patients) and the dopamine dysregulation syndrome of compulsive levodopa overuse, alongside the distinct repetitive behaviour of punding. The management lever is to lower the dopaminergic exposure, chiefly by reducing the agonist, supported by deep brain stimulation where appropriate and cognitive-behavioural therapy, while tapering slowly to avoid a withdrawal state. (Kaufman's Clinical Neurology for Psychiatrists.)

Alongside the drug adjustment, cognitive-behavioural therapy may reduce the severity of the impulse control behaviours and is a reasonable addition where it is available; the method itself belongs to the Psychotherapies, clinical assessment, MSE and nosology notes. Because the allowed evidence base here names no specific guideline, the safest counsel is to work from the reasoning above, screen actively, reduce the agonist first, and check current movement-disorder guidance for the detailed thresholds. The management of dopamine dysregulation syndrome differs in one crucial respect already made: its levodopa overuse must be tapered slowly to avoid

the withdrawal state, not reduced at the pace one might use for an agonist-driven impulse control disorder.

> The dopamine agonist is the most powerful driver of impulse control disorders in Parkinson disease, and reducing it or performing deep brain stimulation usually resolves them; dopamine dysregulation syndrome is instead the compulsive overuse of levodopa, and must be tapered slowly to avoid a withdrawal state.

10 · Cognitive impairment and Parkinson disease dementia

Cognitive decline is not an incidental extra in Parkinson disease; for a large share of patients it is where the illness eventually arrives. The motor picture of tremor, rigidity and bradykinesia is what brings the patient to the neurologist, but the cognitive syndrome that develops in established disease is what drives institutionalisation, caregiver burden and mortality, and it is squarely the psychiatrist's problem. The marks concentrate here for two reasons. The first is that the profile is distinctive: this is the textbook example of a subcortical dementia, and telling it apart from the cortical dementia of Alzheimer disease is a recurring examination task. The second is that its neurochemistry is counter-intuitive and clinically load-bearing. The dementia is not a dopamine problem, which is why decades of dopaminergic treatment do nothing for it, and recognising the prominent cholinergic deficit that underlies it is what points to the one class of drug that helps. This section works through how common the dementia is, what it looks like, how it is screened and tracked, how it is separated from dementia with Lewy bodies, and why its chemistry dictates its treatment.

10.1 How common the dementia is, and what predicts it

Dementia is a common endpoint of Parkinson disease rather than a rare complication, affecting a large share of patients over the course of the illness, and the risk is not evenly distributed. Its frequency rises in proportion to the patient's age, to the duration of the illness and to the burden of physical impairment, so the oldest patients with the longest-standing and most disabling disease are the ones in whom it should be actively anticipated. There is also a motor-subtype signal worth carrying: dementia is more frequent when the disease is dominated by akinesia and rigidity than when tremor predominates, so an akinetic-rigid presentation is a cognitive risk marker as well as a motor phenotype.

Timing matters for how the diagnosis is framed. Dementia typically develops later in the disease rather than in the early years, though mild cognitive impairment may already be present at or near diagnosis; a frank dementia that appears within months of the first motor signs should therefore prompt a rethink of the diagnosis rather than a label of Parkinson disease dementia. When the syndrome is established, the formal label under DSM-5 is **Major Neurocognitive Disorder Due to Parkinson's disease**, with the corresponding category sitting among the dementias in current international classifications. The stepwise predictors and the early-preservation rule together give a practical answer to whom to screen and when.

- Older age at the point of assessment.

- Longer duration of established movement disorder.
- Greater physical and motor impairment.
- An akinetic-rigid rather than tremor-dominant phenotype.

24-50%	2.3 points/yr	more than 1 year
OF PD PATIENTS AFFECTED; SHARE RISES WITH AGE AND DURATION	MEAN MMSE DECLINE IN PD (COHORT AVERAGE)	DEMENTIA AFTER PD DEFINES PDD, NOT DLB

10.2 The clinical profile: the archetypal subcortical dementia

What the dementia of Parkinson disease looks like matters as much as how common it is, because its shape is what separates it from the other dementias a psychiatrist meets. It is the classic example of a **subcortical dementia**, a useful shorthand more than a rigid category. The cognitive picture is dominated by inattention, poor memory and a characteristic difficulty in shifting mental sets, the executive inflexibility of a patient who cannot readily move from one rule or task to the next. Overlying all of it is **bradyphrenia**, a slowing of thought that is the cognitive counterpart of the bradykinesia seen in the limbs: the patient thinks slowly in the same way that they move slowly, and given time will often arrive at the right answer.

Two further features anchor the subcortical label. Gait impairment is almost invariable, so the dementia travels with a disorder of movement rather than appearing in an otherwise intact body, and language function is comparatively preserved, in contrast to the early linguistic breakdown of a cortical dementia. That combination, slow but not empty thinking, retrieval-type memory failure, executive rigidity, a disordered gait and spared language, is the signature to carry into the examination. It also has a practical corollary: because effortful retrieval and slowed processing dominate, a patient may perform far better when given time and cues than a brief bedside impression suggests, and cognition can be underestimated if it is assessed in a hurry.

MNEMONIC

Slow thinking, stuck sets, sound speech, shaky gait

The subcortical signature of Parkinson disease dementia: **slow thinking** is bradyphrenia, **stuck sets** is the difficulty shifting mental sets, **sound speech** is the preserved language function, and **shaky gait** is the almost invariable gait impairment, with inattention and poor memory completing the picture.

10.3 Subcortical against cortical: telling it from Alzheimer dementia

The single most examined discrimination is between the subcortical dementia of Parkinson disease and the cortical dementia of Alzheimer disease, because the two are predicted and managed differently and because the contrast crystallises what "subcortical" means. Parkinson disease dementia differs clinically from Alzheimer disease dementia along several axes at once, and it is more useful to hold the whole pattern than any single sign. The Alzheimer patient loses the memory trace itself and, before long, language; the Parkinson patient retrieves slowly from a memory that is comparatively better preserved and keeps their words. The table below sets the two profiles side by side.

DOMAIN	SUBCORTICAL PATTERN (PARKINSON DISEASE DEMENTIA)	CORTICAL PATTERN (ALZHEIMER TYPE)
Cognitive tempo	Bradyphrenia: markedly slowed thinking	Processing speed relatively preserved until late
Memory	Poor, inattentive, retrieval-type failure	Failure of encoding and storage, aided little by cueing
Set-shifting	Prominent difficulty shifting mental sets	Executive change tends to come later
Language	Comparatively preserved	Aphasic breakdown relatively early
Gait	Impairment almost invariable	Typically spared until late

The distinction is not merely academic. A retrieval failure that improves with cueing, cognition that is slowed rather than absent, and early gait disturbance should steer the clinician towards a subcortical process and away from an Alzheimer-type diagnosis, with consequences for prognosis, for what the family is told, and for which drugs are worth trying.

10.4 Screening and tracking the cognitive decline

Because the decline is gradual and the early years are usually spared, the practical question is which bedside instrument to use and how fast to expect change. Two brief cognitive tests are both valid for detecting cognitive impairment in Parkinson disease: the Mini-Mental State Examination and the **Montreal Cognitive Assessment (MoCA)**. They are not equivalent for this purpose. The MoCA is the more sensitive of the two, largely because it loads more heavily on the executive and attentional functions that fail first in a subcortical dementia, whereas the MMSE leans on the orientation and memory items that a Parkinson patient can pass until relatively late. For screening a patient at risk, the more sensitive instrument is the better first choice.

Rate of change is worth knowing for counselling and for spotting an accelerating course. On average, cohorts of patients with Parkinson disease lose about **2.3 points annually** on the MMSE, though individual rates vary widely with baseline cognition, education and phenotype, so the figure is a rough cohort benchmark rather than a precise individual expectation; a markedly steeper fall should still prompt a search for a superimposed process such as an intercurrent delirium or a second pathology. The detailed administration, scoring and cut-offs of these instruments are not reproduced here; they belong to the Psychotherapies, clinical assessment, MSE and nosology notes. What matters at the point of care is the choice of the more sensitive test and a realistic expectation of how quickly the numbers move.

GOOD TO REMEMBER

When you screen a Parkinson patient for cognitive impairment, reach for the more sensitive Montreal Cognitive Assessment rather than the MMSE, because the executive and attentional deficits of a subcortical dementia are exactly what the MMSE tends to miss. A normal MMSE does not reassure you that cognition is intact.

10.5 The one-year rule: separating it from dementia with Lewy bodies

Parkinson disease dementia and dementia with Lewy bodies share a pathology and, once both are advanced, share a clinical picture; what separates them at the bedside is nothing more principled than timing. The convention is an arbitrary **one-year rule**. Parkinson disease dementia is diagnosed when the dementia begins **more than 1 year** after a well-established parkinsonism, that is, when a patient who has had the movement disorder for years later becomes demented. Dementia with Lewy bodies is the mirror image: the dementia arrives before the parkinsonism, at the same time as it, or within a year of it, and some patients with the Lewy body dementia never develop parkinsonism at all.

The direction of that rule is the part candidates reverse under pressure, so it is worth fixing: an established movement disorder first with dementia later is Parkinson disease dementia; cognition first, or together with the movement disorder, is dementia with Lewy bodies. Once both dementia and parkinsonism are well established, the two seldom differ clinically, and it is reasonable to regard them as two ends of a single nosological continuum, sometimes grouped together as **Lewy body dementia**. The practical value of holding them as one continuum is that it stops the clinician forcing a false either-or at the bedside and instead brings the same vigilance to both: the same alertness to fluctuating cognition and to the perceptual disturbances that attend the Lewy body pathology, and the same caution before any drug that could destabilise an already fragile brain. The full diagnostic rule for dementia with Lewy bodies, its core clinical features and the neuroleptic sensitivity that governs its management belong to the Dementias and neurocognitive disorders notes and are not reproduced here; what a reader needs at this point is the timing discriminator and the recognition that the boundary is a convention rather than a biological threshold.

TRAP **Treating the one-year rule as a real biological boundary, and getting its direction backwards.** The split between Parkinson disease dementia and dementia with Lewy bodies is arbitrary, not a threshold with a mechanism behind it. Candidates lose the mark by reversing it: dementia appearing more than a year after an established movement disorder is Parkinson disease dementia, while dementia that precedes or coincides with the parkinsonism, or arrives within a year of it, points to dementia with Lewy bodies.

10.6 Why it is a cholinergic, not a dopaminergic, dementia

The most clinically load-bearing fact about this dementia is what does not cause it. Of the potential mechanisms, the evidence does not implicate dopamine deficiency: the simplest demonstration is that dopaminergic medicines, which transform the motor disorder, neither prevent nor relieve the dementia. The cognitive syndrome and the motor syndrome are driven by different lesions, and the drug that fixes one leaves the other untouched. This dissociation is the single idea from which the treatment of the dementia follows, and it explains why long-term levodopa does nothing to protect cognition.

What the evidence does point to is a cholinergic lesion. A likely contributor is an **acetylcholine deficiency**, and imaging supports it directly: positron emission tomography has shown a cortical cholinergic deficit in Parkinson patients with dementia that is more pronounced than that seen

in Alzheimer disease, itself the prototype of a cholinergic dementia. That the cholinergic loss should run deeper here than in the disease we most associate with cholinergic failure is a striking and examinable point. It reframes the dementia as a disorder of a different transmitter system from the one the motor disease has trained us to watch, and it makes a specific class of drug rational.

RULE **The dementia of Parkinson disease turns on a prominent cortical cholinergic deficit, not on dopamine deficiency.** Because dopaminergic medicines do not prevent or alleviate it, adding or increasing dopaminergic drugs is not a treatment for the cognitive decline; the cortical cholinergic deficit is the rational target, which is why a cholinesterase inhibitor, and not more dopamine, is the drug worth trying.

10.7 What follows for treatment, and what does not work

Management of the cognitive syndrome is mostly an outpatient, shared-care matter between neurology, psychiatry and the family, with admission reserved for the complications of advanced disease rather than for the dementia itself. The realistic targets are modest: slowing decline, protecting function and treating the neuropsychiatric features that ride alongside the cognitive loss, rather than reversing anything. It is worth being honest with families that the dementia is not reversible, and in particular that neither the dopaminergic medicines nor deep brain stimulation, whatever they do for the movement disorder, undo the cognitive decline; the psychiatric effects of the stimulation itself are a separate matter treated in their own right.

Where a drug can help, it follows from the chemistry. A **cholinesterase inhibitor** may provide modest symptomatic benefit for the cognitive impairment and, as a useful bonus, reduce the visual hallucinations that so often complicate the disease, so a single agent can address both the cognition and part of the psychosis that Parkinson disease otherwise obliges the clinician to treat with particular caution over antipsychotic choice. That dual action is worth pausing on, because it lets one rational choice serve two of the disease's hardest problems at once and spares the patient a second, riskier drug. Because no guideline is carried in the evidence here, the specific agent, dose and titration should be taken from current disease-specific guidance rather than from memory; the teaching point that survives is the class and its dual benefit.

It helps to frame the effort by phase. In the short term the aim is to establish the diagnosis honestly, set expectations, and remove the reversible aggravators that make any dementia look worse than it is. In the medium term it is to hold function with a cholinesterase inhibitor where it is tolerated and to keep the neuropsychiatric complications in check. In the long term the work shifts towards the family and towards planning for dependency, because this is a progressive disorder for which no available treatment alters the underlying trajectory. Across all of it, the non-drug measures carry as much weight as any prescription: caregiver education and support, treating a superimposed delirium promptly, and correcting the sensory and sleep problems that magnify confusion are the interventions that most often change how a patient actually does.

PITFALL

Reading the slowed, effortful cognition of a Parkinson patient as depression or as "just the bradykinesia", and either missing the dementia or escalating dopaminergic drugs in the hope of sharpening the mind. More dopamine does not treat this dementia and can precipitate hallucinations and confusion; the slowing to recognise is bradyphrenia, the cognitive counterpart of the motor slowing, not a low mood and not a dose that is merely too small.

10.8 Pulling the picture together

Set out in one line, Parkinson disease dementia is a late, subcortical, cholinergic dementia. It is late because cognition is usually intact for the first years of the movement disorder; it is subcortical because it slows thinking and disturbs gait while sparing language; and it is cholinergic because dopamine deficiency does not explain it and a cortical acetylcholine deficit does. Each of those three adjectives earns its place in an answer, and each carries a clinical consequence. The late onset is what the one-year rule uses to separate it from dementia with Lewy bodies, the subcortical profile is what distinguishes it from Alzheimer disease and tells you to screen with the more sensitive instrument, and the cholinergic basis is what makes a cholinesterase inhibitor, rather than more dopaminergic drug, the rational treatment.

Held together this way the topic is coherent rather than a list of facts: one pathology expressing itself late, in a recognisable cognitive shape, through a transmitter system that is not the one the motor disease taught us to watch. That is the frame to reproduce under examination pressure and to carry to the bedside.

Parkinson disease dementia is a late-onset, subcortical, cholinergic dementia: it appears more than a year after established parkinsonism, slows thinking while sparing language, and responds to a cholinesterase inhibitor and not to more dopamine.

11 · Deep brain stimulation and its psychiatric effects in Parkinson disease

Deep brain stimulation is where the psychiatrist meets the functional neurosurgeon. For the candidate this is a compact topic that carries marks out of proportion to its length, because it sits at the junction of movement-disorder neurology, functional neurosurgery and clinical psychiatry. The examiner is almost never testing operative technique. The questions turn on what the procedure can and cannot do for the parkinsonian patient, and on the mood and behavioural changes that follow it, some unwelcome and some beneficial. A psychiatrist is drawn in twice over: before surgery to help judge candidacy and to set expectations, and afterwards to recognise and manage the neuropsychiatric sequelae. The reasoning below is therefore squarely clinical rather than surgical, and it rewards a reader who can separate the motor promise of the procedure from its psychiatric fine print.

STN	GPi	Advanced PD
SUBTHALAMIC NUCLEUS, THE STANDARD MOTOR TARGET	GLOBUS PALLIDUS INTERNA, THE PALLIDAL ALTERNATIVE	THE ESTABLISHED INDICATION FOR STIMULATION

11.1 The procedure and where the electrodes sit

Deep brain stimulation is a functional neurosurgical procedure in which fine electrodes are implanted stereotactically into a deep grey-matter target and connected to an implanted pulse generator. In Parkinson disease the two established targets are the **subthalamic nucleus** and the **globus pallidus interna**, and the leads are tunnelled under the skin to a pacemaker-like device placed in the subcutaneous tissue of the chest, as shown in the accompanying figure. Once the system is switched on it delivers continuous high-frequency current, and because the stimulation is programmable and can be turned off, its effects are in principle adjustable and reversible in a way that a lesioning operation is not. The high frequency is the point: rather than destroying tissue, it modulates the pathological activity of the target and its connected motor network while the tissue itself is left intact, so a setting that later proves troublesome can simply be dialled back or off. This is the feature that makes the technique attractive in a progressive disease whose drug requirements keep changing.

The operation is not without hazard, and the candidate should be able to name its principal surgical risks:

- cerebral haemorrhage along the electrode track,
- infection of the implanted hardware, and
- fracture or failure of an electrode.

None of these is common, but each can be serious, and the risk of an intracranial bleed in particular is what keeps stimulation a treatment for carefully selected advanced disease rather than an early-stage convenience. Understanding the hardware also explains several of the psychiatric observations that follow, because mood and behaviour can shift both with the anatomical target chosen and with the way the current and the drugs are subsequently balanced against each other.

11.2 The motor payoff and the drug-sparing effect

The reason a patient accepts intracranial surgery is the motor benefit, and in advanced disease it can be striking. Stimulation of the subthalamic nucleus significantly relieves the motor symptoms of advanced disease, and the practical consequence for the patient is threefold. First, the involuntary writhing movements that chronic dopaminergic therapy eventually produces, the **dyskinesias**, are greatly reduced. Second, the abrupt swings between mobility and immobility, the **on-off fluctuations** that come to dominate late disease, become less severe. Third, because the stimulator now carries part of the therapeutic load, the patient can usually reduce the dopaminergic drug regimen while still maintaining mobility.

That drug-sparing effect is worth dwelling on, because it is at once a benefit and a hidden variable. A patient who was cycling through large, frequent doses of levodopa with distressing dyskinesias may, after stimulation, hold steadier on much less medication. The dyskinesias were largely a complication of the drugs themselves, so lowering the drugs while the stimulator maintains movement is precisely what abolishes them. But the same medication change alters the patient's dopaminergic tone, and dopaminergic tone is tightly bound up with mood, motivation

and reward. The motor win and the later mood story are therefore two faces of the same postoperative rebalancing, which is why a purely motor account of the procedure misses half of what the psychiatrist needs to know. Reading the operation as only a movement intervention is the commonest way to be caught out on the psychiatric half of the question.

11.3 The ceiling of benefit and the dopamine-resistant features

The single most examined idea here is that stimulation has a ceiling. It relieves the features of Parkinson disease that are dopaminergic and were levodopa-responsive, and it does little for the features that were never dopamine-driven: the **axial features** of gait and balance, and the non-motor burden of cognition and mood. One point cuts the other way and is worth banking: stimulation is not established to hasten cognitive deterioration, so the fear that an implant will accelerate a vulnerable patient into dementia is not borne out. That reassurance is narrow, though, because stimulation does not treat cognition and can still affect specific cognitive functions, so a cognitively vulnerable patient needs formal pre-operative cognitive assessment rather than blanket reassurance. The two-column summary opposite is worth memorising in exactly that shape, because the examiner's favourite error lives in the right-hand column.

PARKINSONIAN FEATURE	EFFECT OF SUBTHALAMIC OR PALLIDAL STIMULATION
Dyskinesias of chronic dopaminergic therapy	Greatly reduced
On-off motor fluctuations	Reduced
Overall dopaminergic drug burden	Usually lowered, with mobility maintained
Gait impairment	Not improved
Postural instability	Not improved
Cognitive impairment	Not improved, and not accelerated
Depression	Not a treatment target; mood may improve or worsen and needs monitoring

The reason for that ceiling is worth understanding rather than simply memorising. The motor features that respond are generated within the dopaminergic basal-ganglia loops that stimulation can reach and re-balance. Gait, balance, cognition and mood, by contrast, depend on circuits and transmitter systems that degenerate alongside the dopaminergic ones but lie outside the reach of a single deep electrode. A focal intervention on one node of one circuit cannot restore what is failing diffusely across several, which is why the ceiling is a property of the disease rather than a shortcoming of the technique, and why no refinement of the current will lift it.

RULE **Stimulation modulates the motor circuit; it does not cure the disease.** It re-balances an overactive output and lets the drugs come down, but the neurodegeneration continues and the dopamine-resistant features advance on their own timetable. Frame the procedure to patients as symptom control for a defined set of motor problems, never as a brake on the illness.

TRAP **Assuming stimulation improves every parkinsonian feature.** Candidates reason that if the technique helps the motor state it must also help the falls, the freezing of gait, the cognitive slowing and the low mood. It does not. Those are exactly the features that did not respond to levodopa, and stimulation obeys the same rule as the drug it substitutes for. A patient who is falling and cognitively declining will keep falling and declining after a technically perfect operation.

11.4 The neuropsychiatric footprint: mood, apathy and suicidality

Because the procedure rebalances dopaminergic circuits, it has a genuine psychiatric footprint, and this is the part of the topic the psychiatry examiner cares about most. In a study of parkinsonian patients undergoing stimulation, and depending on the target chosen, the postoperative dopaminergic drug regimen and other postoperative factors, some patients developed a new depression or had an existing one worsen, approximately **0.5% to 1.0%** had suicidal ideation or suicide attempts, and a larger proportion showed **apathy**. The reassuring counterpoint is that in many of these patients the disturbance was mild, transient, or amenable to treatment, so the finding argues for vigilance and structured follow-up rather than for withholding a procedure that can transform the motor state. Apathy deserves separate emphasis because it is quiet: it does not distress the patient in the way a low mood does, it is easily read by the family as laziness or depression, and it can persist even when the mood itself has recovered. At the bedside the discrimination that matters is between apathy and depression, because the two can look alike from across the room yet call for different responses: the apathetic patient has lost the drive to initiate but not necessarily the capacity for pleasure or the sense of hopelessness, and collapsing the two into one is how a treatable low mood gets missed, or an inert but not unhappy patient gets pushed with a drug that does little for drive.

MNEMONIC

Suicidality, Apathy, Depression

SAD is the postoperative neuropsychiatric watch-list to run after stimulation for Parkinson disease. **S**uicidal ideation or attempts in a small minority, **A**pathy in a larger share of patients, and **D**epression that is either new or a worsening of what was there before. Screen for the three, and remember that the presence of any of them is more often a signal to review the drugs and the stimulation than to abandon a working implant.

GOOD TO REMEMBER

A fall in mood, drive or motivation after stimulation is frequently mild, self-limiting or treatable. The instinct to switch off a stimulator that is controlling the motor state is usually wrong. The better first moves are to review the postoperative dopaminergic regimen, to treat the mood syndrome on its own merits, and to reassess before disturbing a system that is doing its motor job.

11.5 What shapes the psychiatric outcome

The direction of mood change after stimulation is not random. The same study frames the psychiatric outcome as contingent on three things: the anatomical target, the postoperative

dopaminergic medication regimen, and other postoperative factors. Each is a lever the clinician can think with. The target determines which neighbouring circuits the current spreads into. The medication regimen matters because stimulation typically allows the dopaminergic drugs to be cut, and a reduction in dopaminergic tone can of itself lower mood and drive; a patient whose motivation collapses after surgery may be tracking the drug change as much as the current. The third category, other postoperative factors, is a reminder that adjustment to a major operation, to a suddenly altered motor identity, and to shifting roles within the family all bear on how a patient feels once the novelty has passed.

This is also where the topic brushes against its neighbours without owning them. The impulse control disorders and the dopamine dysregulation syndrome that complicate dopaminergic therapy are a distinct behavioural problem taken up separately in these notes, and the low mood and anxiety of Parkinson disease as non-motor symptoms belong to that separate discussion too. What this topic owns is the narrower claim that the stimulation, the drug change it permits, and the perioperative course together set the psychiatric outcome, and that no single one of them explains it alone.

PITFALL

Attributing every postoperative mood change to the stimulator. Because the drug regimen is almost always reduced after implantation, a new depression or a new apathy may be driven by the falling dopaminergic dose rather than by the current. Reviewing, and where appropriate adjusting, the dopaminergic regimen is part of the workup of post-stimulation mood change, not an afterthought reached only once the stimulation settings have been blamed and found innocent.

11.6 From movement disorder to psychiatric tool

The psychiatric footprint of stimulation is not only a liability, and the other direction of the story is how the technique entered psychiatry at all. Deep brain stimulation is established in the treatment of Parkinson disease, where implantation of electrodes in the subthalamic nucleus significantly alleviates the motor symptoms of advanced disease. In the course of that work it was noticed that stimulation sometimes improved mood and **obsessive symptomatology** in parkinsonian patients. That incidental observation, set against a rapidly growing understanding of the neural circuitry that underlies psychiatric disorders, prompted formal studies of stimulation in patients with treatment-refractory depression and obsessive-compulsive disorder.

For the examination it is enough to hold the logic in sequence: a motor treatment produced an unexpected psychiatric dividend, circuit neuroscience supplied a rationale, and the technique was carried across into refractory psychiatric illness. The detailed management of treatment-refractory depression itself, and where a device intervention sits among its other options, belongs to the Mood disorders: pharmacotherapy notes, and this topic does not reproduce it. What Parkinson disease contributes to the wider story is the proof of principle that focal, adjustable stimulation of a deep target can move mood and obsessional symptoms, for better as much as for worse. For the parkinsonian patient in front of you, that same duality is the practical lesson: the current that steadies the motor state acts on circuits that also carry mood and drive, so the motor

and the psychiatric consequences of stimulation are never fully separable and are best reviewed together at every programming visit rather than handed off to different clinics.

11.7 Selecting the patient and the psychiatrist's role

Everything above converges on candidacy. The ideal candidate has advanced disease with disabling dyskinesias and on-off fluctuations that remain levodopa-responsive, because those are the features stimulation reliably helps. The features that predict a poor return are exactly the ones it does not touch: prominent gait and balance failure, and cognitive impairment. Pre-existing cognitive decline weighs twice, once because stimulation will not improve it and again because a cognitively frail patient tolerates the procedure and its later adjustments less well. Distinguishing Parkinson disease dementia, which is taken up separately in these notes, from dementia with Lewy bodies, whose diagnostic rule and neuroleptic sensitivity belong to the Dementias and neurocognitive disorders notes, is part of that cognitive assessment, and the standardised cognitive instruments used to make it are described in the Psychotherapies, clinical assessment, MSE and nosology notes.

The psychiatrist's contribution is concrete on both sides of the operation. Before surgery it is screening for a mood disorder and for suicide risk, and setting expectations the patient and family can actually hold. A documented pre-operative psychiatric baseline is quietly valuable here, because it is what later lets the team decide whether a postoperative change is genuinely new or simply the illness the patient already carried, and whether it is tracking the surgery, the drug reduction or the ordinary passage of time. Afterwards it is monitoring for the depression, apathy and suicidal ideation that can follow, and treating them without reflexively sacrificing the motor benefit that justified the surgery in the first place. The choice of antipsychotic in Parkinson disease psychosis is a separate problem again, addressed elsewhere in these notes and kept out of this one.

IN INDIA

At the movement-disorder clinics where stimulation is offered, the psychiatrist is often the clinician who frames the goal for a family weighing a major operation. The clinical decision to communicate is precise: stimulation targets the drug-refractory motor fluctuations and dyskinesias of advanced disease, and it does not treat the falls, the cognitive decline or the low mood that most erode independence. Screen mood and suicide risk before referral, and monitor them afterwards, as a built-in part of the pathway rather than something bolted on when a crisis has already appeared.

11.8 Pulling it together

Stimulation earns its place in the neuropsychiatry syllabus because it runs in two directions at once. It is a mechanical, adjustable intervention that reliably improves a defined slice of advanced Parkinson disease and reliably leaves the rest untouched, and it carries a psychiatric footprint that also runs both ways: capable of lowering mood, flattening motivation and, rarely, provoking suicidal thoughts, yet also capable of lifting mood and obsessional symptoms and, in that guise, of crossing into psychiatry as a treatment in its own right. Hold the motor ceiling and the

neuropsychiatric watch-list in mind together and the topic answers itself, in the examination and at the bedside alike.

Deep brain stimulation is symptomatic circuit modulation for advanced, drug-refractory Parkinson disease: it cuts dyskinesias, on-off fluctuations and drug burden, does little for the levodopa-resistant gait and postural instability, does not treat cognition or depression, and carries a small but real neuropsychiatric footprint of depression, apathy and rare suicidality.

Huntington disease and other movement disorders

12 · Huntington disease: genetics, CAG repeats, anticipation and trinucleotide pathology

Two facts decide almost everything in a Huntington pedigree: how long the CAG repeat is, and which parent the expanded allele was inherited through. Huntington disease is the model autosomal dominant neurodegeneration and the cleanest teaching example of a trinucleotide-repeat disorder, which is why examiners return to it so reliably. The genetics are deterministic in a way little else in psychiatry is, because a single expanded gene inherited from one affected parent will, given time, produce a defined disease with motor, psychiatric and cognitive components. This section builds the genetics from the molecular lesion upward, taking in the gene, the repeat, the penetrance bands, the instability that drives anticipation, and the relationship between repeat length and age at onset, and it marks the exact points where confident memory misleads. The clinical and cognitive syndrome, and the management of chorea, are taken up in the companion account of the psychiatric and cognitive features of Huntington disease and are only named here.

12.1 The disease and how it is inherited

Huntington disease, once called Huntington chorea, is an **autosomal dominant** neurodegenerative disorder characterised by midlife onset, a relentlessly progressive course, and a combination of motor, psychiatric and cognitive symptoms. Because the mutation is dominant, one copy of a fully expanded allele is sufficient to cause disease, and each child of an affected parent has an independent **50%** chance of inheriting the abnormal gene. There is no recessive carrier state, and a fully penetrant allele does not skip generations, although a reduced-penetrance allele can make a pedigree appear to skip one: a person who inherits a fully expanded allele and lives long enough will develop the illness.

The mutation lies in the **huntingtin (HTT) gene** on chromosome 4. Its cytogenetic address is 4p16.3, near the telomere of the short arm, and the lesion is an expansion of the triplet CAG within the gene rather than a point mutation or a deletion. This matters for how the disease behaves in a family, because a repeat can be counted, banded and tracked across generations in a way that a diffuse structural mutation cannot. The determinism of the inheritance is also what gives the disorder its particular weight in genetic counselling, a task handled separately in the account of predictive testing in Huntington disease.

~5/100,000	4.2 ± 0.8	0.57	± 1 triplet
HD PREVALENCE, UNITED STATES	MEAN CAG GAIN PER PATERNAL TRANSMISSION	R-SQUARED, REPEAT LENGTH VS AGE AT ONSET	LABORATORY ERROR AT THE BAND MARGINS

12.2 The molecular lesion: an expanded polyglutamine tract

The CAG repeat is not tucked away in an untranslated region; it sits in the coding sequence, in frame, so the expanded run of CAG triplets is transcribed and translated into an expanded run of glutamine residues in the huntingtin protein. Huntington disease is therefore one of a group of **13** neurodegenerative diseases caused by a **CAG trinucleotide repeat expansion**, where CAG denotes cytosine, adenine and guanine. Their shared final common pathway is a **polyglutamine** tract, and proteins carrying more than about **35 to 40** consecutive glutamine residues are thought to become neurotoxins, misfolding and aggregating in ways the neuron cannot clear.

This makes the mutation a toxic gain of function rather than a simple loss of the normal protein, and that distinction is worth holding onto because it explains the dominance. A recessive loss-of-function disorder needs both copies of a gene to fail before disease appears; here a single expanded allele produces a protein that actively harms the cell, so one copy is enough and the inheritance is dominant. The expanded huntingtin and the fragments cleaved from it accumulate and injure neurons, with the striatum among the most vulnerable regions, and the slow attrition of these neurons produces the chorea, the behavioural change and the cognitive decline that define the illness. The accompanying figure brings the gene, the repeat and the vulnerable striatum into a single view so that the molecular lesion and its target can be held together.

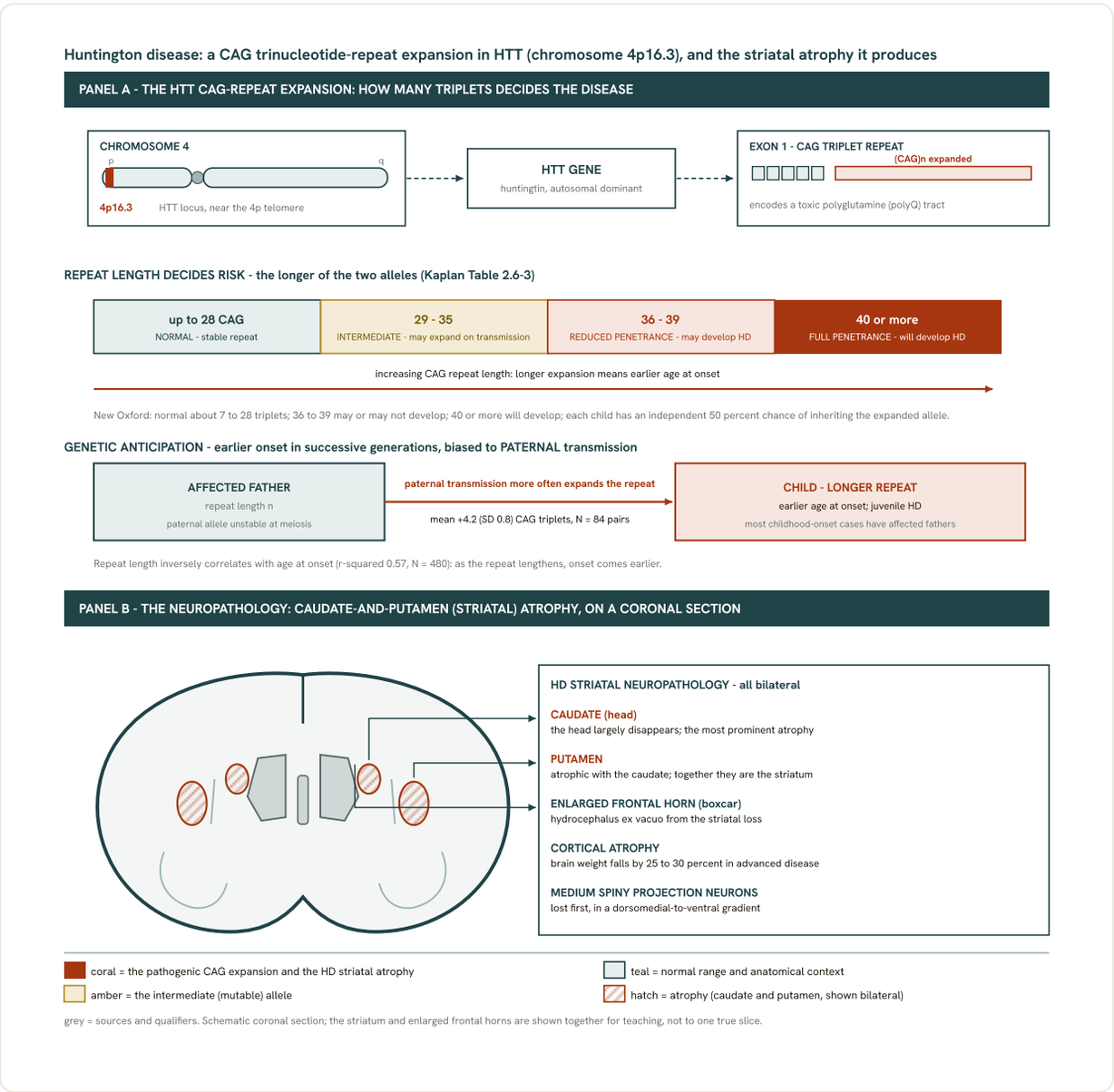


Fig 35.5 **Huntington disease genetics and neuropathology.** HD is an autosomal dominant disorder caused by a CAG trinucleotide-repeat expansion in the first exon of HTT at 4p16.3; the longer of the two alleles decides risk (up to 28 normal, 29 to 35 intermediate, 36 to 39 reduced penetrance, 40 or more full penetrance), and the repeat expands preferentially on paternal transmission, producing anticipation and juvenile-onset disease. The signature neuropathology is bilateral striatal (caudate and putamen) atrophy with enlarged frontal horns. (Kaplan and Sadock CTP 2024, and New Oxford Textbook of Psychiatry.)

The polyglutamine mechanism also explains two features that recur across this disease family and organise the rest of this section. The length of the repeat determines both whether disease appears at all and, if it does, roughly when; and the repeat is not faithfully copied from one generation to the next. Everything that follows, the penetrance bands, the phenomenon of anticipation and the inverse relationship with age at onset, is a downstream reading of those two properties of an unstable coding repeat.

RULE **An expanded CAG repeat becomes an expanded polyglutamine tract that poisons the neuron.** The repeat is in-frame and coding, so its length is read twice over: once as the number of glutamines that decide whether the protein is toxic, and again as the variable that sets penetrance and, inversely, the age at which the disease begins.

12.3 Reading the repeat length: the penetrance bands

Diagnostic genetic testing reports the number of CAG triplets in the longer of a person's two HTT alleles, and it is that count which is interpreted against a small number of bands. The bands are not arbitrary cut-points; they mark biologically meaningful transitions from an allele that is stable and harmless, through a mutable range that will not cause disease in the carrier but can expand in transmission, to alleles that carry **reduced penetrance** and finally to those with **full penetrance**, where the disease is certain in anyone who lives long enough. The interpretation table below follows the scheme set out in Kaplan and Sadock's Comprehensive Textbook of Psychiatry.

CAG REPEAT LENGTH	INTERPRETATION	PRACTICAL MEANING
Below 29	Not at risk; repeat length stable	Will not develop HD and does not transmit an expanding allele
29 to 35	Not at risk, though a few HD cases have been reported	Carrier is not expected to develop HD, though rare cases occur, and may pass an expanded allele to a child
36 to 39	May develop HD; risk rises with longer repeats	Reduced penetrance: disease may or may not appear in a lifetime
40 and greater	Will develop HD	Full penetrance; earlier onset with longer expansions

The single most examined transition is the step from the reduced-penetrance band to the fully penetrant one, because it is the point at which a result stops being probabilistic and becomes a certainty of eventual disease. It is worth being able to state the two break points without hesitation.

MNEMONIC

36 may, 40 will

The two break points that matter clinically: at a repeat length of 36 to 39 a person **may** develop Huntington disease, and at 40 and greater a person **will** develop it. Below that, the reassurance is qualified rather than absolute, which is exactly the ground the next section works over.

12.4 Where does normal end? The intermediate-allele band

The clean-looking table above hides a genuine disagreement between authoritative sources, and it is one examiners exploit. The trouble is not the disease-causing end of the scale, where the sources agree, but the lower boundary: where does the normal range stop, and what should the band just above it be called? The 29 to 35 range is the classic **intermediate allele**, a length that will not make its carrier ill but is unstable enough to lengthen into the pathological range when transmitted. Whether that band is filed under normal or set apart as a distinct category is where the sources part company.

TRAP **Assuming there is a single agreed number at which "normal" ends.** There is not. Kaplan and Sadock's Comprehensive Textbook of Psychiatry lists repeats below 29 and the 29 to 35 band as two separate rows, both classed as not at risk, whereas the New Oxford Textbook of Psychiatry puts the normal range at about 7 to 28 triplets and treats 29 to 35 as a distinct intermediate band. The sources agree on what decides who falls ill, reduced penetrance in the 36 to 39 band and full penetrance at 40 or more, but not on where normality stops or on whether 29 to 35 is named as healthy or as a mutable intermediate allele. Memorise a single boundary for "normal" and you will be caught precisely here.

The reason the disagreement is not merely academic is transmission. A person in the intermediate band is genuinely reassured about their own risk, yet the same instability that keeps them below the disease threshold is what can carry their child above it, so the counselling given to a carrier and to their offspring is not the same conversation. That asymmetry is the whole practical point of naming the band at all.

PITFALL

Reading a single borderline repeat count as an exact figure. Even the best laboratories carry an error of about plus or minus 1 triplet, so a result reported at the join between two bands cannot be treated as precise. A count of 35 against 36, or 39 against 40, sits inside the assay's own uncertainty, and such a result should be interpreted with that margin in mind rather than as a hard line cleanly crossed or not crossed.

12.5 Repeat instability and genetic anticipation

The repeat is **unstable at meiosis**: it is not copied faithfully from parent to child, and its length can change, usually by growing, when the gene is transmitted. That instability is markedly greater in the male germline, so the number of CAG triplets is more likely to increase when the gene passes through the father. The visible consequence in a family is **anticipation**, a fall in the age at onset across successive generations. Anticipation in Huntington disease is neither a statistical illusion nor an artefact of better detection; it follows mechanically from the combination of a strong correlation between repeat length and earlier onset and a tendency for the repeat to lengthen, most of all in paternal transmission.

The practical genetics of that instability reduce to a few points worth carrying:

- Repeat length can change between generations, so a child's count is not simply the parent's count read forward.
- The change is usually an increase, and increases are more likely in paternal transmission than in maternal transmission.
- Because expansion outweighs contraction, anticipation tends to run in a single direction down a pedigree, toward earlier onset.

A mother transmits the disorder with the same dominant probability, but the allele she passes is on average more stable, so maternally inherited disease tends to run truer to the parental age at

onset while paternally inherited disease is the one that can leap earlier and harder. That single asymmetry accounts for a large part of what makes Huntington pedigrees look the way they do.

GOOD TO REMEMBER

When you take a family history in a suspected Huntington case, ask which parent was affected and at what age they first presented. A pedigree in which each generation declares itself earlier than the last, particularly down a paternal line, is the clinical signature of an expanding repeat, and it should raise the possibility of a large expansion and an early, and in a child atypical, presentation before genetic results are back.

12.6 Repeat length and the age at onset

Repeat length predicts the age at onset, but only in part. Across large series the relationship is clear and monotonic: as the number of CAG repeats increases, the age at onset becomes earlier, so the longest expansions tend to declare themselves youngest and the shortest disease-causing alleles tend to present latest. This inverse relationship is one of the most reproducible quantitative findings in the disorder, and it is what underlies both anticipation and the juvenile presentations.

The crucial qualification is that the correlation, though strong, is far from complete. In the reference series relating repeat length to onset, repeat length accounted for rather more than half of the variance in age at onset and no more, which means a large share of the timing is set by other factors, among them modifying genes, environment and chance. The clinical translation is important and often examined. You can tell a person with a fully penetrant expansion that they will in time develop the disease, but you cannot read a precise age at onset off their repeat number, because two people carrying the same count can fall ill years apart. Repeat length bands the risk and shifts the expected decade; it is not a clock, and it should never be counselled as one. This is also why the shortest disease-causing alleles are the hardest to counsel: an allele just into the reduced-penetrance range may never declare itself in a normal lifespan, so the same length can mean lifelong health in one person and late disease in another, and honest counselling has to hold both possibilities open rather than collapse them into a single predicted age.

12.7 Juvenile onset and the transmission asymmetry

A minority of patients present in childhood or adolescence, and the genetics of this juvenile onset follow directly from everything above. It is the province of the largest expansions, and because those large expansions arise predominantly in the male germline, childhood onset is almost always inherited through an affected father. The chain from very long repeats, through paternal transmission, to the earliest onset is one of the most testable facts in the whole topic, and it ties the phenomenon of anticipation to its most extreme expression.

What the clean textbook sources withhold here is a number. They describe juvenile Huntington disease clinically and they tie it firmly to paternal transmission and to large expansions, but in these passages they do not state a specific CAG threshold that defines the juvenile or Westphal variant. It is tempting to supply the figure that circulates in teaching, and it is deliberately not asserted here, because the sources this account rests on do not carry it, and a remembered cut-off

is exactly the kind of confidently held number that turns out to be wrong. The distinct clinical picture of juvenile disease belongs to the companion account of the psychiatric and cognitive features of Huntington disease, and it is named here rather than taught.

12.8 How common it is, and the clinical bottom line

Huntington disease is uncommon but not rare, and its frequency varies markedly by population. In the United States the prevalence is about 5 cases per 100,000, with similar rates across most of Europe, while the New Oxford Textbook of Psychiatry gives a range of about 6 to 14 cases per 100,000 for North America, Western Europe and Australia. The disorder is much less common across Asia, roughly an order of magnitude lower in Japan and low in China, and it is also low in Finland and in Africa. Against this general pattern sit striking local concentrations, the best known being the communities around Lake Maracaibo in Venezuela, whose large affected pedigrees were central to mapping the gene.

For the practising clinician the genetics collapse into a compact frame. A patient with a suggestive movement disorder and a dominant family history in which onset marches earlier down the generations is very likely to be carrying an expanding CAG repeat, and the length of that repeat will place them in one of the penetrance bands and set the rough decade of their risk. Everything downstream, the counselling, the predictive-testing decision and the management of the psychiatric and cognitive syndrome, builds on that genetic core, and each is handled in its own companion account within these notes.

IN INDIA

Because Huntington disease is substantially less common across Asia than in Western populations, a young Indian patient presenting with chorea should not be labelled with an inherited polyglutamine disorder before acquired and treatable causes of chorea have been actively excluded. The lower pre-test probability of Huntington disease raises the relative weight of the reversible mimics, and when the diagnosis is genuinely suspected it is confirmatory genetic testing, not clinical impression, that should settle it.

Huntington disease is autosomal dominant: a CAG expansion of 40 or more triplets in HTT is fully penetrant, 36 to 39 carries reduced penetrance, the repeat lengthens and drives anticipation especially through the father, and longer repeats mean earlier onset.

13 · Predictive genetic testing and counselling in Huntington disease

Huntington disease is where predictive genetics first had to grow up. It is one of the few neuropsychiatric disorders with a **clearly defined genetic etiology** that can be identified in a person who is entirely well, years or decades before the first involuntary movement or the first change in mood. That single fact converts a family history into a testable question, and the question is not a laboratory formality: it asks a healthy adult whether they wish to know a diagnosis for which there is as yet no disease-modifying cure. A test run on a person who already has chorea and cognitive change merely confirms what the clinic already suspects; the whole

weight of this topic falls on the other use, testing a well relative who carries no signs at all, because there the result creates knowledge rather than explaining an illness that has already declared itself. The marks in this area sit almost entirely on the counselling around the test rather than on the assay itself. Examiners want to see that you understand who should be tested, how the result is interpreted, what it cannot tell you, and why the process is wrapped in mandatory counselling rather than handed over like a routine blood report.

1993	50%	40+	+/-1
DIRECT GENE TEST AVAILABLE SINCE	OFFSPRING RISK, EACH CHILD	CAG REPEATS: DISEASE CERTAIN	TRIPLET LABORATORY ERROR

13.1 A disorder built for the presymptomatic question

Ever since the causative gene was identified in **1993**, it has been possible to test directly for the Huntington repeat expansion using a simple PCR-based assay on DNA extracted from a blood sample, with testing offered through both commercial and academic centres. The molecular basis of the expansion, the phenomenon of anticipation and the instability of the repeat across generations belong to the account of the disease's genetics and are not the concern of the test itself; here the repeat length is simply the quantity the laboratory measures and the clinician interprets. What makes this disorder the teaching case for the whole of predictive medicine is the combination of a single, fully penetrant-at-threshold gene, an autosomal dominant pattern that puts identifiable relatives at high risk, and a long presymptomatic interval in which a well person can be given a near-certain answer about their future. That is a rare and uncomfortable position in clinical practice. Most of the conditions we screen for are probabilistic, modifiable, or both. Here the reader is dealing with a result that is close to deterministic and, for now, not modifiable, which is precisely why the ethical and counselling scaffolding around it is so heavy. A well person offered this test is being offered information rather than treatment, and information that cannot at present be acted on medically. That is why the right to decline, the right not to know, sits at the centre of the process and is protected as carefully as the right to be tested; a relative who decides they would rather live without the answer has made a legitimate choice, not a failure of nerve. The clinician neither steers the patient toward the certainty of a result nor toward the comfort of ignorance, and this deliberately even-handed stance is what marks predictive counselling out from most of medicine, where the clinician usually has a preferred direction. **Predictive testing** in this setting is therefore never framed as a laboratory decision. It is a considered choice made by an informed at-risk adult, and the clinician's task is to protect the quality of that choice rather than to encourage or discourage the test.

13.2 The fifty per cent rule and what a result means for a family

Huntington disease follows an **autosomal dominant** pattern, so a child of an affected parent carries a **50%** risk of developing the disorder. Each offspring, regardless of sex, has an independent one-in-two chance of inheriting the abnormal gene, and the word independent matters at the bedside: a family with three unaffected adult children has not "used up" its risk, and a sibling's negative result says nothing about the person in front of you. The genetic architecture also means the test is never truly about one individual. Because the abnormal allele

must have come from a parent, a positive predictive result in a young adult can retrospectively disclose the status of a parent who chose not to know, and a sibling's positive result, by confirming the gene is in the family, can raise the odds for relatives whose parental status was until then uncertain. This is the feature that raises the ethical issues the examiners expect you to name: a defined genetic disorder that can be diagnosed before symptoms creates real risks of discrimination in employment and insurance, and it forces questions about who else in the pedigree acquires knowledge they did not ask for. The discrimination risk is not hypothetical: a result sitting in a medical record can shape access to life cover or a post long before any symptom appears, which is one reason the decision to test is treated as private and considered rather than routine. The confidentiality problem is sharper still inside the family, because knowledge of one member's status leaks probabilistically onto the others. A young adult who tests positive has, in effect, said something about the parent from whom the gene descended, and a person who tests may reveal odds for siblings who wanted no part of the question. A counsellor cannot simply order the assay and report the number; the wider pedigree implications are worked through in advance, with the person helped to think about what they are willing to know and what they may inadvertently disclose. None of this is a reason to withhold testing from a competent adult who wants it. It is the reason the request is worked through slowly, with the wider family implications made explicit before any sample is drawn, so that the person understands they may be answering a question for relatives as well as for themselves.

13.3 Reading the repeat-length result

Interpretation rests on a small set of **repeat-length categories**, counted in CAG triplets, that translate a raw laboratory number into a counselling message. The categories used to interpret a predictive result are set out in the accompanying figure and in the table below.

CAG REPEAT LENGTH	INTERPRETATION FOR COUNSELLING
Under 29	Not at risk
29 to 35	Not at risk
36 to 39	Reduced penetrance: may or may not develop the disease
40 and greater	Will develop the disease

The clinically decisive band is the one in the middle. A repeat in the **reduced penetrance** range is not a normal result and not a diagnosis; it is a genuine uncertainty that has to be counselled as such. The lower bands are reported as not at risk of developing the disorder, while a result at the top of the scale carries the weight of a near-certain future diagnosis and must be delivered with the support that fact demands. The value of collapsing a continuous repeat count into these discrete messages is that patients do not act on triplet numbers; they act on whether they are, are not, or might one day become affected, and the categories are built to deliver exactly that judgement rather than a figure to be reinterpreted at home.

RULE **Under 36 repeats is not at risk, 36 to 39 is reduced penetrance where disease may or may not occur, and 40 or more means the disease will develop.** These three messages, not the raw triplet count, are what the patient leaves the room with. The counsellor's job is to convert a number on a report into the correct one of these statements and to make sure the intermediate band is never rounded up into a certainty or down into an all-clear.

13.4 The reduced-penetrance band is not a verdict

The single most common error in this topic, in the examination and in the clinic, is to treat a result in the reduced-penetrance range as though it were a diagnosis. The temptation is understandable: the patient came for a yes or a no, the number is above the not-at-risk threshold, and it feels honest to say the gene is present. But the categories are explicit that a repeat in this band means the disease may or may not develop, and a counsellor who collapses that into "you will get Huntington disease" has told the patient something the test does not support. The reverse error, reassuring the patient that a borderline expansion is nothing to worry about, is just as wrong. Both mistakes usually stem from a wish to give the family a clean answer where the biology does not provide one. The counsellor's task in this band is to hold the uncertainty open without inflating it into doom or dismissing it into nothing, to explain that a repeat in this range means the disease may occur and may not, and to help the patient plan around a probability rather than a promise. That is harder work than delivering an unambiguous positive or negative, and it is precisely where skilled counselling earns its keep; the honest answer here is a considered "we cannot be sure", which is a more difficult thing to say well than either a yes or a no.

TRAP **A result in the 36 to 39 band counselled as a certain future diagnosis.** Candidates who have memorised only "expansion equals disease" fall straight into it. The band carries reduced penetrance by definition, so the honest message is that the disorder may or may not occur, and the patient must be counselled to that uncertainty rather than to a verdict the laboratory has not delivered.

13.5 Laboratory limits and the borderline result

A predictive result is only as clean as the assay behind it, and the assay has a small but consequential margin. Even the best laboratories carry an error of +/-1 triplet, so a value sitting on the boundary of a category is inherently ambiguous: a report of 35 or 36, or of 39 or 40, may straddle the line between not at risk and reduced penetrance, or between reduced penetrance and certainty. A borderline number is therefore not something to interpret at face value; it is a signal to slow down, to discuss the uncertainty explicitly, and where necessary to confirm before any life-altering message is given. The safe habit is to treat any value within a triplet of a category boundary as provisional until it has been talked through and, where the stakes justify it, verified, rather than reading the printed number as though the assay were exact. A second, quieter trap lives in the raw report itself.

PITFALL

When the laboratory detects only a single allele of normal length, it is tempting to read this as a reassuring homozygous-normal result. In fact it usually means that both alleles happen to be the same length, and the finding must be interpreted with the laboratory rather than taken as excluding an expansion. Reading a single reported allele as an all-clear is a technical error that can hand a patient the wrong future.

13.6 Who asks to be tested, and who is counselled out

Uptake is far lower than the availability of the test would predict. Only a minority of at-risk individuals actually request predictive testing, and when they do the reasons are usually concrete rather than abstract curiosity. The commonest drivers cluster around a few life decisions:

- childbearing and reproductive planning
- long-term personal and career planning
- financial and insurance decisions

Just as important as who asks is who is counselled out. Those in an active major depressive episode are excluded from predictive testing until the depression is treated, because a result of either direction delivered into an active depressive episode carries an unacceptable psychological risk. This is not a bureaucratic hurdle; it is a clinical judgement that protects the patient from receiving a heavy answer at the point of least resilience. The pattern of who comes forward tells its own story. The people who request the test are usually facing a decision the answer would genuinely change, which is why reproductive and long-term planning dominate the stated reasons; abstract curiosity rarely survives the reality of an unmodifiable result, and many at-risk relatives who have thought hard about it choose to remain untested and live with the ambiguity. That self-selection is not an accident of the service but part of what keeps it safe, because the people who reach the sample are, on the whole, the people most prepared to use what it tells them.

GOOD TO REMEMBER

Screen for and treat major depression before offering premanifest testing, not after. Active major depression is an exclusion to the test, and stabilising mood first is what keeps the eventual result something the patient can absorb rather than something that lands on an unguarded moment.

13.7 The counselling protocol, before and after the test

Expert counselling is mandatory before **premanifest testing** is obtained, and the process is deliberately structured as **pre-test and post-test counselling** rather than a single consent conversation. The pre-test work ensures the person genuinely understands the potential psychological consequences of both a positive and a negative result and the real risks of discrimination in employment and insurance, and it checks that the decision is their own and not driven by a relative or an insurer. The post-test work carries the person through disclosure and the period that follows, whichever way the result falls, because the difficult phase is often not the

moment of the answer but the weeks after it. The reasoning behind the protocol is that a near-deterministic, presymptomatic genetic result is qualitatively different from an ordinary investigation and must be handled with matching care; the specific structure follows current predictive-testing guidance rather than any single fixed rule. The division into a before and an after is deliberate and worth understanding rather than memorising. The pre-test phase protects the quality of the decision, making sure the person has weighed a positive outcome against a negative one, understands the discrimination and family consequences, and is choosing freely rather than under pressure from a partner or an insurer. The post-test phase protects the person through the adjustment that follows the result, which for many is slower and harder than the moment of disclosure itself, and which is where an untested support gap does its damage. Consent for a predictive test is therefore not a signature captured on the day but a process that opens well before the sample is drawn and continues long after the answer is given. The pathway from referral through pre-test counselling to result disclosure and post-test support is summarised in the accompanying figure.

No premanifest test in Huntington disease without structured pre-test and post-test counselling, and active major depression is a contraindication to testing.

13.8 Reproductive options and the relief paradox

For a person already known to carry the abnormal gene, the predictive question extends into the next generation, and two established options exist. **Prenatal diagnosis** early in pregnancy allows the fetus to be tested, and **preimplantation genetic testing** of embryos generated by IVF allows unaffected embryos to be selected before a pregnancy is established. Both keep the choice about transmission in the hands of the carrier rather than leaving it to chance, and both belong in the counselling conversation for anyone whose result is positive and who is thinking about children. The chapter closes on a finding that surprises trainees. Given how heavy a positive answer is, one might expect testing to leave most people worse off, yet the opposite is generally observed: most patients feel relieved to learn their status, whether that status is positive or negative. The likely explanation is not that the news is easy but that the cohort is selected. The people who reach the test are those who have chosen it and worked through what it means, and those in an active depressive episode have been counselled out, so the group that actually receives results is unusually prepared for them. Put another way, the reassurance seen at follow-up is bought by the front-end work: the counselling that prepares people for either answer and the exclusion that keeps the most vulnerable out of the queue until they are well. Strip either safeguard away and the same result would land very differently, which is why the finding is so often misread. It does not show that the news is easy to bear; it shows that a well-run process can make even hard news bearable. That relief is a product of the protocol, not a reason to relax it, and it is the strongest practical argument for keeping the counselling around the test as rigorous as the test is simple.

14 · The psychiatric and cognitive features of Huntington disease and their management

Huntington disease is where the psychiatrist meets a movement disorder that is also a dementia and a mood disorder, and often meets it before the neurologist has made the diagnosis. The chorea is what names the illness, but for the patient and the family the psychiatric and cognitive changes are frequently the earlier and the more disabling burden, and they are where a large share of the clinical management sits. Marks concentrate on this material for three reasons that are worth holding in mind as the topic unfolds. The suicide risk is genuinely high and it is high early, before motor disease and sometimes before the person even knows their risk. The cognitive decline is the textbook example of a subcortical dementia and is regularly contrasted with the cortical picture of Alzheimer disease. And the drugs that most reliably control the chorea are the same drugs that can deepen depression and precipitate suicidality, which turns the management into a safety problem before it is a symptom-control problem. The genetics of the trinucleotide repeat expansion, and the predictive testing and counselling that flow from it, are taken up separately in this chapter and are named rather than re-taught here; this section works from the neuropathology through the psychiatric spectrum, the suicide risk, the cognitive profile and, finally, the management of the chorea and its psychiatric hazards.

14.1 The neuropathology that shapes the whole syndrome

The clinical picture reads directly off the pathology, so it is worth grounding first. The most prominent change is bilateral striatal atrophy: the caudate and the putamen waste, the head of the caudate largely disappears, and the frontal horn of the lateral ventricle enlarges to fill the space it leaves, producing the **hydrocephalus ex vacuo** that is visible on MRI and on gross specimen alike. The picture is one of an atrophic striatum with a dilated ventricle and a thinned cortex. The cerebral cortex itself becomes markedly atrophied, while other basal ganglia structures, particularly the globus pallidus and the subthalamic nucleus, are spared relatively more, and in advanced disease the brain may lose **25% to 30%** of its weight.

Within the striatum the cell loss is selective and ordered. It falls chiefly on the **medium spiny projection neurons**, in a gradient with the earliest and most severe loss in the dorsomedial striatum, while in the cortex it is the large neurons of the deeper laminae, layers III, IV and V, that are depleted. This anatomy explains the triad. Degeneration of the striatal output disinhibits movement and generates the chorea; disruption of the parallel frontostriatal circuits that loop through the same territory produces the executive slowing, the apathy and the personality change; and the diffuse cortical involvement underlies the later global cognitive decline. The psychiatric and cognitive features are therefore not incidental comorbidity but expressions of the same circuit pathology that drives the movement disorder.

14.2 The psychiatric spectrum and how often it appears

Psychiatric disturbance in Huntington disease is common, disabling and, importantly, not merely a psychological reaction to a fatal diagnosis. Over the course of the illness the great majority of patients develop some form of noncognitive psychiatric disorder, typically within 10 to 15 years of motor onset, and a substantial minority, up to 20%, present to services with psychiatric

symptoms in the first instance. The syndromes span the whole of psychopathology. Depression dominates; beyond those meeting criteria for a major depressive episode, a further 10% to 20% carry a different, non-major depressive syndrome. Psychotic phenomena occur across the illness, and a minority develop mania, which is easily mistaken for the disinhibition of the frontostriatal syndrome rather than recognised as an affective switch. The distinction is not academic: a sustained, mood-congruent elevation with reduced sleep and grandiosity calls for mood stabilisation, whereas the flat, undirected disinhibition of circuit damage does not, and treating one as the other wastes time and risks harm.

up to 80%	11% to 13%	30% to 40%	up to 10%
DEVELOP A NONCOGNITIVE PSYCHIATRIC DISORDER DURING THE ILLNESS	LIFETIME PREVALENCE OF PSYCHOTIC PHENOMENA	DEVELOP MAJOR DEPRESSION	DEVELOP MANIA

The practical consequence is that a patient with Huntington disease may need treatment for a mood disorder, a psychosis or both, and the primary nosology and pharmacotherapy of those syndromes are not rewritten by the neurological diagnosis. The general management of depression belongs to the Mood disorders: pharmacotherapy notes, and the general management of psychosis to the Schizophrenia: management, antipsychotics and adverse effects notes; what changes here is the safety framing, which the sections that follow develop.

14.3 Apathy, irritability and the personality change that comes first

If depression is the most frequent syndrome, personality change is the most characteristic, occurring in up to 50% of patients by the middle of the disease course. The two features that dominate this change, and that families find most troublesome, are **apathy** and irritability, and their importance to the examiner is that they may appear before there is any overt movement disorder at all. A patient who is gene-positive but pre-manifest, or in whom the chorea is still subtle, may present to psychiatry with a slow erosion of drive, initiative and emotional engagement long before a neurologist would call the disease clinically manifest.

Apathy here should not be collapsed into depression. It is a loss of motivation and goal-directed behaviour that can occur with a relatively preserved, non-dysphoric mood, and it tracks the frontostriatal circuit disruption described earlier rather than a primary affective disturbance. Distinguishing the two matters because the apathetic patient will not respond to, and may be worsened by, the sedating strategies that suit an agitated depression, whereas the irritability, which can shade into aggression and impulsivity, may itself demand containment. Because these changes can predate the movement disorder, they are frequently the reason such a patient is first brought for neurological and diagnostic assessment; the separate question of predictive testing in still-asymptomatic relatives is taken up separately in this chapter.

14.4 Suicide: the safety-critical feature

No fact in this topic is more important to carry into a clinic than the suicide risk. It is much higher than in the general population, it is present across the illness, and it is present in the prodrome, sometimes before the patient is even aware of being at risk. Lifetime suicidal ideation

has been estimated at 20%, and the lifetime rate of completed suicide at 6.6%. Prospective data from the ENROLL-HD cohort put the incident rate of suicide among gene carriers at 72 per 100,000 person-years and of suicide attempts at 306 to 375 per 100,000 person-years, figures that run at approximately **10 times** the rate in non-carriers.

Two clinical implications follow. First, suicide screening cannot be confined to the depressed or to the advanced patient; it belongs at every contact, including the pre-manifest phase and the period around genetic testing, when the disclosure of risk is itself a hazard. Second, the choice of antidepressant is shaped by the risk. Because overdose is a real danger in this population, antidepressants that are less toxic in overdose are preferred.

RULE **Screen for suicide at every stage of Huntington disease, including the prodrome.** The elevated risk begins before motor onset and before diagnosis, and it can be driven by the disclosure of genetic status rather than by symptom burden, so a screen that waits for depression or for clinical manifestation is a screen that comes too late.

GOOD TO REMEMBER

When treating depression in Huntington disease, the raised suicide risk pushes the choice toward selective serotonin reuptake inhibitors, which are less toxic in overdose than the tricyclic antidepressants or the monoamine oxidase inhibitors. The reasoning is a safety one and applies before any question of comparative efficacy.

14.5 The cognitive profile: a subcortical dementia

The dementia of Huntington disease is the standard clinical example of a **subcortical dementia**, and its shape is examined precisely because it contrasts with the cortical pattern of Alzheimer disease. Cognitive decline broadly parallels the movement abnormalities and, like the earliest psychiatric features, it begins well before the disease is clinically manifest, emerging as much as 10 years before motor onset. The first casualties are cognitive flexibility and processing speed, so the pre-manifest patient struggles with task-switching and multitasking while more elementary functions are still intact.

A useful four-domain model orders the deficits by prominence in early to middle disease, and it is the ordering rather than any single item that repays memory.

MNEMONIC

Visuospatial, Executive, Memory, Verbal

The relative prominence of cognitive deficits in early to middle Huntington disease runs in that order: visuospatial deficits are the most pronounced, followed by executive dysfunction, then the less prominent memory and verbal deficits. Reading the domains in descending order captures why the picture looks nothing like an amnestic Alzheimer presentation.

Because the pathology is subcortical and frontostriatal rather than temporoparietal, the cortical hallmarks are muted: aphasia and agnosia are far less evident than in Alzheimer disease, and the patient relatively preserves language and recognition while losing speed, sequencing and

visuospatial competence. Tracked with a bedside instrument, the decline is gradual, with the MMSE score falling by roughly **1 to 2 points per year**. The MMSE and the MoCA are named here only as the tools used to follow the trajectory; their construction and scoring belong to the Psychotherapies, clinical assessment, MSE and nosology notes.

TRAP **Concluding that cognition is intact because memory and language are preserved.** Candidates primed on the amnestic, aphasic profile of Alzheimer disease look for those deficits, fail to find them, and miss a subcortical dementia that is already advanced in executive speed and visuospatial processing. In Huntington disease the deficit falls hardest on how fast and how flexibly the patient thinks; naming and recognition are relatively better preserved, though free recall is not spared.

14.6 Treating the chorea: VMAT2 inhibition and its alternatives

The disabling involuntary movements are treated by depleting presynaptic dopamine, and the mainstay agents are the **VMAT2 inhibitors**. Tetrabenazine and reserpine both act at the vesicular monoamine transporter to cause presynaptic depletion of catecholamines, the difference being that tetrabenazine is reversible while reserpine is irreversible. For the **chorea** of Huntington disease, tetrabenazine is begun at a starting dose of **12.5 mg daily**, and most patients can be managed on 50 mg a day or less. It is extensively metabolised by CYP2D6, and for the chorea, CYP2D6 genotyping is recommended for any patient who needs more than 50 mg daily. Its adverse effects include hypotension, parkinsonism and, critically, depression with suicidality.

The deuterated derivative, deutetrabenazine (Austedo), is FDA-approved specifically for chorea associated with Huntington disease and offers a smoother pharmacokinetic profile. For chorea in Huntington disease it is dosed across a range of 6 to 48 mg/day, started at 6 mg once daily and titrated upward in 6 mg/day steps at weekly intervals, with any total of 12 mg/day or more given in two divided doses and a maximum of 48 mg/day. Its schedule for chorea begins lower than the schedule used for tardive dyskinesia, a distinction worth keeping straight because the two indications share the drug but not the starting dose. The broader phenomenology of chorea, and the wider hyperkinetic movement-disorder overlap that includes Sydenham chorea, are addressed separately in this chapter; the concern here is its pharmacological control.

AGENT	MECHANISM	DOSE FOR CHOREA IN HUNTINGTON DISEASE	PRINCIPAL CAUTIONS
Tetrabenazine	Reversible VMAT2 inhibitor; presynaptic catecholamine depletion	Start 12.5 mg daily; most managed on 50 mg a day or less	Hypotension, parkinsonism, depression with suicidality; CYP2D6 genotyping if more than 50 mg daily
Deutetrabenazine	Deuterated VMAT2 inhibitor	6 to 48 mg/day, initial 6 mg once daily, maximum 48 mg/day	Black box warning for depression and suicidality
High-potency typical antipsychotic (haloperidol, fluphenazine)	Dopamine receptor blockade	0.5 to 2.0 mg/day	May worsen voluntary movement or apathy, or cause akathisia or excess sedation

Where a VMAT2 inhibitor is unsuitable, the chorea may also respond to low doses of a high-potency typical antipsychotic such as haloperidol or fluphenazine, and to benzodiazepines, to the dopamine-depleting agent reserpine, or to amantadine, which acts not by depleting dopamine but as an NMDA antagonist. None of these is free: as the next section sets out, the dopamine-depleting strategy carries its own affective cost.

14.7 The depression and suicidality loop in chorea treatment

The reason chorea management is a safety problem is that it collides with the suicide risk already established. Deutetrabenazine carries a **black box warning** for depression and suicidality in patients with Huntington disease, and tetrabenazine likewise can cause depression with suicidality. The clinical logic is uncomfortable but clear: the drug most effective against the movement disorder can worsen the very mood disturbance that already drives the elevated suicide rate. Deutetrabenazine is accordingly contraindicated in several situations that the clinician must be able to recite.

- In a Huntington patient who is suicidal, or who has untreated or inadequately treated depression.
- In hepatic impairment.
- In a patient taking a monoamine oxidase inhibitor.
- In a patient taking reserpine, tetrabenazine or valbenazine.

The practical rule that emerges is to reserve the VMAT2 inhibitors as a first-line choice for chorea for patients who are free of depressive symptoms and suicidal behaviour, and to monitor everyone on these drugs, together with their caregivers, for the emergence or worsening of depression, suicidality or unusual behaviour. The alternatives do not escape the dilemma. The dopamine-depleting agents, chiefly reserpine, increase the risk of depression in their own right, and the high-potency antipsychotics used for chorea may worsen voluntary movement or apathy, or add akathisia and sedation, so no route to chorea control is affectively neutral.

PITFALL

Starting tetrabenazine or deutetrabenazine to quieten distressing chorea in a patient who is quietly depressed or has voiced suicidal thoughts. It is an intuitive move, because the chorea is what is visible in the room, but in a patient with an untreated or inadequately treated depression it is contraindicated and can precipitate exactly the outcome the clinician most fears. Treat and stabilise the mood first.

In Huntington disease the suicide risk is high from the prodrome onward, and the VMAT2 inhibitors that control the chorea can deepen depression and suicidality, so never start one in a patient who is actively suicidal or whose depression is untreated or inadequately treated.

14.8 Course, prognosis and juvenile-onset disease

Huntington disease is relentlessly progressive and ultimately fatal, and framing the psychiatric care within that trajectory is part of managing it honestly. Death usually occurs 15 to 20 years after disease onset, and it comes most often not from the movement disorder as such but from its downstream consequences: the swallowing difficulties of advanced disease, which cause suffocation or aspiration pneumonia, and general debilitation. This shape matters for psychiatry because it defines the horizon against which decisions about aggressive symptom control, capacity, advance planning and the family's own bereavement are made, and it is why the depression of the middle years cannot be treated as though recovery to a normal life expectancy were on offer.

A distinct presentation deserves separate recognition. **Juvenile-onset Huntington disease** does not look like the adult chorea. It typically presents with bradykinesia, rigidity and dystonia, sometimes with seizures or myoclonus, and with chorea that is minimal or absent, and it follows a more rapid and more severe course than the typical adult form. The repeat length that underlies this earlier, more aggressive onset belongs to the genetics of the disease taken up separately in this chapter, and no numeric threshold defining juvenile onset is asserted here. Recognising the akinetic-rigid juvenile picture as Huntington disease at all is the clinical point, because the absent chorea can send the unwary toward an entirely different differential.

15 · Sydenham chorea, Tourette syndrome, Wilson disease and the hyperkinetic overlap

Three of the movement disorders a psychiatrist must know are united less by a shared pathology than by a shared danger: each can wear the mask of a primary psychiatric illness, and each is treatable when it is recognised for what it is. This section teaches Sydenham chorea, the post-streptococcal chorea of childhood, and the movement-disorder and neuropsychiatric lens of Wilson disease, and it sets both inside a broader hyperkinetic overlap that links post-infectious tics and obsessive-compulsive symptoms to the archetypal chronic tic disorder. Marks cluster here because the psychiatric surface of each condition misleads: emotional lability and obsessions in a choreic child, or a first psychotic episode in a young adult who in fact has a copper-storage disease. The diagnostic criteria of Tourette syndrome belong to the Child behavioural, emotional and other disorders notes and are named here, not reproduced;

the full hepatic and metabolic account of Wilson disease belongs to the Endocrine and metabolic psychiatry notes, and this section keeps to the brain.

15.1 Sydenham chorea: the only neurologic face of rheumatic fever

Sydenham chorea is the neurologic expression of acute rheumatic fever, and the exam-defining fact is worth stating plainly at the outset: it is the only recognised neurologic manifestation of rheumatic fever. It appears in about **20%** of patients with rheumatic fever, characteristically weeks to months after the throat infection that set the illness in motion, so that by the time the chorea declares itself the preceding streptococcal sore throat may be long forgotten. That latency is a trap for the unwary, who look for an acute infection and find none.

The disorder belongs to a family of post-infectious, immune-mediated diseases that follow infection with group A beta-haemolytic streptococcus. It helps to hold the whole set together, because they share a post-streptococcal, immune-mediated basis and differ in the organ the immune response strikes:

- acute rheumatic fever, of which Sydenham chorea is the sole neurologic manifestation;
- poststreptococcal reactive arthritis, striking the joints;
- PANDAS, a proposed disorder linked to the basal-ganglia circuitry of tics and obsessions; and
- poststreptococcal glomerulonephritis, striking the kidney.

For a psychiatrist the practical message of that list is that a recent streptococcal infection can express itself neuropsychiatrically, and that the interval between throat and brain can be long enough to hide the connection unless it is actively sought.

15.2 Molecular mimicry, the basal-ganglia circuit and the choreic picture

The pathophysiology is autoimmune and turns on molecular mimicry. Antibodies raised against the streptococcus cross-react with epitopes on the basal ganglia, and in doing so they disrupt the **cortical-basal ganglia-thalamo-cortical (CBGTC) circuits** whose task is to sculpt movement, mood and cognition into coordinated output. Because those loops carry motor, behavioural and cognitive traffic together, the clinical syndrome is never purely motor: the lesion that produces the chorea produces the psychiatric symptoms discussed below. Structural neuroimaging fits the model, showing volumetric increases in the caudate, putamen and globus pallidus, the very nuclei the antibodies target.

Clinically, Sydenham chorea usually declares itself between the ages of 5 and 15 years, with a female predominance of about 2:1. The onset of the movements is characteristically abrupt. They are choreoathetoid, restless and flowing, and they are accompanied by a striking hypotonia that can, in severe cases, leave the child floppy and weak; tics may occur, and when the disorder is severe the speech becomes dysarthric, slurred and explosive. The whole picture is easily mistaken for clumsiness, fidgetiness or a functional disorder before its post-infectious basis is recognised, which is exactly why the abrupt onset and the antecedent infection matter so much to the history.

15.3 The neuropsychiatric burden and its link to persistence

For the psychiatrist this is the important half of the disorder, because the behavioural disturbance is not incidental. Psychiatric symptoms are present in up to **70%** of children with Sydenham chorea, spanning emotional lability, anxiety, depression, obsessive-compulsive symptoms and features of attention-deficit hyperactivity, with psychosis occurring occasionally. Obsessive-compulsive symptomatology deserves separate mention: reported OCD prevalence reaches up to 40%, and it is higher in children whose chorea persists beyond 2 years. That correlation is instructive, tying the durability of the movement disorder to the durability of the psychiatric one and pointing back to a shared basal-ganglia substrate.

The overlap with obsessive-compulsive disorder is not coincidental. OCD is itself understood as a disorder of the cortico-striatal loops, so Sydenham chorea offers an unusually clean natural experiment in which a discrete immune insult to the striatum produces obsessions and compulsions alongside the movement disorder. The clinical corollary is simple: a child who presents with an abrupt obsessional illness together with a movement disorder is telling a single story, not two, and the obsessional symptoms should be screened for deliberately rather than waited for.

15.4 Protecting the heart and treating the brain

Management of Sydenham chorea sits largely in the outpatient setting, shared between paediatrics, cardiology and psychiatry, and it has two distinct targets that must not be run together. The first is cardiac protection. Because the chorea marks a child who has had rheumatic fever, that child needs long-term **benzathine penicillin** prophylaxis to reduce the risk of rheumatic heart disease. This is secondary prophylaxis against future streptococcal infection, not treatment of the chorea, and it is the single most consequential decision in the whole encounter, because the threat to life is cardiac rather than neurologic.

The second target is the neuropsychiatric syndrome itself, and here management is multimodal. It draws on cognitive behavioural therapy and SSRIs for the obsessional and affective symptoms, and, in more severe or refractory disease, on immune-directed treatments, namely corticosteroids, intravenous immunoglobulin and plasmapheresis, for the underlying autoimmune process, while antibiotics such as penicillin, a cephalosporin or amoxicillin treat any active streptococcal infection. It is worth being explicit about phase, because the targets change over time. The chorea itself is frequently self-limiting and often needs no specific suppression at all; when the movements are genuinely disabling, sodium valproate or carbamazepine is commonly used first, with dopamine antagonists or a VMAT2 inhibitor reserved for selected cases, so the Huntington regimen is not simply carried across. The obsessional and affective symptoms are treated over the medium term as they would be in any child, and the prophylaxis is the long-term commitment that outlasts every other element of care. Where a management question rests on formal guidance, name the reasoning and defer to current rheumatic-fever guidance rather than a remembered figure, because the allowed evidence base here fixes the principle of long-term prophylaxis without fixing a dose or an interval.

RULE **Sydenham chorea is the only recognised neurologic manifestation of rheumatic fever, and finding it obliges long-term secondary penicillin prophylaxis.** The chorea itself is largely self-limiting and its psychiatric symptoms are treatable, but the disease that produced them threatens the heart valves for years. Naming the chorea and stopping there, without instituting prophylaxis, misses the point of the diagnosis.

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Where rheumatic fever remains common, new-onset chorea in a child should place Sydenham chorea high on the differential and prompt its investigation, while other urgent causes of chorea, including Wilson disease, are excluded in parallel. Once Sydenham chorea is confirmed, the clinical priority is not the movement disorder but securing long-term secondary penicillin prophylaxis to protect the developing heart. Keep the diagnosis high in the differential of any child presenting with an abrupt movement or obsessional disorder, and examine, or arrange examination of, the heart before the encounter ends.

15.5 The hyperkinetic overlap: PANDAS, PANS and the tic disorders

Sydenham chorea sits at one end of a broader hyperkinetic overlap in which post-infectious immune activity, tics and obsessive-compulsive symptoms run together. Its closest relative is **PANDAS**, the paediatric autoimmune neuropsychiatric disorders associated with streptococcus, a proposed and still contested construct, which presents with obsessive-compulsive disorder and/or tics rather than with chorea. Its cardinal features are a prepubertal onset, an abrupt onset over roughly **24 to 48 hours** followed by a relapsing-remitting course, and a temporal relationship to streptococcal infection. The abruptness is the clinical signature: an obsessional illness that switches on almost overnight in a prepubertal child should raise the question.

The discriminator from Sydenham chorea that examiners favour is the movement itself, and it is set out in the accompanying comparison of the two syndromes.

AXIS	SYDENHAM CHOREA	PANDAS
Defining phenotype	Choreoathetoid movements	Obsessive-compulsive symptoms and/or tics
Age at onset	Childhood	Prepubertal, required
Course	Often self-limiting; can persist	Relapsing-remitting

The archetypal chronic tic disorder against which these post-infectious pictures are measured is **Tourette syndrome**; its diagnostic criteria and phenomenology belong to the Child behavioural, emotional and other disorders notes and are cross-referred here, not reproduced. The wider research construct of PANS, the paediatric acute-onset neuropsychiatric syndrome, makes the boundaries explicit, its criteria expressly excluding cases better explained by Tourette disorder, Sydenham chorea or systemic lupus erythematosus. Those exclusions are worth remembering because they define the overlap by what it is not: PANS is a diagnosis of exclusion that presupposes you have already thought of, and ruled out, the very disorders taught in this section.

TRAP **Collapsing PANDAS and Sydenham chorea into a single diagnosis.** They share a streptococcal trigger and a basal-ganglia target, but the movements separate them: the choreiform movements of Sydenham chorea almost always cause functional impairment, whereas those in PANDAS cause none. A child with disabling chorea is not a PANDAS case, and a child with abrupt obsessions and no functional movement disorder is not Sydenham chorea.

15.6 Wilson disease: copper, the ATP7B gene and the corneal ring

The second treatable masquerader in this group is a disorder of a single metal. Wilson disease, historically named hepatolenticular degeneration, is an autosomal recessive disorder in which mutations in the copper-transporting gene **ATP7B** leave the body unable to handle copper, which accumulates in the liver, brain and other tissues and drives hepatic cirrhosis and neuronal degeneration. For the neuropsychiatrist the important target is the brain, where the basal ganglia appear to be particularly affected, which is why the disorder earns its place among the movement disorders. Onset is typically in the second or third decade, with a mean age of onset of 17 years, and it is uncommon, with a frequency of about 1/30,000.

The one physical sign every candidate is expected to know is the **Kayser-Fleischer rings**, deposits of copper in Descemet's membrane at the corneal periphery, near the limbus, that may be seen on direct inspection but are found more reliably with a slit-lamp examination. Their great limitation is that they are often absent early in the disease, so their presence supports the diagnosis while their absence never excludes it.

PITFALL

Excluding Wilson disease because the Kayser-Fleischer rings are not there. They are often absent early in the disease, particularly in patients presenting with liver disease rather than neurologic signs, so a normal slit-lamp examination reassures nobody. If the clinical suspicion is present, pursue the copper studies regardless of the eye.

15.7 The movement disorder and the psychiatric masquerade

Wilson disease announces itself through one of three doors, and which door a given patient walks through decides who sees them first.

40%	40%	up to 20%
FIRST PRESENT WITH HEPATIC ABNORMALITIES	FIRST PRESENT WITH NEUROLOGIC SIGNS	FIRST PRESENT WITH PSYCHIATRIC ABNORMALITIES

The neurologic syndrome, which correlates with the copper load in brain and cerebrospinal fluid, is a movement disorder in the fullest sense, encompassing dysdiadochokinesis, dysarthria, tremor, dystonia, rigidity, choreoathetosis, bradykinesia, masked facies and micrographia; seizures occur in about 6%. The coexistence of hyperkinetic and hypokinetic signs in the same patient, tremor and dystonia alongside bradykinesia and a masked face, is itself a clue that the lesion sits in the basal ganglia rather than in a single transmitter system. On imaging there is increased T2 signal in the basal ganglia, including the putamen, and the midbrain may show the

nonspecific panda sign, a tegmental hyperintensity with relative preservation of the red nuclei and substantia nigra.

The psychiatric profile is where the disease earns its place in a psychiatry curriculum, because it can precede or overshadow the neurologic signs and it broadly resembles that of Huntington disease. The commonest features are personality change, that is irritability, aggressiveness and emotional lability, and depression, which can deepen into major depression with suicidality. Around **10%** of patients present with psychosis. Tellingly, psychiatric symptom severity correlates more strongly with the neurologic deficits than with the state of the liver, which underscores that this is a brain disease presenting to psychiatry, not merely a hepatic complication spilling over.

TRAP **Reading a young adult's first psychotic episode as primary schizophrenia or bipolar disorder without excluding Wilson disease.** Because the presentation can be purely psychiatric, the copper story is missed for years and the illness is misdiagnosed as schizophrenia or bipolar disorder. In a young patient with new psychosis, especially with any movement abnormality, personality change or hepatic history, the diagnosis must be actively excluded before it is called primary.

15.8 Making the diagnosis and clearing the copper

The diagnostic work-up follows the copper. Serum **ceruloplasmin** is below normal in 95% of patients, which makes it the natural first screen, but it must be read with two caveats: it is also low physiologically in newborns and in about 20% of heterozygous carriers, so a low value supports the diagnosis without clinching it. A raised copper concentration in a 24-hour urine collection is generally regarded as diagnostic, and liver biopsy showing increased hepatic copper remains the gold standard for confirmation. The tests form a ladder from an easy screen to a definitive but invasive confirmation, and in practice the diagnosis is assembled from the pattern rather than from any single result.

Treatment rests on a single principle: remove the copper, or stop it entering. The two chelating strategies mobilise stored copper so that it can be excreted, while blocking absorption prevents further loading from the diet, and the choice between them turns on the stage of disease and on tolerability rather than on any single rule. The urgency is real. Untreated, the disease is fatal, with death occurring within about 5 years, and outcomes are best when treatment begins early, before copper does irreversible damage, which is the whole argument for thinking of the diagnosis early. Because the disorder is autosomal recessive, a confirmed case also reframes the family: asymptomatic siblings share the same inheritance risk and are the people most likely to benefit from being found before their copper does its damage. This is one of the few movement and psychiatric disorders in which a specific and effective treatment exists, and in which the price of a delayed diagnosis is measured in irreversible neurologic damage and death. The detailed hepatic and metabolic management belongs to the Endocrine and metabolic psychiatry notes.

MNEMONIC

Chelate or block: penicillamine, trientine, tetrathiomolybdate, zinc

The two strategies against copper in Wilson disease: **chelate** and remove it with D-penicillamine, trientine or tetrathiomolybdate, or **block** its absorption from the gut with zinc salts.

GOOD TO REMEMBER

Wilson disease is the treatable one. Keep the threshold low to send a serum ceruloplasmin, a 24-hour urinary copper and a slit-lamp examination in any young adult presenting with an unexplained movement disorder or a first psychiatric illness, because early treatment gives the best outcome and delay costs irreversible damage. The test that starts the whole cascade is cheap; the diagnosis it catches is otherwise lethal.

In any patient in the second or third decade with an unexplained movement disorder or a first psychiatric illness, actively exclude Wilson disease: it is the treatable copper-storage disease that is otherwise fatal, and it is the diagnosis in this group you cannot afford to miss.

Autoimmune and infective encephalitides

16 · Anti-NMDA receptor encephalitis: course, antibody, tumour association and treatment

A young woman is brought in floridly psychotic, agitated and terrified, and within a fortnight she is seizing while her pulse and blood pressure swing out of control. The reflex of a psychiatric ward is an antipsychotic and a working diagnosis of a primary psychotic illness. That reflex, here, can miss a treatable neurological disease that opened with an entirely psychiatric face. The disorder that has taught a generation of psychiatrists this lesson is **anti-NMDA receptor encephalitis**, and the principle it drives home is simple: new psychosis in a young person that arrives with, or is quickly overtaken by, neurological signs is an autoimmune encephalitis until it is excluded. The marks cluster on this topic for three reasons worth separating. It is common, it is treatable, and it is the cleanest worked example medicine has of a single antibody producing a recognisable psychiatric syndrome. What follows defines the disorder, works through the antibody and the mechanism that ties it to psychosis and amnesia, describes who it strikes and the staged course it runs, sets out the tumour it so often conceals, and closes on the investigations and the immunotherapy that can reverse it.

16.1 The commonest autoimmune encephalopathy, and why psychiatry meets it first

Anti-NMDA receptor encephalitis, usually abbreviated NMDARE, is now thought to be the most common cause of autoimmune encephalopathy. That single fact reorganises the differential of acute psychosis in a young patient, because it means an antibody-mediated brain disease is not an exotic zebra to be considered last but a leading and eminently treatable cause to be considered early. What makes it a psychiatric problem before it is a neurological one is the way it announces

itself. A typically young adult female patient presents first with mood symptoms, agitation, psychosis or other variable psychiatric manifestations, and she may spend her first days under psychiatric rather than neurological care. The behavioural change, the paranoia, the disorganisation and the affective instability are convincing enough that a primary psychiatric label is the natural first guess.

The clinical weight of getting this right is asymmetric, and that asymmetry is the whole reason the disorder is taught so hard. A misjudged primary psychotic illness is merely treated late; a missed autoimmune encephalitis progresses to seizures, a movement disorder and autonomic collapse while the treatable window narrows. Because a treatable encephalitis can hide behind a psychiatric presentation and because it responds to immunotherapy, a new psychosis that carries any neurological colour warrants the antibody workup early. The cost of a paired antibody panel is trivial against the cost of watching a reversible encephalitis declare itself over the following weeks.

Commonest	**Young women**	**Ovarian teratoma**	**Treatable**
CAUSE OF AUTOIMMUNE ENCEPHALOPATHY	THE TYPICAL PATIENT, THOUGH ANY AGE OR SEX CAN BE AFFECTED	THE COMMONEST ASSOCIATED TUMOUR	MOST IMPROVE WITH IMMUNOTHERAPY

RULE **New psychosis in a young person that is joined by neurological signs is an autoimmune encephalitis until it is excluded.** The disorder is now regarded as the most common cause of autoimmune encephalopathy, and, unlike a primary psychotic illness, it is often reversible with immunotherapy once the antibody is cleared. The cost of missing it is high and the cost of testing for it is low, which is why the reflex to investigate should be automatic.

16.2 The antibody and how it unsettles the mind

The disease is defined by its antibody, and the mechanism is unusually satisfying because it explains the clinical picture rather than merely labelling it. Patients develop antibodies against the **GluN1 (NR1) subunit** of the NMDA receptor. The antibody does not simply flag the receptor for destruction; it binds the extracellular domain and causes the receptors to cross-link and be internalised, drawing them off the synaptic surface. The result is a reversible loss of functioning NMDA receptors, a state of **NMDAR hypofunction**, rather than the death of the neuron itself. That distinction carries the clinical message: because the neurons survive and only their surface receptors are stripped away, restoring the receptor population can restore the patient, which is the molecular reason the disease is treatable.

NMDA receptors sit at the centre of synaptic strengthening, so their loss has predictable consequences. The hypofunction produces defects in synaptic plasticity, and the failure of synaptic potentiation in particular maps onto the working-memory impairment these patients show. Because NMDA-receptor signalling is not confined to one region but woven through cortical, limbic and subcortical circuits, a single molecular lesion can express itself at once as disordered thought, disturbed memory, abnormal movement and autonomic dysregulation, which is why the clinical syndrome is so much broader than the tidy phrase of a receptor antibody would suggest. The same receptor hypofunction is the state implicated in glutamatergic

models of psychosis, which is why the psychiatric presentation can be indistinguishable at onset from a primary psychotic illness: the disease behaves, in effect, as a naturally occurring pharmacological model of psychosis produced by an autoantibody. Holding the mechanism in mind also frames the prognosis honestly. Most patients improve with immunotherapies, but recovery is not universal, and some are left with residual symptoms or a relapsing course even after the acute illness resolves.

16.3 Who it strikes

The archetype is worth learning precisely, and so is its exception. The characteristic patient is a young adult woman, and the disorder is decidedly commoner in that group, which is also the group in whom the tumour association is strongest. But the archetype is a centre of gravity, not a boundary. The disease can present in either sex and has been documented across the lifespan, from young children to older adults. An examiner who hands you a boy, a man or an older patient with a subacute psychosis and a movement disorder is often testing exactly this point: that the demographic is a clue, not a rule, and that a presentation which fits the syndrome should not be dismissed because the patient is the wrong age or sex.

The practical consequence is that the diagnosis rests on the pattern of illness rather than on demographics. A stereotyped psychiatric onset followed by neurological deterioration should trigger the workup whoever the patient is, while the young-woman archetype simply raises the prior probability and sharpens the search for an underlying tumour. Anchoring too hard on the typical patient is one of the reliable ways the diagnosis is missed.

16.4 The staged clinical course

In the older framing, NMDA receptor encephalitis is a variety of **paraneoplastic limbic encephalitis**, and like other limbic encephalitides it runs a recognisable staged course. It typically opens with several days of progressively severe amnesia and behavioural disturbance, the memory failure and change in conduct that first bring the patient to attention. This prodrome is then overtaken by the phase that defines the disease: psychosis, seizures, involuntary movements and autonomic instability which eclipse the earlier amnestic and behavioural picture. The tempo is the point. This is not a static psychosis but an evolving encephalitis, and the arrival of seizures, a movement disorder or swings in heart rate, blood pressure and temperature over days to weeks is the signature that separates it from a primary psychiatric illness.

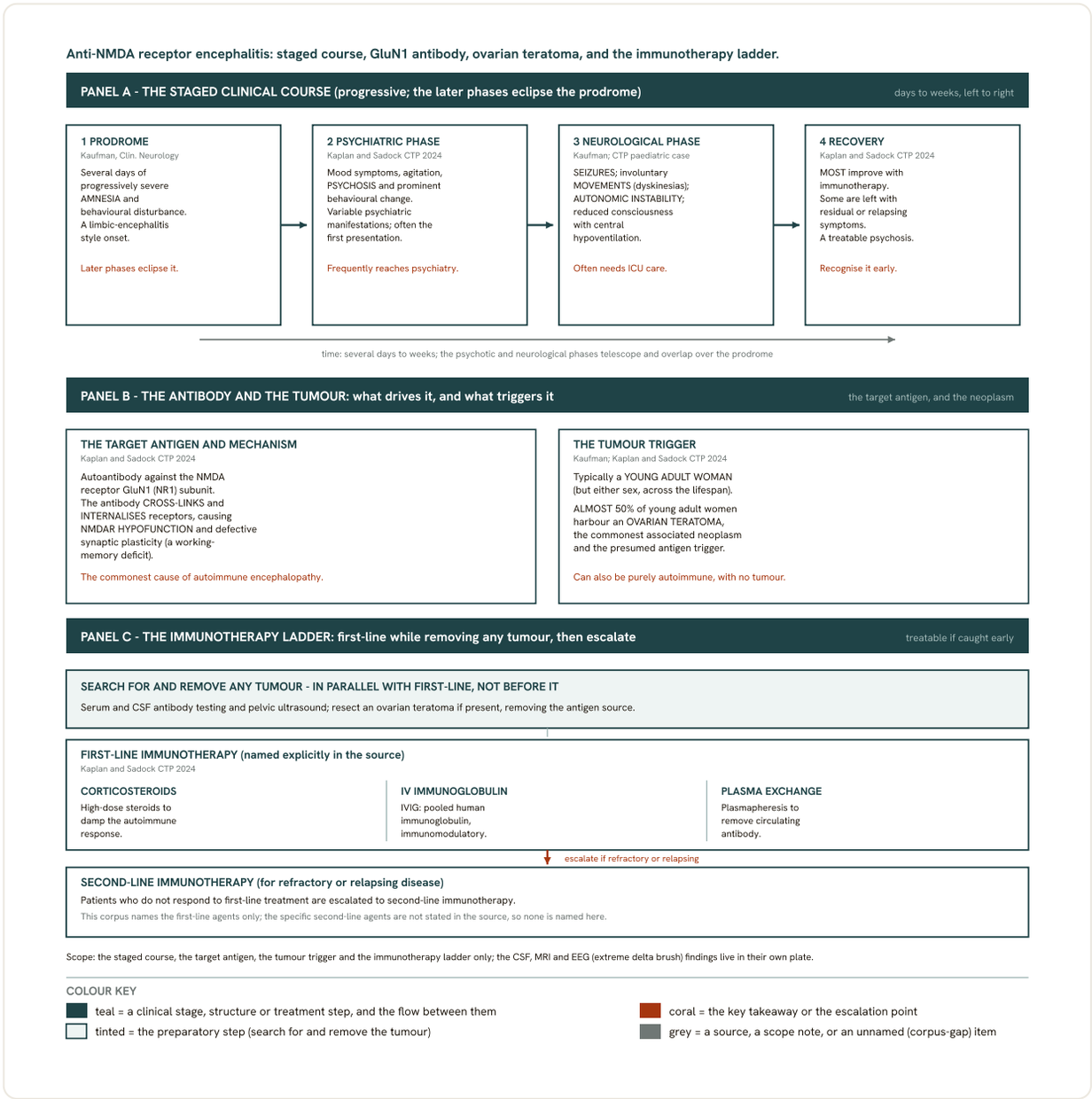


Fig 35.6 Anti-NMDA receptor encephalitis: the staged course and the treatment ladder. An autoantibody against the NMDA receptor GluN1 (NR1) subunit cross-links and internalises the receptor, producing NMDAR hypofunction; the illness runs a staged course from a prodrome of progressive amnesia and behavioural change, through a psychiatric or psychotic phase that often reaches psychiatry first, into a neurological phase of seizures, involuntary movements, autonomic instability and reduced consciousness that eclipses the prodrome, and then recovery, since most patients improve with immunotherapy. Almost 50 percent of young adult women harbour an ovarian teratoma, the presumed antigen trigger and the commonest associated neoplasm. Treatment starts first-line immunotherapy (corticosteroids, with intravenous immunoglobulin and/or plasma exchange) while searching for and removing any tumour, escalating to second-line immunotherapy in refractory or relapsing disease; the source names the first-line agents only, so no second-line agent is named here. (Kaufman, Clinical Neurology for Psychiatrists; Kaplan and Sadock CTP 2024.)

The autonomic phase is the dangerous one. Autonomic instability can escalate to the point of requiring intensive monitoring and support, and it is this stage, rather than the psychosis, that threatens life. The psychiatric phase itself frequently includes catatonia-like features; their formal phenomenology, the structured rating of catatonia and the distinction from primary catatonia belong to the Other psychotic disorders, delusional syndromes and catatonia notes and are named here rather than reproduced. The teaching point is the trajectory: a young patient who

moves from behavioural change and amnesia into psychosis, seizures, abnormal movements and dysautonomia over a short span is showing the natural history of this disease.

MNEMONIC

Amnesia, Psychosis, Seizures, Movements, Autonomic storm

The sequence in which the disease unfolds: an **A**mnestic and behavioural prodrome, then **P**sychosis, **S**eizures, involuntary **M**ovements and finally the **A**utonomic instability that eclipses the prodrome and endangers the patient.

16.5 The tumour it so often hides

The paraneoplastic label points to the search that must always follow the diagnosis. Overall, **almost 50%** of young adult women with the disorder harbour an **ovarian teratoma**, a germ-cell tumour that contains neural tissue and is presumed to trigger the antibody response by presenting nervous-system antigens to the immune system. The teratoma is the most common neoplasm associated with the disease, though a minority of patients are found to have other tumours, and, importantly, the syndrome can also occur as a pure autoimmune disorder with no underlying tumour at all. Finding and removing the teratoma is not incidental to treatment; it withdraws the antigenic drive and is part of definitive management.

The clinical corollary is that a search for the tumour is mandatory once the antibody is found, concentrated on the ovaries in the group most likely to carry one. The absence of a tumour on first imaging does not close the question, both because occult teratomas are easily missed and because the disease genuinely occurs without one, so the tumour search is sustained rather than performed once and forgotten.

TRAP **The tumour figure belongs to young adult women, not to every patient.** The frequently quoted teratoma association is the yield in young adult women specifically. Extend it to a man, a child or an older woman and it no longer holds, because it is the ovarian teratoma that anchors the number and those groups far less often carry one. A stem that hands you an older man and asks for the expected tumour yield is testing whether you kept the qualifier attached to the number.

16.6 Reading the investigations

The investigations are as much about not being falsely reassured as about confirming the diagnosis. The single most important habit is to distrust a normal scan. In most cases the MRI initially shows no abnormality, so an unremarkable early scan is exactly what the disease predicts and is never grounds to abandon the diagnosis. The cerebrospinal fluid is more informative. It usually shows a **lymphocytic pleocytosis**, the mark of an inflammatory process in the central nervous system, and it typically contains **oligoclonal bands**, which are nonspecific and appear equally in the CSF of multiple sclerosis and other inflammatory CNS illness; routine CSF can also be normal, and a bland tap does not exclude the disease.

The confirmatory test is the antibody itself, and it should be sent in both compartments. NMDA-receptor antibodies are found in both CSF and serum, but cerebrospinal fluid testing is the more

sensitive and specific of the two and carries the greater diagnostic weight, and CSF titres track the clinical course more closely than serum. Sending only one compartment is a mistake, because the two do not always agree, and a definite case can be positive in the CSF while negative in the serum. The electroencephalogram adds a suggestive but not decisive sign. The **extreme delta brush** pattern combines rhythmic or periodic delta slowing with overriding bursts of rhythmic beta activity at **20 to 30 Hz**, resembling the beta-delta complexes seen in neonates, with little reactivity or variability in sleep. It has been described in many patients with the disease, but it is explicitly nonspecific and its absence proves nothing.

INVESTIGATION	CHARACTERISTIC FINDING	WHAT IT DOES AND DOES NOT MEAN
MRI brain	Often normal at first	A normal early scan is expected and never excludes the disease
Routine CSF studies	Lymphocytic pleocytosis with oligoclonal bands	Supports CNS inflammation but is not specific, and normal routine CSF does not exclude the disease; oligoclonal bands also occur in multiple sclerosis
NMDAR antibody, paired serum and CSF	CSF IgG anti-GluN1 the more sensitive and specific; send paired serum too	Confirmatory; send both, but give the CSF result the greater diagnostic weight
EEG	Extreme delta brush	Suggestive but nonspecific; its absence does not exclude the disease

PITFALL

Treating a single antibody result as the end of the matter. Because cerebrospinal fluid testing is more sensitive and specific than serum, a definite case can be positive in the CSF while negative in the serum, so a diagnosis suspected on clinical grounds is not excluded by one negative compartment; a serum-positive but CSF-negative result should itself be read with caution. Sending serum and CSF together, and interpreting them together, is what avoids both traps.

16.7 Reversing it: immunotherapy and the tumour

Management follows directly from the mechanism, and it is genuinely a treatment of the disease rather than of the symptom. Care is inpatient, shared between neurology and psychiatry, and the sickest patients, those in the seizure and autonomic phase, need intensive monitoring and support. The target shifts with the phase of the illness: in the acute phase the priorities are controlling seizures and supporting autonomic function while the immune attack is brought under control; over the medium term the aim is to clear the pathogenic antibody and remove its source; and in the long term the concern is surveillance for relapse. The workup that opens management is serum and CSF antibody testing together with pelvic ultrasound, the imaging aimed squarely at the ovarian teratoma that may be driving the whole process.

The treatment itself combines removing the antigenic source with suppressing and clearing the antibody, and the components are worth listing because examiners ask for them by name.

- Removal of the tumour where one is found, which withdraws the antigenic drive and can itself turn the illness around.
- First-line immunosuppression with corticosteroids.
- Intravenous immunoglobulin, to neutralise and help clear the circulating antibody.
- Plasma exchange, to physically remove antibody from the circulation.
- Second-line immunotherapy for patients who do not respond to the first-line measures, the specific agents of which sit beyond the scope of these notes.

Steroids, with immunoglobulin and/or plasma exchange, are the first-line immunotherapy, deployed alongside tumour removal, and second-line immunotherapy is held for the non-responders. The reason this ladder works at all returns to the mechanism: the neurons are not dead, only stripped of surface receptors, so lowering the antibody load lets the receptor population, and the patient, recover.

GOOD TO REMEMBER

Once the diagnosis is suspected, do not wait for the picture to complete before acting. Send the paired serum and CSF antibodies and image the pelvis for a teratoma, and begin first-line immunotherapy while the tumour search proceeds; treatment and the hunt for the tumour run in parallel, not in sequence.

16.8 Prognosis and the psychiatric bottom line

The prognosis is the reason this disease rewards vigilance. Most patients improve with immunotherapies, which places NMDA receptor encephalitis among the small and precious group of psychoses that are genuinely reversible. But recovery is neither guaranteed nor always complete: some patients are left with residual deficits, and some run a relapsing course that requires continued surveillance and, at relapse, renewed treatment. Recovery can also be slow, unfolding over months rather than days, so the absence of an immediate response is not a reason to abandon immunotherapy. The corollary for counselling families is honest patience: improvement is the expectation rather than the exception, but it is measured in weeks and months, and an early plateau does not predict the eventual ceiling of recovery.

For the psychiatrist the lesson consolidates into a single habit of mind. The disorder is common, it wears a psychiatric mask, and it is treatable, so the differential of a young person with new psychosis and any neurological colour to the illness must include an antibody-mediated encephalitis, and the investigation must be sent rather than deferred. The whole clinical value of knowing this disease lies in acting on the suspicion early, because the treatment can only return what the antibody has not yet permanently taken.

Anti-NMDA receptor encephalitis is the commonest and a treatable autoimmune cause of new psychosis in a young patient: suspect it when a psychiatric onset is joined by neurological signs, confirm it with paired serum and CSF antibodies, hunt the ovarian teratoma, and treat with tumour removal and immunotherapy.

17 · The autoimmune limbic encephalitis spectrum

A patient in the fifth or sixth decade who over a few weeks loses recent memory, turns anxious or frankly psychotic and begins to have seizures has, until proven otherwise, an inflamed limbic system rather than a new primary psychiatric illness. The autoimmune limbic encephalitides are a family of immune-mediated inflammatory syndromes centred on the medial temporal structures, and they matter to the psychiatrist for a plain reason: their earliest and loudest features are psychiatric, so they arrive first in the psychiatry clinic and are readily mistaken for a mood, anxiety or psychotic disorder of middle-life onset. The marks concentrate here because the cost of that mistake is high. Many of these syndromes are driven by antibodies that are themselves the disease and are therefore reversible with immunotherapy, so a syndrome recognised is a syndrome that can be treated, while one dismissed as functional hardens into a fixed amnestic and cognitive deficit. This section sets out what defines the limbic syndrome and its mesial temporal substrate, the single organising distinction between the two classes of autoantibody, the specific antibody syndromes that carry named clinical signatures, and the tumour associations that make a new limbic encephalitis a reason to hunt for an occult cancer. Anti-NMDA receptor encephalitis, the most fully characterised member of the spectrum, and the red-flag approach to autoimmune psychosis are each addressed separately and are only named here.

17.1 The limbic syndrome and its mesial temporal substrate

The term **limbic encephalitis** describes an inflammatory process that settles on the limbic circuitry of the medial temporal lobes and expresses itself as a recognisable subacute syndrome: impairment of the formation of new memories, disturbance of mood and behaviour, psychiatric symptoms ranging from anxiety and irritability to hallucinations and delusions, and, very often, temporal lobe seizures. The tempo is the first diagnostic clue. Where a degenerative dementia evolves over years and a delirium over hours, the limbic encephalitides declare themselves subacutely, over days to weeks and sometimes across a couple of months, a march too fast for neurodegeneration and too sustained for delirium, and it is this cadence, more than any single symptom, that should prompt the question in the first place.

The anatomy explains the clinical picture and anchors the investigations. Whatever antibody or tumour underlies it, the disorder reflects medial, or mesial, temporal lobe dysfunction, so testing tracks that territory: magnetic resonance imaging may show acute swelling and signal change in the mesial temporal lobes, or atrophy later, the electroencephalogram may show spikes or slow waves emanating from the temporal lobes, and serum frequently carries antibodies reacting with limbic neurons such as anti-VGKC, anti-Hu or anti-Ma2 (Kaufman's Clinical Neurology for

Psychiatrists). Because the mesial temporal lobe houses the hippocampal machinery of episodic memory and sits at the heart of the limbic emotional circuit, the same lesion that erodes the ability to lay down new memories also destabilises affect and releases the temporal cortex into epileptic activity.

Mesial temporal	LGI1	CASPR2
MRI ATROPHY AND TEMPORAL-LOBE EEG DISCHARGES	AUTOIMMUNE CAUSE OF SIADH AND HYPONATRAEMIA	MORVAN SYNDROME AND AGRYPNIA EXCITATA

17.2 Two classes of antibody, and why the class predicts the outcome

The single most useful idea in this field is that the responsible autoantibodies fall into **two** mechanistically distinct classes, and that knowing which class you face predicts the tumour association, the reversibility and the response to treatment before any of those is formally established. The division is by the location of the target antigen. One class is directed against **intracellular** antigens, the classical onconeural targets such as anti-Hu, anti-Ma2 and anti-CRMP5. The other is directed against **extracellular, synaptic** antigens on the neuronal surface: the N-methyl-D-aspartate (NMDA) receptor, the AMPA receptor, gamma-aminobutyric acid (GABA) receptors, and the voltage-gated potassium channel complex antibodies, that is, LGI1 and Caspr2.

The mechanistic corollary is what makes the distinction worth memorising. An intracellular antigen is not accessible to a circulating antibody in a living neuron, so an antibody against it cannot itself be the effector of injury; it is a marker of a cytotoxic T-lymphocyte response that attacks the neuron directly and destroys it. Those syndromes are therefore tightly bound to an underlying cancer, tend to produce fixed neuronal loss, and respond poorly to antibody-directed immunotherapy because the damage is largely done by the time the diagnosis is made. A cell-surface synaptic antigen, by contrast, is exposed where antibody can reach it, so the antibody is itself pathogenic, typically by cross-linking and internalising the receptor or blocking its function. Because the neuron is disabled rather than killed, these syndromes are more often reversible, and they are the ones that reward immunotherapy. That is the whole reason the class matters at the bedside.

RULE **Classify the antibody by where its antigen sits, because the location predicts the biology.** Antibodies to intracellular antigens (anti-Hu, anti-Ma2, anti-CRMP5) are markers of a T-cell-mediated, cancer-associated, largely irreversible process; antibodies to cell-surface synaptic antigens are directly pathogenic and define the reversible, immunotherapy-responsive end of the spectrum. The target's address, not the antibody's name, is the organising fact.

FEATURE	INTRACELLULAR, ONCONEURAL ANTIBODIES	CELL-SURFACE, SYNAPTIC ANTIBODIES
Representative targets	Anti-Hu, anti-Ma2, anti-CRMP5	NMDA and AMPA receptors, GABA receptors, VGKC-complex (LGI1, Caspr2)
Role of the antibody	Marker of a cytotoxic T-cell response	Directly pathogenic effector
Antigen reachable in life	No, it lies inside the neuron	Yes, it sits on the cell surface
Typical reversibility	Usually fixed neuronal loss	Often reversible
Response to immunotherapy	Generally poor	Generally good

17.3 The VGKC-complex antibodies: LGI1 and Caspr2

Among the cell-surface antibodies, the group historically labelled anti-voltage-gated potassium channel antibodies deserves particular care, because the label is a partial misnomer that still appears on laboratory reports. The antibodies in this **VGKC-complex** do not, for the most part, bind the potassium channel pore itself; they bind proteins associated with the channel complex, and the two that matter clinically are **LGI1** and **Caspr2**. Recognising that a positive VGKC-complex result actually points to one of **two** named antibodies, each with its own clinical signature, is the difference between a vague immunological curiosity and an actionable diagnosis.

The two members separate along clinical lines. Caspr2 antibodies are the ones tied to the peripheral and autonomic overactivity syndrome, whereas LGI1 antibodies produce a predominantly limbic and amnestic picture and carry a characteristic metabolic marker of their own. The discipline that matters, for the examination and the clinic alike, is to resist collapsing the pair back into a single undifferentiated VGKC antibody once the specific target is known, because the target is what tells you which syndrome to expect and which associations to pursue.

PITFALL

Reading a positive VGKC-complex antibody as an antibody against the potassium channel itself. The clinically meaningful antibodies in the complex are directed at the associated proteins LGI1 and Caspr2, not the channel pore, and it is the specific target that carries the syndrome. Treating the older channel label as the diagnosis stops the workup one step short of the answer.

17.4 Anti-LGI1 antibodies and the clue of hyponatraemia

LGI1 antibodies have a metabolic fingerprint that is disproportionately useful to the psychiatrist, because it is cheap to find and easy to overlook. LGI1-antibody disease is one of the recognised autoimmune causes of the syndrome of inappropriate antidiuretic hormone secretion, and therefore of hyponatraemia (Localization in Clinical Neurology). In a patient presenting with a subacute amnestic and behavioural syndrome, an unexplained low serum sodium is a quiet pointer that the process may be autoimmune rather than primary psychiatric, and it is exactly the kind of routine result that is filed and forgotten once the working diagnosis has settled on depression or late-onset psychosis.

The pointer has to be read with the psychiatrist's own prescribing in mind, because the same source lists several drugs among the causes of inappropriate antidiuretic hormone secretion, and two of them are squarely psychiatric: carbamazepine and chlorpromazine both feature, alongside agents such as vincristine, chlorpropamide and cyclophosphamide. A hyponatraemia that emerges only after a mood stabiliser or an antipsychotic has been started is more likely iatrogenic than autoimmune, so the finding narrows the field only when the drug chart has been cleared first. Used that way, serum sodium becomes a small but genuine discriminator rather than a distraction.

GOOD TO REMEMBER

In a middle-aged patient with a subacute amnestic or psychotic presentation, check the serum sodium and read it in context. An autoimmune hyponatraemia driven by LGI1 antibodies is treatable, but the identical biochemistry follows carbamazepine or chlorpromazine, so clear the drug chart before you attribute a low sodium to the antibody.

17.5 Morvan syndrome and agrypnia excitata

The Caspr2 syndrome has a presentation that lands directly in psychiatric territory and is worth carrying by its eponym. When agitation combines with severe, intractable insomnia and signs of sympathetic overactivity, the constellation is called **agrypnia excitata**, and it should raise the question of **Morvan syndrome**, associated with antibodies to Caspr2 and, less commonly, LGI1. The name captures the essence: a state of pathological wakefulness driven from the brain rather than chosen by the patient, in which the normal architecture of sleep collapses and the patient is left agitated, sleepless and autonomically overdriven.

For the psychiatrist the hazard is the resemblance. A patient who has not slept for days, who is restless and agitated, and whose pulse, blood pressure and sweating betray an overactive sympathetic system looks, at first glance, exactly like severe agitated mania, an agitated depression or a stimulant state, and the reflex is to reach for sedation and an antipsychotic. The insomnia of agrypnia excitata, however, is not the reduced need for sleep of mania but an inability to generate sleep at all, and it keeps company with the autonomic and, often, peripheral neuromuscular features that betray its neurological origin. Reading the whole picture, rather than the mood-and-sleep fragment that happens to fit a primary diagnosis, is what turns the case toward the correct workup.

MNEMONIC

Agitation, Insomnia, Sympathetic overdrive

The three strands of **agrypnia excitata** in Morvan syndrome: **A**gitation, intractable **I**nsomnia and **S**ympathetic hyperactivity. Hold the triad together and the Caspr2 syndrome separates itself from the agitated states of primary psychiatry.

TRAP **Reading agrypnia excitata as agitated mania and treating it with sedation and antipsychotics alone.** The intractable insomnia, agitation and sympathetic overactivity of Morvan syndrome mimic a manic or mixed affective state, but the sleeplessness is a failure to generate sleep rather than a reduced need for it, and it travels with autonomic and peripheral nerve signs. Anchoring on the affective surface misses a treatable antibody-mediated disease.

17.6 The paraneoplastic associations and the search for a tumour

A limbic encephalitis can be the first announcement of a cancer that is otherwise silent, which is why a new subacute limbic syndrome is, among other things, a reason to look for a tumour. When the encephalitis is **paraneoplastic**, the antibody and the tumour tend to travel together, and the antibodies that accompany it include anti-Hu, anti-Ma, anti-amphiphysin, anti-VGKC and anti-GAD, alongside the anti-NMDA receptor antibody. The clinical value of the pairing is that the antibody hands you a shortlist of tumours to exclude, and treating a tumour that is found is essential and may stabilise the syndrome, though recovery is often limited in the intracellular, onconeural disease where cytotoxic T-cell damage is already done.

The tumours to exclude in paraneoplastic limbic encephalitis are a compact set worth committing to memory.

- Small-cell lung cancer.
- Testicular tumours.
- Breast cancer.
- Ovarian teratoma, the association that connects this spectrum to anti-NMDA receptor encephalitis.
- Thymoma, which also points toward the neuromuscular associations of the VGKC-complex antibodies.

Two of these deserve the extra beat. The ovarian teratoma link is the thread that ties the limbic spectrum to anti-NMDA receptor encephalitis, which is listed among the limbic-encephalitis antibodies and is addressed separately in its own right; the operational point to carry here is simply that a limbic syndrome in a young woman is a reason to image the ovaries. The thymoma link runs the other way, toward the peripheral and autonomic phenomena of the Caspr2 and VGKC-complex antibodies, and reminds you that the chest as well as the abdomen belongs in the tumour search.

17.7 Confirming the diagnosis: antibodies, imaging and the EEG

Confirmation rests on the convergence of three lines of evidence, each of which reflects the mesial temporal target of the disease. Structural imaging comes first. Magnetic resonance imaging may show atrophy of the mesial temporal lobes, and in the acute phase those structures may instead look swollen and signal-bright, so the scan is read for change in the limbic territory rather than for a single fixed appearance. The electroencephalogram is the second line, and it localises the irritable tissue, showing spikes or slow waves emanating from the temporal lobes and corroborating both the seizures and the anatomical focus. The third and most specific line is

serology: the serum frequently contains antibodies that react with limbic neurons, and a sensible panel samples both classes, including anti-VGKC, anti-Hu and anti-Ma2 among others.

Two habits of interpretation keep the workup honest. First, antibody testing is most informative when serum and cerebrospinal fluid are examined together rather than serum alone, because the compartment in which an antibody is found carries information the serum result cannot give by itself. Second, and more important at the bedside, these investigations are supportive and not perfectly sensitive early in the illness: an unremarkable scan or a non-specific tracing in the first days does not overturn a strong clinical suspicion, and this is a syndrome in which the tempo and the constellation of features carry as much weight as any single test. The diagnosis is assembled from the whole, not conceded on one normal result.

IN INDIA

Where the infective encephalitides dominate the differential of a subacute encephalopathy, the autoimmune limbic syndrome must still be actively tested for rather than assumed away, precisely because it is the treatable and often reversible member of the group. When herpes simplex, Japanese encephalitis, cerebral malaria and tuberculous meningitis have been addressed, an antibody-mediated encephalitis that was never considered is a reversible diagnosis missed. Keep it on the list, send the antibody panel, and let mesial temporal imaging and the electroencephalogram support the search rather than waiting for a textbook scan before believing it.

17.8 Why the psychiatrist is the first line of recognition

These often present with psychiatric features first and neurological ones second. A patient whose subacute change is dominated by anxiety, depression, psychosis, personality change or a disorder of sleep will be brought to a psychiatrist, and the window in which immunotherapy can reverse the illness is open at exactly that first contact. The clinician who holds the pattern in mind, a subacute course, prominent psychiatric features, memory impairment, seizures, and perhaps a quiet hyponatraemia or an intractable insomnia, is the one placed to act while action still helps. That is the whole argument for teaching this spectrum to psychiatrists rather than leaving it to neurology.

Two adjacent problems complete the map without belonging to this section. The specific red-flag features that should tip an apparently primary psychiatric presentation toward investigation for an autoimmune cause, and the immunotherapy by which such an autoimmune psychosis is actually treated, are developed separately and are not reproduced here. So too is anti-NMDA receptor encephalitis, the prototype of the antibody-mediated encephalitides, whose course, antibody and tumour associations and treatment are addressed in their own right. What this section asks the reader to carry is narrower and prior to both: the recognition that a new psychiatric syndrome in the wrong demographic, on the wrong timescale and with the wrong companions may be an inflamed limbic system asking for an antibody test.

A subacute psychiatric syndrome with memory impairment and seizures, especially alongside an unexplained hyponatraemia or an intractable insomnia, is a limbic encephalitis until the workup excludes it, and a single normal antibody panel or scan does not overturn a strong clinical suspicion.

18 · Autoimmune psychosis: red flags, the psychiatric differential and immunotherapy

A few psychoses are immunological emergencies wearing a psychiatric mask. A small but consequential group of patients reach a psychiatrist with what looks like a first episode of schizophrenia, an agitated mania, or a psychosis that will not settle on any antipsychotic, and are in fact suffering an **autoimmune or paraneoplastic encephalopathy**. The reason this topic earns marks is not that the syndrome is common but that it is treatable and eminently missable. The presentation is psychiatric, the cause is neurological, and the clinician who meets the patient first is usually the psychiatrist. This section teaches the one decision that matters: recognising when a psychiatric picture is atypical enough to warrant a search for neuronal antibodies, and knowing what that search and its treatment involve. It teaches the anti-NMDA-receptor-encephalitis-versus-catatonia distinction and the discrimination from a primary psychosis, and cross-refers the phenomenology and nosology that other chapters own.

18.1 Why the psychiatrist owns this question

The clinical logic begins with an observation from Kaplan and Sadock's *Comprehensive Textbook of Psychiatry*: these disorders should be suspected when a patient shows an atypical presentation of psychiatric illness, and above all when there are comorbid neurologic signs or symptoms. That pairing, an unusual psychiatric syndrome sitting alongside a neurological abnormality, is the whole of the **red flags** concept. The word doing the work is "atypical". A presentation is atypical when it departs from the natural history the clinician expects: the age is wrong, the onset is too abrupt, there is no prodrome, cognition is disturbed out of proportion to the affective or psychotic content, or the syndrome refuses to answer to treatment that should work. The presenting picture is itself protean, because an antibody-mediated disturbance of cortical and limbic circuits can surface as any of the functions those circuits carry: cognitive impairment, mood symptoms, frank psychosis, seizures, and movement abnormalities all appear, in varying combinations, and occasionally the illness presents with psychiatric symptoms and no neurologic symptoms at all.

The psychiatrist owns the recognition step because the referral pathway hands these patients to psychiatry before neurology ever sees them. What raises the stakes is that the underlying process is one most patients recover from once it is treated. The asymmetry of the two possible errors is what should set the threshold to investigate. Over-investigating a primary psychosis costs a venesection, a lumbar puncture, and a scan; under-investigating an encephalitis lets a treatable illness run as though it were incurable. When the downside of the two mistakes is that unequal, the rational clinician sets a low bar for ordering the antibody panel and accepts a high proportion of negative results as the price of not missing the positive one. The task, then, is not to make an

antibody diagnosis at the bedside but to hold the suspicion long enough to order the right investigations before a primary psychiatric label closes the case.

RULE **New or refractory psychosis carrying any neurological sign is an autoimmune encephalopathy until serum and CSF antibodies say otherwise.** The default in a young person with an abrupt, treatment-resistant psychosis and a soft neurological finding is not "unusual schizophrenia" but "encephalopathy not yet excluded". The exclusion is a laboratory and imaging exercise, not a clinical impression, because the treatable cause and the primary psychiatric one can look identical on interview alone.

18.2 The red-flag panel: what should stop you

Not every unusual psychosis needs an antibody screen, so the panel of features that should stop a clinician deserves to be memorised. The signal is tempo and neurology. A psychosis that evolves over days rather than months, that clouds cognition as it advances, or that brings seizures, abnormal movements, or autonomic disturbance is behaving unlike a primary psychiatric illness. The accompanying figure sets out this red-flag panel: the rapid-onset or treatment-refractory psychosis, the prominent neurological accompaniment, and the demographic and temporal cues that together justify a search for neuronal antibodies.

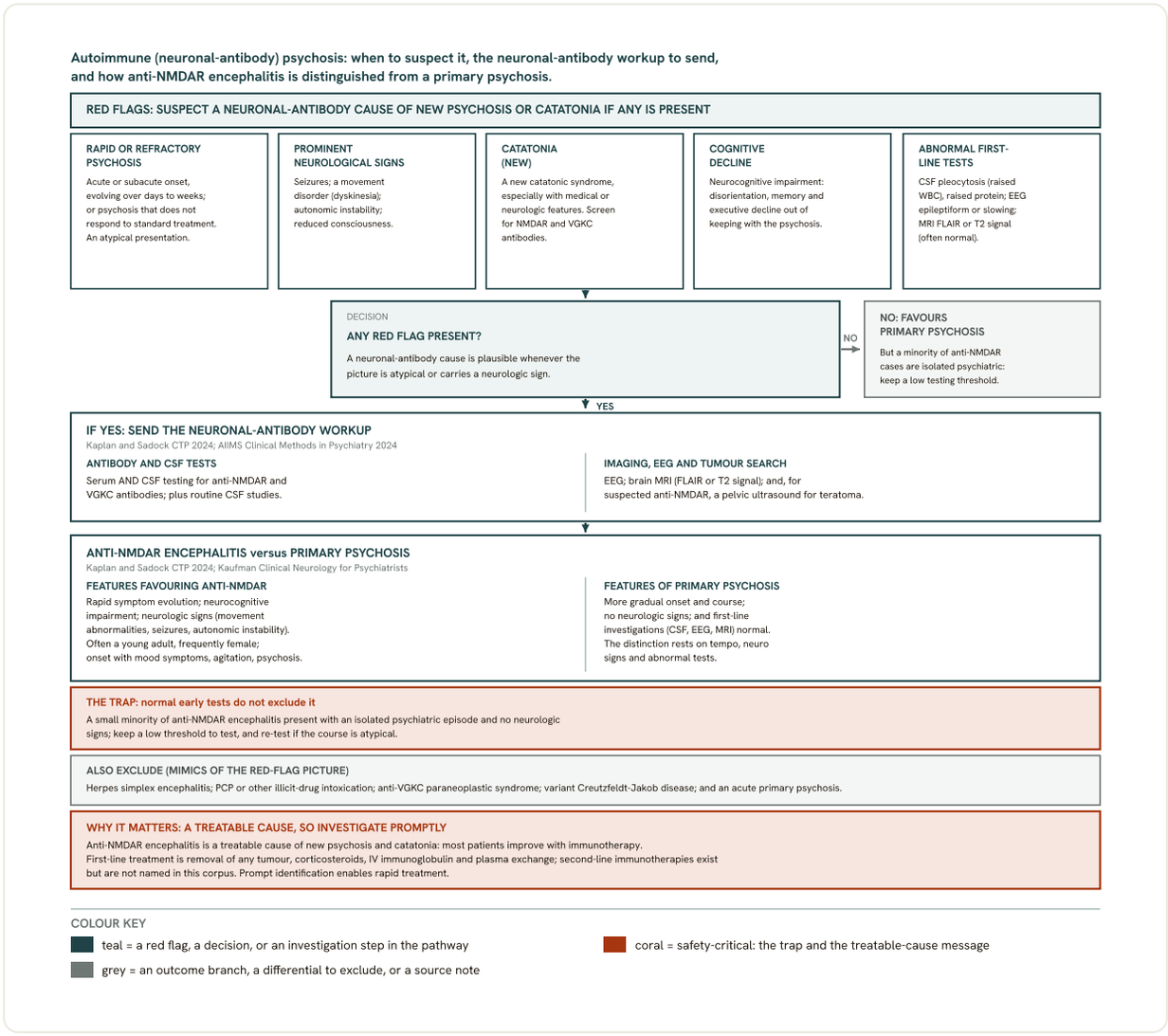


Fig 35.7 Autoimmune (neuronal-antibody) psychosis: the red-flag panel that prompts a neuronal-antibody search. New psychosis or catatonia that is rapid or treatment-refractory, carries neurologic signs (seizures, a movement disorder, autonomic instability, reduced consciousness), shows cognitive decline, or has abnormal first-line tests (CSF pleocytosis, an epileptiform or slow EEG, FLAIR or T2 MRI change) should trigger serum and CSF anti-NMDAR and VGKC antibody testing, routine CSF, EEG, MRI and a search for an underlying tumour. Anti-NMDAR encephalitis is told from a primary psychosis by its rapid tempo, neurocognitive impairment and neurologic signs, but a minority present with isolated psychiatric symptoms, so a treatable diagnosis is not excluded by normal early tests. (Kaplan and Sadock 2024; Kaufman's Clinical Neurology for Psychiatrists; AIIMS Clinical Methods in Psychiatry 2024.)

Read the panel as a trigger, not a diagnosis. Any one of its elements appearing in a patient who would otherwise be filed as a first psychotic episode is enough to move to investigation, because these features are not what a mood or psychotic disorder ordinarily generates and their presence, the neurological ones most of all, raises the prior probability. The individual cues cluster into a memorable spine.

MNEMONIC

Fast onset, Loss of cognition, Abnormal movements and autonomic signs, Generalised seizures

FLAG the psychosis that raises the red flag: **F**ast onset, the **rapid symptom evolution** that a primary psychosis rarely shows; **L**oss of cognition, an early neurocognitive disturbance out of keeping with the affective or psychotic content; **A**bnormal movements and autonomic instability; and **G**eneralised or focal seizures. Each of these is a discriminator that points the assessment away from a primary psychiatric diagnosis and toward an encephalopathic one, and although their weight varies, the neurological and paraclinical ones carrying the most, any single member is enough to keep the autoimmune question open.

18.3 From suspicion to the investigation set

Once an autoimmune or paraneoplastic encephalopathy is suspected, the investigation set is fixed and worth carrying as a unit. The *Comprehensive Textbook of Psychiatry* names four core studies to consider: serum and CSF antibody testing, routine CSF examination, the electroencephalogram, and brain MRI. Serum and CSF are both sampled because the two compartments do not always agree, and the antibody may be demonstrable in one when it is absent or equivocal in the other; a serum result alone can therefore mislead in either direction. The reasoning behind each study is what makes the panel memorable, because the yield is characteristic rather than dramatic and a clinician who expects a florid abnormality will be falsely reassured by a subtle one.

INVESTIGATION	WHAT IT MAY SHOW IN AUTOIMMUNE ENCEPHALOPATHY
Serum and CSF antibody testing	The neuronal antibody itself; sampled in both compartments because they may not agree
Routine CSF studies	Mildly to moderately elevated white cell count and protein, a modest inflammatory signal
EEG	Seizure activity, epileptiform discharges, or focal or generalised slowing
Brain MRI	Often normal; may show signal hyperintensities on FLAIR or T2-weighted sequences

The clinical grammar of the table is that a negative-looking result rarely closes the question. A modestly raised cell count is still an inflammatory finding, generalised slowing on the EEG is still an encephalopathic sign, and a scan reported as normal simply throws the diagnostic weight back onto the antibody and the CSF.

PITFALL

A normal brain MRI does not exclude autoimmune encephalitis. The *Comprehensive Textbook of Psychiatry* is explicit that imaging is often normal, so a clean scan reassures no one; the weight then falls on the clinical picture with the antibody and CSF results, not on the film. The same caution applies to a bland EEG. Treating a normal MRI as a negative test is how a treatable encephalopathy gets relabelled as a primary psychosis and discharged.

18.4 The autoantibody screen and the Indian workup

Indian teaching places the same investigations inside the everyday workup of a striking psychiatric presentation, which is what makes the screen practical rather than exotic. The AIIMS text *Clinical Methods in Psychiatry* sets out the laboratory investigations for catatonia and, among its special tests, lists CSF examination together with an **autoantibody screen** for N-methyl-D-aspartate (NMDA) receptor antibodies and voltage-gated potassium channel antibodies, alongside creatine phosphokinase, serum iron, brain imaging, an EEG to rule out epilepsy, and a drug screen. Sitting the antibody screen inside a standing investigation list, rather than leaving it to be remembered case by case, is precisely what stops it being forgotten in the patient who needs it most. The value is that the autoimmune question is asked routinely of a presentation the psychiatrist meets often, so the treatable cause is looked for before the psychiatric label has hardened.

IN INDIA

When a patient presents with catatonia or an atypical, treatment-refractory psychosis, keep the autoantibody screen for NMDA receptor and voltage-gated potassium channel antibodies, together with a CSF examination, on the investigation list rather than reserving it for the obvious neurological case. Following the AIIMS *Clinical Methods in Psychiatry* workup means the treatable encephalopathy is looked for as a matter of routine and not rescued late in the admission.

18.5 Anti-NMDA receptor encephalitis as an organic cause of catatonia

The pivot of this whole topic is that catatonia, so readily assumed to be psychiatric, has an organic differential the psychiatrist must actively hold. The *Maudsley Prescribing Guidelines* note that a catatonic syndrome is most commonly associated with psychiatric conditions such as bipolar disorder, schizophrenia, and major depressive disorder, but may also arise from a range of underlying medical conditions. Among those medical causes it lists autoimmune encephalitis, of which **anti-NMDA receptor encephalitis** is the archetype; systemic lupus erythematosus; and infections, especially of the central nervous system. The phenomenology of catatonia itself, the Bush-Francis rating, the lorazepam challenge, and malignant catatonia belong to the Other psychotic disorders, delusional syndromes and catatonia notes and are not re-taught here; what this section owns is the recognition that the antibody-mediated encephalitis sits on that organic list at all.

The practical consequence is that a catatonic presentation is never a licence to stop investigating. Reading catatonia as automatically confirming a mood or psychotic disorder is precisely how an antibody-mediated encephalitis is missed, because the psychiatric syndrome is genuine and the

organic cause hides behind it rather than replacing it. The medical differential is the reason the catatonia workup carries a CSF examination and an antibody screen in the first place, and it is why a patient who meets the criteria for catatonia still earns the full red-flag panel.

18.6 Telling autoimmune psychosis from a primary psychosis

When the encephalitis does declare itself psychiatrically, it does so in a recognisable way. The *Comprehensive Textbook of Psychiatry* describes a typically young adult female patient who initially presents with mood symptoms, agitation, psychosis, or other variable psychiatric manifestations, so at first contact the picture overlaps entirely with a primary psychiatric illness and the interview alone cannot separate them. The discriminators are not in the psychiatric symptoms but in what accompanies and surrounds them: a rapid evolution of symptoms, an early **neurocognitive impairment**, and neurologic signs such as movement abnormalities, seizures, and autonomic instability. It is the trajectory and the neurology, not the content of the delusions or the mood state, that break the tie. Two pulls toward the organic diagnosis are worth naming: the mismatch between how severe the syndrome is and how briefly it has taken to appear, and the company it keeps in a movement disorder or a seizure. Neither is proof, and each can occur in a primary disorder, but together they lift the prior enough to justify running the antibody workup in parallel with, rather than after, the steps taken to keep an agitated and confused patient safe. Waiting for the psychiatric picture to declare itself before investigating only delays the point at which appropriate treatment can begin. Where these accompaniments are present, the workup follows with serum and CSF antibody testing and with pelvic imaging in search of an underlying tumour, since an occult neoplasm can drive the process. The primary nosology of schizophrenia belongs to the Schizophrenia: management, antipsychotics and adverse effects notes, and that of depression to the Mood disorders: pharmacotherapy notes; the task retained here is only the discrimination.

> **GOOD TO REMEMBER**
>
> In a first psychotic episode that evolves over days, clouds cognition early, or brings a seizure or an abnormal movement, send serum and CSF for neuronal antibodies and, where anti-NMDA receptor encephalitis is suspected in a young woman, image the pelvis for a teratoma, before you commit to a primary psychiatric diagnosis. The demographic cue, a young woman with an abrupt psychiatric presentation, should raise rather than lower the index of suspicion.

18.7 The diagnostic trap and the mimics

The examination trap in this whole area is a single sentence. A small minority of patients present with an **isolated psychiatric presentation**, that is, psychiatric symptoms with no accompanying neurologic signs, so the reassuring absence of neurology does not exclude the diagnosis and the very feature a clinician leans on to feel safe is the one the syndrome exploits. Around this trap sits a differential the clinician must run before landing anywhere. Kaufman's *Clinical Neurology for Psychiatrists* notes that the picture may initially be mistaken for several other conditions, each of which can imitate the abrupt neuropsychiatric onset.

- Herpes simplex encephalitis, whose viral neuropsychiatry the chapter treats in its own right.

- Phencyclidine or other illicit drug intoxication, which can reproduce the psychosis and the dyskinesia.
- An anti-voltage-gated-potassium-channel antibody paraneoplastic syndrome, part of the limbic-encephalitis spectrum.
- Variant Creutzfeldt-Jakob disease.
- An acute, that is primary, psychosis.

TRAP **"No neurological signs, therefore not autoimmune."** Candidates anchor on the classic case with seizures and dyskinesias and forget that a small minority present with psychiatric symptoms alone. The examiner rewards the answer that keeps the antibody screen in play for the purely psychiatric presentation, because that is the patient the syndrome is most easily lost in.

A first psychotic episode that evolves rapidly, clouds cognition, or brings seizures or abnormal movements is an autoimmune encephalitis until serum and CSF antibodies say otherwise, and it is treatable.

18.8 The immunotherapy of autoimmune psychosis and its outcome

Management follows the same spine as any organic psychosis: where care happens, what it targets, and the modes available. The locus is inpatient and shared with neurology, because the definitive treatment is not psychiatric and the patient may need seizure and autonomic monitoring the psychiatric ward cannot provide alone. The focus is twofold, holding the acute psychiatric presentation safe while the disease-modifying treatment takes effect. The modes are dominated by **immunotherapy**. The *Comprehensive Textbook of Psychiatry* describes treatment as removal of the tumour if one is found, together with the **first-line** agents corticosteroids, intravenous immunoglobulin, and plasma exchange, and sometimes **second-line** immunotherapies. The corpus names the second-line only as a category and not by agent, so this section names it the same way and no further; the specific second-line drugs should be taken from current specialist guidance rather than assumed. Symptomatic psychiatric control, meanwhile, follows the principles set out in the Schizophrenia: management, antipsychotics and adverse effects notes, adjunctive to the immunotherapy and never a substitute for it. Read against the phases of care, the acute focus is the agitation, psychosis and any catatonic features that make the patient unsafe, held with the symptomatic measures the psychiatric team already commands; the mid-term focus is the immunotherapy course itself, delivered under neurology; and the longer-term focus is relapse surveillance rather than discharge on a first remission.

Serum and CSF	**NMDA and VGKC**	**First-line**	**Most improve**
ANTIBODY TESTING IS THE CORE INVESTIGATION	THE AUTOANTIBODY SCREEN IN A RED-FLAG CATATONIA	CORTICOSTEROIDS, IVIG, PLASMA EXCHANGE	ON IMMUNOTHERAPY; SOME RELAPSE

The outcome message is what makes the recognition worth the effort. The *Comprehensive Textbook of Psychiatry* states that most patients with the encephalitis improve with

immunotherapies, though some are left with residual or relapsing symptoms, and that the prompt identification of these autoimmune and paraneoplastic disorders facilitates the rapid initiation of appropriate treatment. That is the safe and defensible claim: the condition is treatable, and recognising it early lets treatment begin. How much a delay costs a given patient's recovery is a further question the source does not settle, and it should not be asserted beyond what the evidence supports. The teaching point stands on its own without that embellishment: find it, and most patients get better, which is exactly why the red-flag panel and the antibody screen are worth carrying in every atypical psychosis.

19 · Herpes simplex and the viral encephalitides with psychiatric sequelae

A survivor of encephalitis who is left amnesic, prone to seizures and altered in personality has almost always been injured in one place, the limbic system, and one virus reaches that territory more reliably than any other. **Herpes simplex encephalitis** is the reason a psychiatrist needs to know this disease well. It is the most frequent cause of serious, sporadic viral encephalitis, it has a mechanical preference for the parts of the brain that carry memory, emotion and social behaviour, and its survivors are handed to psychiatry with exactly the deficits that define the specialty. The marks here are not about culturing a virus. They reward a reader who can read an acute confusional illness for its temporal-lobe signature, explain why the damage produces the syndrome it does, and recognise a late autoimmune sequel that masquerades as relapse. The acute antimicrobial management of the infection itself belongs to neurology and infectious diseases and is directed by current guidance; what follows is the neuropsychiatry, which is where these patients live for the years afterwards.

HSV-1	Medial temporal	Haemorrhagic	Post-HSV NMDAR
THE COMMONEST SPORADIC, NONEPIDEMIC VIRAL ENCEPHALITIS	HIPPOCAMPUS, AMYGDALA AND UNCUS, DIENCEPHALON SPARED	INFERIOR TEMPORAL AND FRONTAL SURFACE, OFTEN BILATERAL	THE AUTOIMMUNE RELAPSE TO WATCH FOR

19.1 The virus, and the surfaces it attacks

The culprit is **herpes simplex virus type 1**, and the single most useful sentence a candidate can hold is that it is the most frequent cause of serious, sporadic viral encephalitis. The word that carries the weight is sporadic, or nonepidemic: unlike the seasonal and vector-borne encephalitides, this one arrives out of no outbreak and in no particular season, which is precisely why it must stay in the differential of any acute encephalopathy whatever the local epidemiology is doing. It is not a common disease in absolute terms, but among the individual, non-epidemic cases of viral brain infection it is the one you will meet.

Its behaviour inside the skull is stereotyped. The virus has a striking predilection for the undersurface of the frontal and temporal lobes, attacking the inferior and medial surfaces rather than the convexity. That anatomy is the whole clinical story in advance, because those surfaces carry the **limbic system**. The acute illness itself looks like most other encephalitides. There is fever, somnolence and delirium, the syndrome of an acutely inflamed brain, and the delirium here is no different in kind from the acute confusional states set out in the Stroke, TBI, delirium

and focal brain syndromes notes. What sets herpes apart is not the acute encephalopathy but where the inflammation settles, and therefore what it leaves behind. A febrile confusional illness that also brings new focal seizures, dense memory failure or a change of personality is not showing you a generic encephalitis; it is showing you the temporal lobe.

19.2 The neuropathology: acute necrotising damage to the medial temporal lobe

Pathologically the disease is an **acute necrotising encephalitis**, and both words matter. It does not simply inflame tissue and resolve; it kills it, which is why the deficits are so often permanent. The destruction is not diffuse but regional, showing a predilection for **the medial temporal lobe structures**. Postmortem and radiological studies converge on the same map: extensive lesions in the hippocampus, amygdala and uncus, the core of the medial temporal memory and emotion circuitry.

The negative half of that map is as examinable as the positive half. The diencephalon is left intact. This is the anatomical fact that separates the amnesia of herpes from the amnesias produced by deeper, midline injury, and it is worth fixing early, because a resident who knows only that both cause memory loss has not yet learned the discriminator. The virus works from the inferior surface inwards, sparing the thalamic and hypothalamic midline while it destroys the temporal lobe above it. Because the necrosis is haemorrhagic, the damaged tissue is not just non-functional but structurally disrupted, and that disruption is what the imaging and, in severe cases, the cerebrospinal fluid go on to reveal.

MNEMONIC

Hippocampus, Amygdala, Uncus

The three medial temporal structures that acute necrotising herpes simplex encephalitis destroys, while the diencephalon is spared. Fix the trio and you hold both the seat of the amnesia and the reason it is a temporal, not a diencephalic, memory loss.

19.3 The limbic signature: amnesia and complex partial seizures

Because the virus damages the limbic system, it routinely produces two neuropsychiatric consequences that follow directly from the anatomy. The first is **amnesia**. The medial temporal structures, and the hippocampus above all, are where new experience is turned into durable memory, so their destruction leaves the survivor unable to lay down new memories reliably, with older knowledge and general intellect relatively better spared. This is the memory loss of temporal-lobe injury, dominated at the bedside by failed new learning, although extensive injury can also erode remote and semantic memory.

Its counterpart is the amnesia of diencephalic damage, in which the lesion sits in the midline that herpes spares and the medial temporal lobe is intact. The two are anatomical mirror images, and holding that contrast is the point: herpes gives you a temporal, limbic amnesia precisely because the diencephalon is left untouched. The distinction is not academic. It tells you where the lesion is before the scan does, it predicts the shape of the deficit, and it stops a clinician from folding every dense amnesia into a single undifferentiated category. When a survivor of a temporal

encephalitis cannot retain new information, the anatomy has already told you why, and the confabulation, executive and gait features that cluster with midline injury are not what you should expect here. Charting the deficit formally is the work of the standardised cognitive instruments owned by the Psychotherapies, clinical assessment, MSE and nosology notes; the teaching here is only that the loss is temporal in origin and dominated by failed new learning.

The second limbic consequence is seizures. Damage to the temporal limbic cortex is epileptogenic, and it characteristically generates **complex partial seizures**, the focal, awareness-impairing seizures that arise from the mesial temporal lobe. In a survivor these are not incidental; the temporal focus that scarred with the infection remains an irritable one, and a chronic seizure liability is one of the commonest long-term legacies of the disease.

RULE **An acute encephalopathy with temporal-lobe localising features is herpes simplex encephalitis until proven otherwise.** Because herpes is the commonest sporadic viral encephalitis and it preferentially attacks the inferior and medial temporal surface, a febrile confusional illness accompanied by new complex partial seizures, dense anterograde memory failure, aphasia or a change of behaviour points to the temporal lobe, and therefore to this diagnosis, before any less common cause.

19.4 Kluver-Bucy features, aphasia and the frontal behavioural change

The behavioural sequelae are where herpes stops being a neurology problem and becomes a psychiatry one. Where the temporal destruction is one-sided the patient is left amnesic and seizure-prone, but when it involves **both temporal lobes** a further syndrome emerges. Bilateral temporal lobe damage in some survivors produces the human variety of the **Kluver-Bucy syndrome**, the behavioural picture of bilateral amygdala and anterior temporal injury, with altered emotional reactivity and changes in oral and sexual behaviour. The examinable discriminator is the laterality: this syndrome appears only when the damage is bilateral, and permanent temporal injury in this disease is often bilateral, which is why the syndrome is seen at all.

The inferior frontal involvement adds its own layer. Frontal and temporal lobe damage together can produce **aphasia** when the dominant hemisphere is affected, and, from the orbitofrontal and inferior frontal surface, the frontal lobe behavioural disorders of disinhibition, apathy and impaired social judgement. Put together, the survivor a psychiatrist meets may be amnesic, dysphasic, behaviourally disinhibited and emotionally altered, all from a single infection that respected the anatomy of the limbic and inferior frontal surfaces.

NEUROPSYCHIATRIC SEQUEL	ANATOMICAL SUBSTRATE	THE EXAMINABLE POINT
Amnesia	Medial temporal, hippocampus	Temporal, not diencephalic; failed new learning
Complex partial seizures	Mesial temporal irritative focus	A lasting seizure liability in survivors
Kluver-Bucy syndrome	Bilateral amygdala and anterior temporal lobe	Requires bilateral damage
Aphasia and behavioural change	Dominant temporal and inferior frontal surface	The personality change fielded by psychiatry

PITFALL

Reading the survivor as a primary psychiatric disorder. A patient left with the amnesia, disinhibition and altered emotional and sexual behaviour of temporal-lobe injury can be mistaken for a functional or psychotic presentation, especially when the acute illness was mild or was never recognised. The anatomical signature, a temporal amnesia with Kluver-Bucy features after bilateral injury, is what re-anchors the assessment on the brain rather than on the biography.

19.5 Investigation: imaging, the CSF and the electroencephalogram

The diagnostic effort is aimed at demonstrating the temporal-lobe process and excluding its mimics. In herpes and the other encephalitides the useful tests are a defined set:

- Lumbar puncture to examine the cerebrospinal fluid, which in the severe, haemorrhagic case may itself be revealing.
- Computed tomography, widely available and often the first scan to hand, though it is the less sensitive of the two structural tests early in the illness and magnetic resonance imaging is the preferred modality.
- Magnetic resonance imaging, which shows the temporal-lobe changes with far greater sensitivity.
- The electroencephalogram, useful where a temporal focus or a seizure tendency needs to be demonstrated.

On imaging the characteristic finding is hyperintensity in the inferior gyri of the temporal lobe, the radiological face of the same medial temporal disease. Herpes typically causes haemorrhagic inflammation of the inferior surface of the temporal and frontal lobes, and this is often bilateral, so the imaging mirrors the neuropathology structure for structure. In the most severe cases the temporal-lobe process becomes frankly destructive: haemorrhagic infarction allows blood to seep into the cerebrospinal fluid, so a bloody or xanthochromic tap in the right clinical setting is a corroborating sign rather than a red herring. The electroencephalogram contributes by localising, showing a disturbance over the affected temporal region that fits the rest of the picture, though a single recording never excludes the diagnosis. The logic of the investigation is worth making explicit, because each test answers a different question. Imaging asks where the tissue is damaged and shows the temporal-lobe process directly; the cerebrospinal fluid asks whether the illness is

inflammatory and, in the destructive case, betrays the haemorrhage; and the electroencephalogram asks whether that damaged temporal cortex has become electrically irritable. No single one of them is the whole answer, and the diagnosis is read from the pattern they make together against the clinical story rather than from any one result in isolation.

19.6 Managing the neuropsychiatric sequelae

Care runs across settings and phases. The acute illness is severe and is managed as an inpatient by neurology and infectious diseases; the antimicrobial treatment of the infection itself is directed by current guidance and is not reproduced here, and no regimen should be quoted from memory. The psychiatrist's work is what comes after, and it moves from the acute ward, through neurorehabilitation, to long-term outpatient follow-up.

The targets shift with the phase. In the acute and subacute period the problem is the encephalopathy and the emergent seizures. Over the longer term the picture is dominated by the amnesia, the chronic seizure liability, the behavioural change and the mood consequences of a life altered by brain injury. Across those targets the available modes are the familiar ones. The seizure disorder is managed as any structural focal epilepsy would be, under the relevant current guidance, which these notes do not restate. Symptomatic psychotropic treatment of the behavioural and affective sequelae is guided by the specific syndrome rather than by any protocol unique to herpes, and doses are not owned here. Cognitive rehabilitation, structured environmental and behavioural support, and sustained work with the family carry as much of the load as any drug, because a dense amnesia and a disinhibited survivor are managed at least as much by structure and support as by prescription. Where a guideline would ordinarily anchor a management section, the honest position is that the allowed evidence names none specific to this disease, so the reasoning is taught and the reader is pointed to current neurological and psychiatric guidance rather than to a remembered rule.

19.7 The late autoimmune sequel: anti-NMDA receptor encephalitis after herpes

The most important recent addition to this topic is a late complication that turns a recovering patient into a deteriorating one. Some patients, in the weeks after an apparent recovery from the viral illness, develop a fresh neurological and psychiatric decline, and case series have linked this to prior herpes simplex encephalitis. The entity is **anti-NMDA receptor encephalitis**, whose antibody, tumour associations and immunotherapy are set out among the autoimmune encephalitides covered elsewhere in these notes and are not repeated here. What belongs to herpes is the link and its clinical consequence.

The leading explanation is that the destruction of neural tissue by the virus exposes neuronal antigens to the immune system, which then mounts an antibody response against receptors on the surviving neurons; the mechanism is a hypothesis rather than a settled fact, but the clinical rule stands independently of it. A new movement disorder or a new psychiatric and behavioural deterioration arising after the acute infection has apparently settled should not be assumed to be recrudescent infection. It should prompt testing for neuronal surface antibodies, because the treatment that helps an antibody-mediated relapse is not the treatment of the virus. This is the

practical reason a herpes survivor who worsens weeks later is reviewed by the same clinicians rather than discharged as recovered.

TRAP **A fresh deterioration weeks after apparent recovery from herpes simplex encephalitis is not automatically a relapse of the virus.** Candidates and clinicians reflexively read a second decline as recrudescent infection and re-treat the virus, missing the post-herpes anti-NMDA receptor encephalitis that some case series describe. The tell is a new movement disorder or psychiatric change after recovery had begun; the answer is to test for the antibody, not to re-run the original assumption.

19.8 Holding herpes in the differential

The practical synthesis is a discipline about the differential. Herpes leaves a signature that is anatomical before it is serological: an acute confusional illness that carries temporal-lobe features, an amnesia of new learning, complex partial seizures, aphasia or a behavioural change, with imaging that shows the inferior and medial temporal surface. Recognising that signature is what earns the marks and, more importantly, what directs the investigation toward the temporal lobe and the cerebrospinal fluid.

GOOD TO REMEMBER

In a patient with an acute confusional illness and either new complex partial seizures or a dense failure of new memory, image the temporal lobes and examine the cerebrospinal fluid. The inferior temporal and frontal surface is where herpes leaves its mark, and in the severe, haemorrhagic case blood in the CSF is a corroborating clue rather than a distraction.

IN INDIA

The acute encephalitis syndrome here carries a broad endemic and epidemic differential that is set out elsewhere in these notes. The clinical discipline this section adds is to keep herpes simplex encephalitis firmly inside that differential whenever the picture is temporal, precisely because it is sporadic and nonepidemic: it does not announce itself with an outbreak or wait for a season. When a febrile encephalopathy brings temporal-lobe localising features, pursue the localising investigations, imaging of the temporal lobes and examination of the cerebrospinal fluid, rather than anchoring on the endemic causes alone.

Herpes simplex is the commonest sporadic viral encephalitis; it attacks the medial temporal and inferior frontal limbic surfaces, so survivors carry amnesia, complex partial seizures, Kluver-Bucy features and behavioural change, and a fresh deterioration weeks later is anti-NMDA receptor encephalitis until disproved.

Neurosyphilis and CNS infections

20 · Neurosyphilis and general paresis of the insane: stages, features and treatment

A treatable dementia hides inside this topic. Neurosyphilis is the neurological expression of an infection that medicine can cure outright, which is exactly why examiners keep it alive long after the disease itself became uncommon. It is the model of a reversible organic psychosis, and the candidate who recognises it changes the whole trajectory of the patient in front of them. It earns its marks because it sits at the junction of infection, dementia and florid psychiatric disturbance, because its physical signs are unmistakable once they are known, and because it remains a live differential wherever syphilis is still transmitted. This section follows the organism from its silent latency, through the early meningeal and vascular forms, to the two late parenchymatous syndromes of general paresis and tabes dorsalis, and closes on how the diagnosis is secured and treated.

20.1 The organism and the natural history

Neurosyphilis is caused by persistent infection with the spirochaete **Treponema pallidum**, and its neuropsychiatric syndromes are the delayed consequence of that organism seeding the meninges and the cerebral vessels early and, later, the substance of the brain and cord, stages that can overlap rather than following a fixed sequence. The epidemiology carries a strong HIV association: coinfection is actively looked for, and with advanced immunosuppression the disease can run a more aggressive course, though neurosyphilis is seen in HIV-positive and HIV-negative patients alike. A disease once associated with the untreated syphilis of the pre-antibiotic era is therefore looked for actively wherever syphilis is still transmitted, rather than waited for.

An asymptomatic stage, in which the organism is present in the nervous system but clinically silent, precedes overt disease by a variable latency. When neurosyphilis does declare itself, it does so in several symptomatic forms: acute syphilitic meningitis, meningovascular syphilis, general paresis and tabes dorsalis, each with its own tempo and its own signature, and these forms may overlap. The organising axis worth carrying is early versus late. Early neurosyphilis affects the coverings and blood vessels of the nervous system and appears in the first years after infection. Late neurosyphilis is **parenchymatous syphilis**: the organism has invaded the nervous tissue itself, and where it settles decides the syndrome, with infection of the brain producing general paresis and infection of the spinal cord producing tabes dorsalis. This anatomical logic is worth holding onto, because it predicts the clinical picture from first principles: a cerebral parenchymal infection presents as a dementia with psychiatric colouring, whereas a cord infection presents as a sensory and gait disorder, so the same organism produces two syndromes that look nothing like each other.

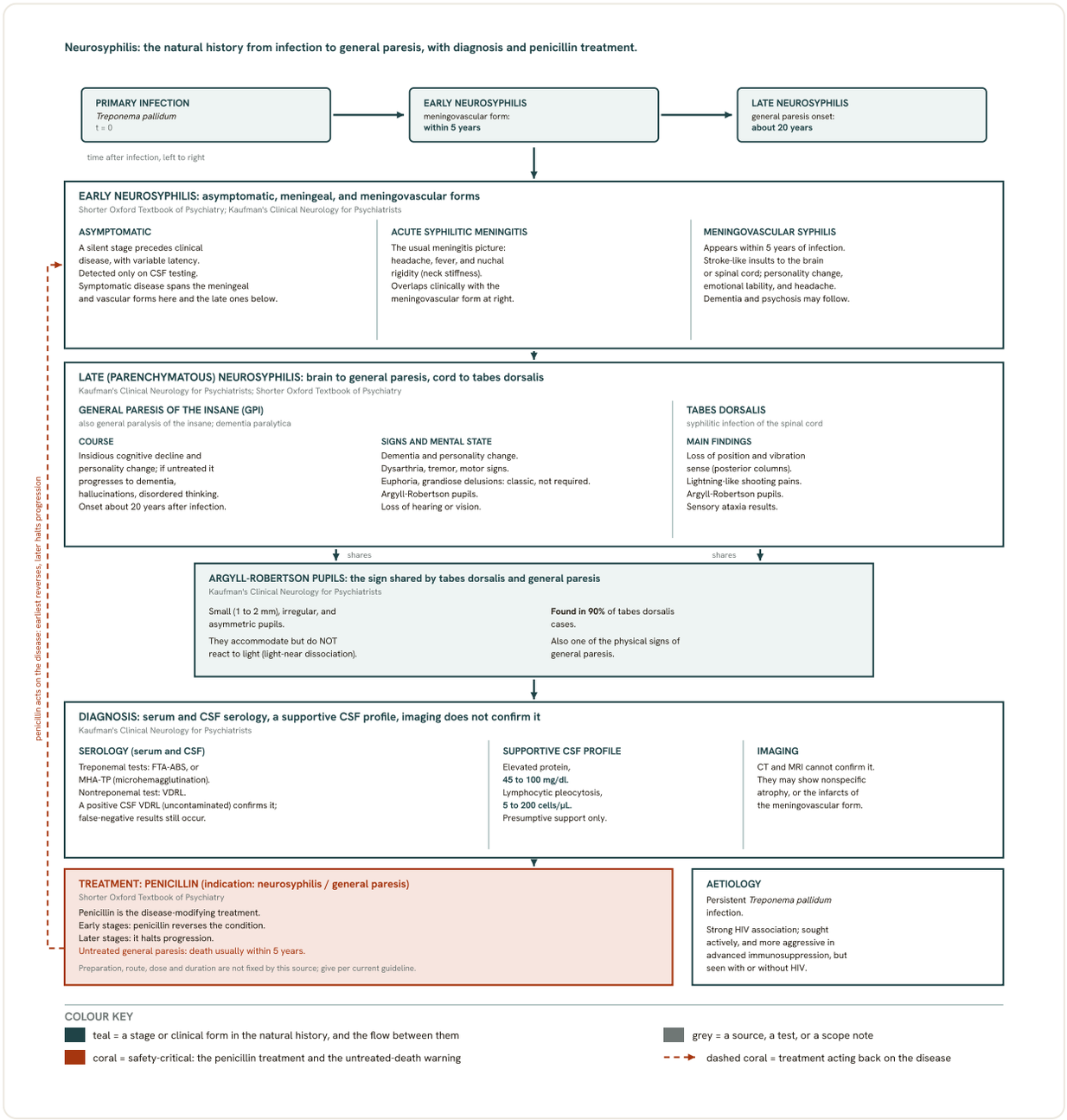


Fig 35.8 **Neurosyphilis across the natural history of syphilis.** Persistent Treponema pallidum infection runs from an asymptomatic stage through early neurosyphilis (acute syphilitic meningitis and meningovascular syphilis, the latter within 5 years) to late parenchymatous disease, in which brain involvement gives general paresis of the insane (dementia, personality change, dysarthria, euphoria with grandiose delusions, and Argyll-Robertson pupils, onset about 20 years after infection) and spinal-cord involvement gives tabes dorsalis; the small, irregular, light-near-dissociated Argyll-Robertson pupil is the shared sign. Diagnosis rests on treponemal and nontreponemal serology in serum and CSF with a supportive CSF profile, since imaging is nonspecific, and penicillin reverses early disease and halts later progression. (Shorter Oxford Textbook of Psychiatry; Kaufman's Clinical Neurology for Psychiatrists.)

The accompanying figure sets this natural history out from silent latency through the meningeal and meningovascular forms to the two late parenchymatous syndromes. The comparison below fixes the same map in a form the reader can scan at the bedside.

FORM	SITE OF INJURY	TYPICAL ONSET	HALLMARK
Acute syphilitic meningitis	Meninges	Early	Headache, fever, nuchal rigidity
Meningovascular syphilis	Cerebral and spinal arteries	Within 5 years	Stroke in the young; personality change, emotional lability
General paresis	Brain parenchyma	About 20 years	Dementia, personality change, dysarthria; florid affective and psychotic features
Tabes dorsalis	Spinal cord	Late	Sensory ataxia, lightning pains, Argyll-Robertson pupils

IN INDIA

Where syphilis remains in active transmission, a treatable spirochaetal cause belongs on the differential of any atypically young patient who presents with a dementia, an unexplained psychosis, or a stroke without vascular risk factors. The clinical decision is worth making a reflex: send a syphilis serology and examine the cerebrospinal fluid before the picture is written off as a primary psychiatric or neurodegenerative disorder, because this is the one such presentation that fully reverses when it is caught early.

20.2 Early neurosyphilis: meningitis and meningovascular disease

The earliest symptomatic form is **acute syphilitic meningitis**, which produces the usual symptoms and signs of meningitis - headache, fever and nuchal rigidity - and is easily missed simply because syphilis is rarely the first organism a clinician thinks of behind a lymphocytic meningitis. It shades into **meningovascular syphilis**, the form in which the inflammatory reaction centres on the walls of the cerebral and spinal arteries and sets up an obliterative endarteritis that narrows and occludes them. The two overlap in time and in mechanism, which is why they are considered together as the early, extra-parenchymatous face of the disease.

Meningovascular syphilis characteristically appears within 5 years of the primary infection, far sooner than the late parenchymatous forms, and it presents with two faces. It may declare itself abruptly as a stroke, an ischaemic insult to the brain or spinal cord occurring in a patient who is too young and too free of atherosclerotic risk factors for ordinary vascular disease. Alternatively it may creep in with personality change, emotional lability and headache. The stroke here is not embolic but the end result of that arteritic narrowing, an infarction in a vessel inflamed from without, which is why it can strike arteries and ages that atherosclerosis would ordinarily spare. Where the vascular injury accumulates, a dementia can follow, and that dementia may be coloured by psychotic symptoms, so the presentation reaches the psychiatrist as readily as the stroke physician. A stroke in the young without an obvious cause is one of the situations in which the syphilis serology earns its keep.

20.3 General paresis: latency, onset and course

The cerebral parenchymatous form, and the one that most concerns psychiatry, is **general paresis**, historically named general paralysis of the insane and also dementia paralytica. It is a disease of long incubation, starting to develop **about 20 years** after the original infection, so the patient who presents has usually long forgotten, or never knew of, the primary chancre. That latency is itself a diagnostic trap: nothing in the recent history points back to an infection acquired a generation earlier, and the connection has to be made from the clinical picture rather than the story.

The onset is insidious. The first changes are nonspecific cognitive impairments and a shift in personality that families register before clinicians do, and which are readily mistaken for depression, for an early dementia of another cause, or simply for ageing. If it is left untreated the process is relentless. The cognitive decline deepens into a frank dementia, and hallucinations and disordered thinking supervene. This drift from the subtle to the florid is what earned general paresis its old reputation as a great imitator of psychiatric illness, and it is the reason a subacute cognitive and personality change of uncertain cause should keep neurosyphilis somewhere on the list. The breadth of that differential is the point. General paresis can be taken in turn for a mood disorder when apathy and slowing dominate, for a primary psychosis when hallucinations and disordered thinking are prominent, and for a degenerative dementia when the cognitive decline leads; only the accompanying organic signs and the serology cut cleanly across all three.

20.4 The clinical picture of general paresis

Fully developed general paresis is a compound of a dementia, a personality change, dysarthria, and a scatter of motor symptoms and signs. Onto that organic base the illness may graft florid affective and psychotic phenomena. The classic portrait is of euphoria and expansive grandiose delusions, the patient of boundless wealth and importance, and it is this image that has fixed the disease in the examination memory. The mental changes seldom come alone, however, and it is the accompanying physical signs that betray the organic nature of the illness and steer the clinician away from a purely psychiatric reading.

TRAP **Grandiosity is the famous sign of general paresis, not a necessary one.** The Shorter Oxford Textbook of Psychiatry preserves the classic teaching of euphoria and grandiose delusions as the signature affective picture, and candidates duly memorise it as though its absence excluded the diagnosis. The examiner's counter is that Kaufman's Clinical Neurology for Psychiatrists records the opposite emphasis, that grandiose delusions, for all their notoriety, in fact arise only rarely. Treat grandiosity as a useful clue when it is present and never as a rule-out when it is not; the constant early thread is the nonspecific decline in cognition and personality, not the mood colouring laid over it.

The organic signature is a set of physical abnormalities that accompany the cognitive impairment: dysarthria, tremors, the Argyll-Robertson pupil, and loss of hearing or vision. The value of these signs is discriminative. A subacute dementia with personality change is a wide differential, but a subacute dementia with dysarthria, a tremor and an abnormal pupil is a narrow one, and it points hard toward an organic and specifically an infective cause. Examining for these

signs is therefore not a formality but the step that reframes the whole presentation. It is also the step that most often fails to happen, because a patient referred for grandiosity or a change in conduct is easily received as a psychiatric admission and never has the pupils, the speech and the gait examined at all.

20.5 Tabes dorsalis

The spinal parenchymatous form is **tabes dorsalis**, a disease of the dorsal columns and dorsal roots that produces a distinctive sensory syndrome rather than a dementia. Because the affected tracts carry proprioception and vibration, the patient loses the sense of where the limbs are in space, and the deficit expresses itself as a sensory ataxia: an unsteady, stamping, high-stepping gait that worsens sharply when the eyes are closed and the visual substitute for position sense is removed.

Its cardinal findings are:

- loss of position and vibration sensation, the deficit that underlies the sensory ataxia;
- lightning-like pains, brief lancinating shocks that shoot through the limbs or trunk;
- Argyll-Robertson pupils.

Tabes matters to the psychiatrist for two reasons beyond its own morbidity. It is the syndrome in which the Argyll-Robertson pupil is most reliably found, so recognising it anchors the pupillary sign, and it may coexist with general paresis in the same patient, so a dementia accompanied by prominent dorsal-column sensory loss should still raise neurosyphilis rather than being split into two unrelated diagnoses.

20.6 The Argyll-Robertson pupil

No physical sign is more firmly bound to neurosyphilis in the examiner's mind than the **Argyll-Robertson pupil**. The pupils are small, measuring 1-2 mm, and they are irregular and asymmetric between the two eyes. Their defining behaviour is a dissociation: they constrict briskly on accommodation, when the patient fixes on a closely held object, yet they fail to constrict to light. This **light-near dissociation** is the whole of the sign, and it is the origin of the bedside shorthand that the pupils accommodate but do not react.

MNEMONIC

Accommodates, but does not react

The Argyll-Robertson pupil keeps its near response and loses its light response: it **accommodates** to a close target **but does not react** to a light shone into it. Small, irregular and asymmetric complete the picture, and the four features together are far more specific than any one alone.

The sign is not merely characteristic but genuinely common in the spinal form. The constellation of small, irregular, unreactive pupils is found in **90%** of tabes dorsalis cases, which is why the pupils are the first thing examined when tabes is suspected. The same pupils appear in general paresis, so across neurosyphilis as a whole the Argyll-Robertson pupil is among the most useful physical signs available without any instrument at all.

20.7 Securing the diagnosis: serology, cerebrospinal fluid and imaging

The diagnosis rests on the laboratory, not the scanner. Serological testing is built on two classes of test that answer different questions. **Treponemal tests**, the fluorescent treponemal antibody absorption test (FTA-ABS) and the treponemal microhaemagglutination assay (MHA-TP), detect antibody directed against the organism itself and establish that infection has occurred. **Nontreponemal tests**, principally the VDRL, detect the reaginic antibody that tracks active disease. A VDRL that is positive in an uncontaminated cerebrospinal-fluid specimen confirms neurosyphilis.

> **PITFALL**
>
> A negative cerebrospinal fluid VDRL does not exclude neurosyphilis. The test is specific but insensitive in the fluid, and false-negative results are well recognised, so a strong clinical picture with a supportive fluid profile is treated and followed as neurosyphilis even when the VDRL there is negative. Reading a negative result as a rule-out is one of the commonest ways the diagnosis is missed.

The cerebrospinal fluid itself supports the diagnosis when it carries the marks of chronic meningeal inflammation: an elevated protein concentration, in the range of 45-100 mg/dl, and a lymphocytic pleocytosis of 5-200 cells/μL. These are supportive rather than confirmatory, and they belong to the presumptive picture that, taken together with the serology and the clinical syndrome, secures the diagnosis. Apart from a reactive cerebrospinal-fluid VDRL, no single result carries the diagnosis by itself, and the working discipline is to weigh the serology, the fluid and the clinical picture as one presumptive case rather than waiting for any one of them to be unequivocal before treating.

> **GOOD TO REMEMBER**
>
> Do not expect imaging to make the diagnosis. In neurosyphilis, CT and MRI cannot confirm the diagnosis: they may show nonspecific cerebral atrophy, perhaps weighted toward the frontal lobe, or the infarcts of the meningovascular form, but no pattern is specific to the infection. A scan is worth doing to exclude other causes, but a normal or nonspecifically atrophic scan neither confirms nor refutes neurosyphilis; the answer lies in the serology and the fluid, and time spent chasing an imaging signature is time lost.

20.8 Treatment and prognosis

The treatment is penicillin, and the single most important thing about it is how sharply the timing changes the result. Given in the early stages, penicillin reverses the condition; given later, once parenchymatous disease is established, it halts further progression but cannot restore what has already been lost. Care is led by the physician, while the psychiatrist manages the behavioural and psychotic disturbance in parallel across the acute and longer-term phases, but the disease-modifying step is antibiotic and it should not wait on the psychiatric picture settling first. The phases of care map cleanly: the acute task is to contain the behavioural disturbance and any agitated or psychotic features and to deliver the antibiotic; the medium-term task is to

consolidate cure and manage the residual cognitive and personality change; and the longer-term task is rehabilitative and social, supporting a patient whose late damage will not fully reverse.

RULE **Penicillin reverses early neurosyphilis and halts it later, so the entire clinical yield of the topic lies in remembering to test for it.** Because the organic damage of the late forms is only partly reversible, both the marks and the patient's outcome turn on making the diagnosis early. There is no version of this disease that is better left untreated, and none in which delay is neutral.

Untreated, the outlook is bleak. Once general paresis has declared itself, death usually follows within **5 years**. That figure is the counterweight to the reversibility above, the same disease resolving on early antibiotic yet killing within a few years when it is left alone. The precise regimen - the drug preparation, dose, route and duration - is a matter for current infectious-disease guidance rather than something this section can settle from its sources; what the examinable core fixes is the principle, that penicillin is curative early and protective late, not the milligrams.

~20 yrs	90%	5 yrs
LATENCY TO GENERAL PARESIS	ARGYLL-ROBERTSON PUPILS IN TABES	SURVIVAL IF UNTREATED

Any young patient with an unexplained dementia, psychosis or stroke earns a syphilis serology and a look at the pupils - neurosyphilis is the treatable one you cannot afford to miss.

21 · Neurocysticercosis and the endemic neuroinfections of India

The neuroinfections in this account are the ones an Indian psychiatrist genuinely meets, and each of them reaches the clinic wearing a psychiatric face. **Neurocysticercosis**, cerebral malaria and Japanese encephalitis together account for much of the seizure activity, cognitive decline, psychosis, delirium and encephalopathy that tropical central nervous system infection contributes to a psychiatric caseload. The marks gather here because the field rewards a clean map: pair each disease with the clinical clue that raises it, the investigation that confirms it, and the neuropsychiatric signature it leaves behind. The accompanying figure sets out that map before the detail is worked through.

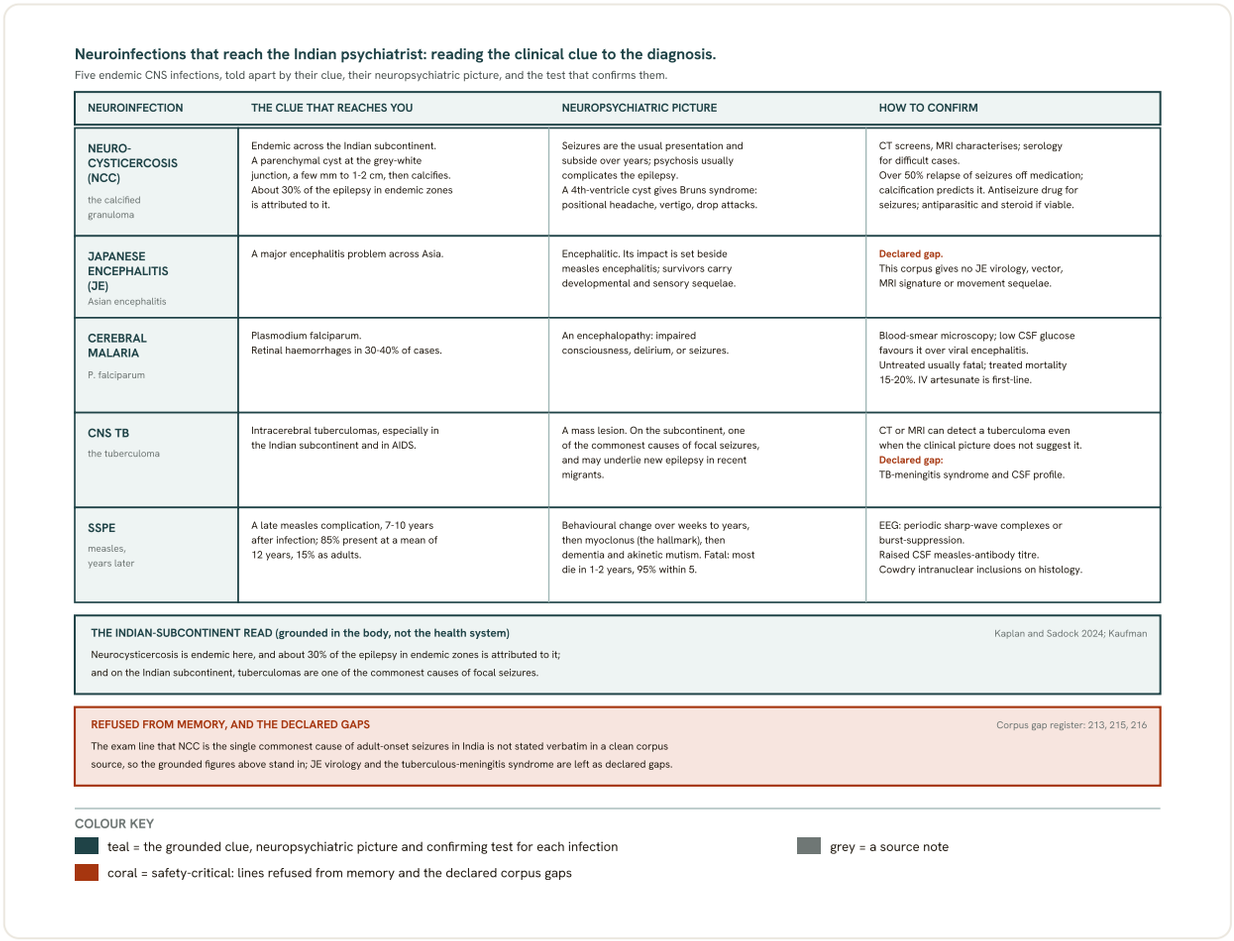


Fig 35.9 Endemic neuroinfections that reach the Indian psychiatrist, read from clinical clue to diagnosis. Neurocysticercosis (a calcified grey-white-junction granuloma, seizures the usual presentation, psychosis usually complicating the epilepsy), Japanese encephalitis (grounded here only as a major Asian encephalitis with measles-like outcomes), cerebral malaria (Plasmodium falciparum encephalopathy, retinal haemorrhages, blood-smear diagnosis, treated mortality of 15 to 20%), CNS tuberculoma (a mass lesion and, on the subcontinent, a leading cause of focal seizures), and subacute sclerosing panencephalitis (a late measles complication with myoclonus, periodic EEG complexes and a raised CSF measles titre). The exam cliche ranking neurocysticercosis first for adult-onset seizures in India is not stated verbatim in the clean corpus, so only the defensible figures are shown; Japanese-encephalitis virology and the tuberculous-meningitis syndrome are marked as declared gaps. (Kaplan and Sadock 2024; Kaufman's Clinical Neurology for Psychiatrists; Companion to Psychiatric Studies.)

Neurocysticercosis is the anchor of this section and is taught in full; cerebral malaria and Japanese encephalitis are the two other endemic neuroinfections taken up here. The chronic and subacute neuroinfections, including CNS tuberculosis, are addressed with the rare chronic infections elsewhere in these notes, and neurosyphilis has its own dedicated account; they are named here only where they belong in a differential.

21.1 The pork tapeworm and how its larva reaches the brain

Neurocysticercosis is disease of the central nervous system produced when the larvae of the pork tapeworm, **Taenia solium**, penetrate the CNS and encyst. Its geography is the geography of poverty and poor sanitation: it is endemic across most of the developing world, including the Indian subcontinent, most of Southeast Asia, sub-Saharan Africa, Central and South America and parts of China. For the clinician the decisive fact about transmission is how the larva reaches a human host. Infection is acquired by the faecal-oral route, through close contact with a Taenia solium carrier who is excreting eggs in the faeces, so the parasite passes from person to person

and the affected patient need not have eaten pork at all. A household or food-handler contact harbouring the adult tapeworm is the reservoir, which is why a contact history is often more revealing than a dietary one.

Once the eggs are ingested the embryos cross the gut wall, disseminate to the tissues, and the larval cysts reach their usual size in **2 to 3 months**. The illness itself, however, typically declares only years after the original infection, when the established cyst begins to degenerate and the host immune system turns on it. That long latency explains why the disease presents in adults with no recalled exposure and no acute prodrome, and why the parasite is so easily missed as the cause of a first seizure. The reason for the delay is immunological: a viable cyst is remarkably well tolerated, dampening and evading the host response so that it can sit quietly in the brain for years, and it is only when the larva dies, whether spontaneously or under treatment, that the surrounding tissue inflames and the disease becomes clinically loud. Holding on to that reversal, that the danger tracks the immune reaction to a dying parasite rather than the living one, is the single idea that runs through the whole of the presentation and the treatment.

21.2 The endemic burden: silent cysts and adult seizures

The public-health weight of neurocysticercosis is easy to underestimate because most infection is silent. In the endemic zones, seroepidemiological work finds specific antibodies in a substantial minority of the general population, and the healed footprint of old cysts, intraparenchymal brain calcification, is present on imaging in a considerable fraction of ordinary people scanned for other reasons; the great majority of these individuals never develop symptoms. What gives the disease its clinical importance is its contribution to epilepsy, and a large share of all epilepsy in the endemic regions is attributable to the parasite. The figures below fix the scale.

30%	**> 10%**	**10 to 20%**
OF EPILEPSY IN ENDEMIC REGIONS ATTRIBUTABLE TO THE PARASITE	OF THE ENDEMIC POPULATION CARRY SPECIFIC SERUM ANTIBODIES	HAVE INTRAPARENCHYMAL CALCIFICATION ON CT, MOSTLY ASYMPTOMATIC

The mechanism that links the parasite to seizures is not the living cyst, which is largely tolerated, but its death: as the larva degenerates and calcifies it becomes an epileptogenic focus in the surrounding cortex. This is why a single calcified or degenerating granuloma is so often the substrate of an adult-onset seizure in an endemic setting, and why such a seizure deserves imaging rather than a reflex diagnosis of idiopathic epilepsy.

IN INDIA

Where cysticercosis is endemic, a first adult-onset seizure is imaged rather than assumed to be idiopathic epilepsy, because a solitary calcified or degenerating granuloma is a common substrate and its seizures are treatable. The clinical decision that follows from the biology is to obtain neuroimaging before committing a patient to a lifelong epilepsy label, and to hold the other great endemic mass lesion, the tuberculoma, in the same differential; that chronic infection is taken up with the subacute neuroinfections elsewhere in these notes.

21.3 Where the cysts lodge and the parenchymal natural history

The lesions of neurocysticercosis are small. Individual cysts range from a few millimetres to 1 to 2 centimetres in size, and they settle characteristically at the grey and white matter junction of the cerebral hemispheres, or within the deep grey matter. That distribution follows the blood supply, since the parasite is delivered haematogenously and lodges where perfusion is richest, and it is the reason the cortical and subcortical seizure focus is the commonest expression of the disease.

The natural history of purely parenchymal disease is comparatively benign. Patients whose lesions are confined to the brain parenchyma typically present with seizures only, and these tend to subside over the years as the cysts involute and calcify. A single cyst moves through a predictable arc, from a viable, fluid-filled vesicle that provokes little reaction, through a degenerating and inflamed phase in which seizures are most likely, to a small calcified scar that marks where it once sat; the calcification seen so often on imaging is simply the end point of that arc. This self-limiting parenchymal course stands in deliberate contrast to the extraparenchymal forms, in which cysts sit in the ventricles or the subarachnoid space, obstruct the flow of cerebrospinal fluid, and turn a nuisance disorder into a neurosurgical emergency. In the subarachnoid space the parasite can excite a dense inflammatory arachnoiditis that entraps vessels and cranial nerves, and in the ventricles it can block cerebrospinal fluid outflow to produce hydrocephalus, so the extraparenchymal disease threatens the patient by mechanisms the parenchymal form never reaches. It is these forms that carry the danger, and they are the subject of the next section.

21.4 The dangerous forms: cysticercotic encephalitis and Bruns syndrome

Two presentations move neurocysticercosis from an outpatient seizure problem to a life-threatening one. The first is **cysticercotic encephalitis**, in which a very large cyst burden provokes severe, diffuse cerebral inflammation with seizures and raised intracranial pressure. It occurs more often in children and young women, a distribution that reflects the intensity of the host immune response rather than any difference in exposure, and it is the immune reaction, not the parasite alone, that threatens the patient.

The second is **Bruns syndrome**, produced by a mobile cyst in the fourth ventricle. When the patient moves the head the cyst intermittently occludes the outflow of cerebrospinal fluid, a **ball-valve mechanism** that generates abrupt, positional surges of intracranial pressure. The clinical picture is characteristic and worth carrying whole:

- Episodic, severe headache.
- Vomiting.
- Vertigo.
- Sudden loss of consciousness precipitated by movement of the head.

TRAP **Reaching for an anthelmintic first in cysticercotic encephalitis.** When a heavy cyst burden is killed all at once the inflammatory storm intensifies, so in this fulminant form antiparasitic treatment given on its own can worsen the illness and prove fatal. The swelling and the host immune reaction are controlled first, and cyst-directed therapy is withheld or deferred until it is safe.

21.5 The neuropsychiatric presentations

The reason neurocysticercosis lands on a psychiatric desk is that its cortical footprint disturbs cognition and, through the epilepsy it causes, mental state. Cognitive impairment is common and spans a wide range, from a mild reduction in cognitive performance through to a severe dementia, depending on lesion burden, location and the seizure history. The formal characterisation of that impairment, with the standardised bedside cognitive instruments, belongs to the Psychotherapies, clinical assessment, MSE and nosology notes; what matters here is that a dementing picture in a patient from an endemic region should prompt a search for calcified cysts rather than an assumption of a primary neurodegenerative process. Because a share of the cognitive disturbance is driven by the seizures and by active inflammation rather than by fixed tissue loss, some of it is potentially modifiable, which is a further reason not to close the assessment at a diagnosis of irreversible dementia.

Psychotic episodes also occur, and the best current reading is that they arise largely as a complication of the epilepsy rather than as a direct parasitic psychosis. The distinction is practical: it directs attention to seizure control and to the peri-ictal and interictal mechanisms of psychosis rather than to the cyst itself. The primary nosology and management of a psychotic illness are set out in the Schizophrenia: management, antipsychotics and adverse effects notes, and of depressive illness in the Mood disorders: pharmacotherapy notes; the point in this chapter is only that this population reaches those diagnoses through an organic, epilepsy-driven route that must be recognised first.

21.6 Diagnosis and the principle of treating the inflammation

Diagnosis rests on neuroimaging. CT of the head is used to screen, MRI of the brain characterises the lesions more precisely, and serology is reserved to confirm the diagnostically difficult case. The imaging also stages the disease, because the number, the location and the calcified or active state of the cysts drive every subsequent decision. Management then runs on two tracks that must be coordinated. The seizures are managed where the patient can be seen safely, in most cases as an outpatient, and usually respond to monotherapy with a first-line antiseizure medication. The underlying infection and its inflammatory consequences are managed according to burden and form, with the fulminant and ventricular presentations of the previous section requiring inpatient and often neurosurgical care for cerebrospinal fluid diversion.

The shape of care follows directly from that staging. Uncomplicated parenchymal disease is managed in the outpatient setting, while the fulminant encephalitic and obstructing ventricular forms need inpatient, emergency and neurosurgical care. The targets shift with time: acute seizure control, and where intracranial pressure is raised the relief of that pressure, come first; eradication of the parasite and control of the inflammation follow; and the prevention of seizure

relapse governs the long term. Across those phases every available mode of treatment is in play, from drug therapy for the seizures, the inflammation and the parasite, through the procedural diversion or removal of an obstructing cyst, to the social and rehabilitative support a patient left with epilepsy or cognitive impairment will need.

RULE **In neurocysticercosis you are treating the host inflammatory response as much as the parasite.** Because it is the death of the cyst that inflames the brain, corticosteroids are used to damp the immune reaction while anthelmintics such as praziquantel and albendazole clear the infection, and antiparasitic therapy is timed and covered by steroid rather than given reflexively. Where a management decision rests on the number and viability of cysts, individualise it against current expert guidance rather than a fixed rule.

GOOD TO REMEMBER

Do not be quick to withdraw antiseizure medication. **More than 50%** of patients relapse after their treatment is stopped, and the risk is higher still with multiple lesions, a history of recurrent seizures, or brain calcification. These features argue for a longer, more cautious course rather than an early trial off medication.

21.7 Cerebral malaria: the falciparum encephalopathy

Of the malaria parasites, **Plasmodium falciparum** carries the particular risk of prominent neuropsychiatric involvement, the syndrome of **cerebral malaria**. It presents as an encephalopathy, with impaired consciousness, delirium or seizures, and it sits within a disease of enormous scale: malaria as a whole affects an estimated 240 million people each year and kills over 500,000, and one study found neurologic involvement in 48% of children with malaria, the risk concentrated in the endemic areas of sub-Saharan Africa. The assessment of the delirium itself is developed in the Stroke, TBI, delirium and focal brain syndromes notes; the task here is to recognise its infective cause.

A physical sign helps at the bedside: retinal haemorrhages are found in **30% to 40%** of cerebral malaria, so the fundus is part of the examination. Diagnosis is confirmed by blood smear microscopy, and where the cerebrospinal fluid is examined a low CSF glucose favours cerebral malaria over a viral encephalitis. Treatment is urgent, because the outcome hinges on it: untreated, cerebral malaria is generally fatal, whereas with treatment mortality falls to **15% to 20%**. Intravenous artesunate is the treatment of choice, alongside the neuropsychiatrically relevant management of cerebral oedema and seizures. In the treated survivor the encephalopathy is often reversible, which sharpens the imperative to reach the diagnosis quickly: this is an illness in which the disturbance of consciousness and behaviour can lift with prompt antimalarial and supportive treatment, and in which delay converts a survivable encephalopathy into a fatal one. For the psychiatrist the practical consequence is that the febrile, confused patient in an endemic setting is a medical emergency to be worked up, not a behavioural problem to be sedated.

PITFALL

Settling on a viral encephalitis, or a primary psychiatric disturbance, in a febrile encephalopathic patient without examining the fundus or reading the CSF glucose. Retinal haemorrhages are present in a large minority of cerebral malaria and point straight to the diagnosis, while a low CSF glucose favours malaria over a viral cause; missing both delays the one treatment that changes the outcome.

IN INDIA

In an endemic area, a febrile encephalopathy, an acute delirium, or a first seizure with fever is investigated with blood smear microscopy before it is attributed to a viral encephalitis or a primary psychiatric disturbance, because falciparum malaria is the one cause here that is both rapidly fatal and rapidly treatable. The clinical decision that follows is to send the smear early and to begin specific antimalarial treatment without waiting once the diagnosis is secure.

21.8 Japanese encephalitis and the endemic differential

The third of the endemic neuroinfections is **Japanese encephalitis**. Across Asia it is a major public-health problem, and the sources used here place its impact alongside that of measles encephalitis, a leading cause of learning disability, sensory impairment and under-five mortality in low-income countries. For the psychiatrist the relevance lies in the survivors, who carry a heavy burden of developmental and sensory sequelae after the acute illness. The detailed virology, vector and movement-disorder aftermath of Japanese encephalitis are not developed from the clean sources available for this account, and are deliberately not asserted here; the reader who needs them should turn to current references.

Holding the three endemic neuroinfections against one another is the most useful way to keep them straight, because each is separated from the others by its clinical clue, its confirmatory test and the psychiatric picture it produces.

ENDEMIC NEUROINFECTION	CLINICAL CLUE	CONFIRMATORY INVESTIGATION	NEUROPSYCHIATRIC SIGNATURE
Neurocysticercosis	Adult-onset seizures, calcified or cystic lesion	CT to screen, MRI to characterise, serology to confirm	Seizures, cognitive decline to dementia, epilepsy-related psychosis
Cerebral malaria	Febrile encephalopathy, falciparum infection, retinal haemorrhage	Blood smear microscopy; low CSF glucose	Impaired consciousness, delirium, seizures
Japanese encephalitis	Major viral encephalitis of Asia	Viral-encephalitis workup	Developmental and sensory sequelae in survivors

In endemic India a new adult seizure with a calcified brain lesion raises neurocysticercosis strongly, but is imaged and worked up against its mimics, the tuberculoma above all; a febrile encephalopathy is treated as cerebral malaria, with other encephalitic causes pursued alongside, until repeated blood smears are negative; and the treatment rules diverge, steroid-covered antiparasitic therapy for selected neurocysticercosis but urgent intravenous artesunate and supportive care, not routine steroids, for cerebral malaria.

22 · SSPE, CNS tuberculosis and the rare chronic neuroinfections

Some infections of the central nervous system announce themselves not with fever and a stiff neck but with a change in behaviour, a slipping intellect or a first psychotic episode, and they do so months or years after the organism first arrived. This section gathers the subacute and chronic neuroinfections that a psychiatrist meets in that disguise: subacute sclerosing panencephalitis, the late and lethal sequel of measles; the tuberculoma, an intracerebral mass that is a leading structural cause of seizures across the Indian subcontinent; and Whipple's disease, a systemic infection whose one pathognomonic sign rescues an otherwise missed and treatable dementia. Marks cluster here for two reasons. The first is that each condition wears a psychiatric or cognitive mask, so the diagnosis is made by the clinician who thinks of it rather than by the one who waits for it. The second is that several are treatable, which makes missing them costly in a way a purely degenerative diagnosis is not. Progressive multifocal leukoencephalopathy is named here only in passing, because its clinical account belongs with the CNS opportunistic infections of HIV; the syphilitic and endemic parasitic neuroinfections are likewise taught in full elsewhere in these notes and are set beside this group only to complete the differential.

22.1 Subacute sclerosing panencephalitis: persistent measles in the brain

Subacute sclerosing panencephalitis (SSPE) is a progressive and ultimately fatal panencephalitis that develops long after an apparently uncomplicated measles infection, and it is thought to arise from persistence of the virus within the central nervous system rather than from a fresh insult. The causative organism is measles, or rubeola, a **single-stranded, negative-sense RNA virus of the Paramyxoviridae family**, the measles morbillivirus. The name itself summarises the pathology: "panencephalitis" for the diffuse involvement of both grey and white matter, "sclerosing" for the gliotic scarring the process leaves behind, and "subacute" for a tempo that is neither the days of an acute encephalitis nor the decades of a degeneration. The interval between the childhood infection and the neurological illness is the fact examiners return to, and it is precisely the fact the sources do not agree on. Kaplan and Sadock's Comprehensive Textbook of Psychiatry places it at **up to 7 to 10 years** after measles. Kaufman's Clinical Neurology for Psychiatrists frames the same interval by the patient's age: in most children and adolescents routine measles precedes SSPE by about 6 years, whereas in adults the interval stretches to about 20 years. The epidemiology explains the divergence. About 85% of patients develop SSPE in childhood, but **15%** develop it as adults, and it is this adult tail, with its far longer latency, that pulls the single "years after measles" answer apart.

TRAP **Quoting a single "years after measles" latency for SSPE as though it were fixed.** The interval genuinely differs by source and by population. Kaplan and Sadock's Comprehensive Textbook of Psychiatry and Kaufman's Clinical Neurology for Psychiatrists give different figures, and Kaufman's own account splits by age, with a short childhood interval and a much longer adult one. What a candidate should carry is not a value but the reason there is no single value: the adult-onset minority acquires measles far earlier relative to the illness, so any one figure is right only for the population it came from.

22.2 The clinical evolution and its psychiatric prodrome

The illness moves through a characteristic sequence, and its opening is the part that reaches psychiatry first. It begins with behavioural change that may last anywhere from weeks to years, accompanied by seizures and lethargy, and only later declares itself neurologically with **myoclonus**, motor and sensory disturbance, and a progressive dementia. That early behavioural phase is deceptively bland: falling school performance, irritability, apathy or a shift in personality in a child or adolescent, with nothing yet to point the clinician at the brain. As the disease advances the myoclonus that is its hallmark becomes unmistakable, jerking the child with a periodicity that mirrors the electroencephalographic discharge, and the patient eventually sinks into **akinetic mutism** before dying. The tempo from there is usually relentless and the outcome almost always fatal, and the figures are worth fixing in the mind.

12 y	1-2 y	95%
MEAN AGE AT ONSET	SURVIVAL FROM ONSET	DIE WITHIN FIVE YEARS

The disease compresses an entire dementing illness into the span of a childhood, and that speed, together with the innocuous opening, is what makes it so easy to mishandle at the start.

MNEMONIC

Behaviour, then Myoclonus, then Mutism

The order in which SSPE unfolds: a **behavioural** prodrome of weeks to years with seizures and lethargy, then the **myoclonic** phase with motor and sensory decline and dementia, ending in akinetic **mutism**. Holding the order helps, because the first stage is the one mistaken for something else.

PITFALL

Reading the early behavioural phase of SSPE as a primary psychiatric or conduct disorder. Because the behavioural change can precede the myoclonus by weeks to years, a declining, irritable adolescent may be managed as depression, oppositional behaviour or a first-episode psychosis until the first myoclonic jerks force a rethink. In a child or adolescent whose behaviour and cognition are deteriorating together, and especially where the measles or vaccination history is uncertain, the possibility should be raised early rather than after the neurology becomes obvious.

22.3 Confirming the diagnosis: cerebrospinal fluid, EEG and neuropathology

Diagnosis rests on demonstrating the immune footprint of persistent measles inside the nervous system, together with a distinctive electrical signature. The confirmatory finding is an elevated

measles antibody titre in the cerebrospinal fluid, which reflects intrathecal synthesis of antibody against the persisting virus. The point of measuring antibody in the fluid rather than in the blood is that intrathecal production signals an active infection behind the blood-brain barrier rather than mere past exposure, which is why the decisive measurement is the cerebrospinal-fluid titre read against the serum, showing antibody made within the nervous system. By contrast, an acute measles-associated neurological illness, rather than SSPE itself, can show a cerebrospinal-fluid picture of lymphocytic pleocytosis, elevated protein and positive measles IgM; in SSPE it is the markedly raised measles antibody titre, produced intrathecally, that carries the diagnosis rather than any attempt to grow the virus.

The electroencephalogram is the bedside investigation candidates are expected to recognise. It is diagnostically helpful in SSPE, classically showing **periodic sharp-wave complexes** or a burst-suppression pattern, with the periodic discharges characteristically time-locked to the myoclonic jerks. The pattern is not entirely specific, but in the right clinical setting it is strongly suggestive and it is the finding most likely to be tested.

Neuropathology completes the picture and supplies the other classic pearl. Histological examination of the brain reveals **intranuclear eosinophilic inclusions, the Cowdry bodies**, within neurons and glia, the morphological trace of the viral persistence that drives the whole illness. Three findings therefore anchor the diagnosis:

- a raised cerebrospinal-fluid measles antibody titre;
- an EEG showing periodic sharp-wave complexes or burst-suppression; and
- the Cowdry bodies on histology.

22.4 The tuberculoma: an intracerebral mass and a cause of seizures

Central-nervous-system tuberculosis most commonly presents as tuberculous meningitis, but it reaches psychiatry chiefly through the **tuberculoma**, an intracerebral mass formed by tuberculous infection. Tuberculomas are seen particularly in patients with AIDS and in people of the Indian subcontinent, and an important practical point is that computed tomography and magnetic resonance imaging can detect them even when the clinical evaluation does not suggest the diagnosis. That radiological visibility matters, because a space-occupying granuloma can sit silently until it irritates the cortex around it.

The commonest way it does so is by provoking seizures. In the Indian subcontinent tuberculomas are one of the most common causes of focal seizures, and such infections may underlie new-onset epilepsy in recent immigrants from endemic regions, so a first focal seizure in a young adult from an endemic area is a radiological question until proven otherwise. For the psychiatrist the relevance is twofold: seizures and their postictal states enter the differential of episodic behavioural disturbance, and the structural lesion itself, depending on where it lies, can contribute to focal cognitive or affective change. Where a tuberculoma sits close to eloquent or limbic cortex, the same lesion that generates the seizures can generate interictal and postictal affective and psychotic phenomena, so the structural diagnosis and the behavioural one are not separate questions but two readings of a single finding.

IN INDIA

Where tuberculosis is endemic, a new focal seizure or an unexplained ring-enhancing intracranial lesion in a young adult should keep the tuberculoma high in the differential, and cross-sectional imaging with computed tomography or magnetic resonance imaging should be obtained early rather than late. The imaging can reveal the lesion when the clinical picture does not point to tuberculosis, so the decision to image should not wait for the disease to look like tuberculosis first.

Tuberculosis of the nervous system is of course wider than the tuberculoma, and it also produces a meningitic illness with its own cerebrospinal-fluid and cranial-nerve signature. That meningitic form and its fluid profile are matters for the general-medicine and neurology texts and are not reconstructed from memory here; what belongs firmly in a psychiatric differential is the recognition that the tuberculoma is a treatable structural cause of seizures and focal deficits that imaging will find.

22.5 Whipple's disease: a systemic infection that reaches the brain

The third disorder in this group is neither viral nor mycobacterial but a systemic infection whose neurological expression is a treatable dementia. **Whipple's disease** is characterised by polyarthralgia and abdominal complaints and, in a minority of patients, by a highly distinctive movement of the eyes and jaw. Its importance to psychiatry is captured in a single phrase from the literature: it is a treatable cause to keep in mind in the demented patient. The systemic features usually precede the neurological ones by years, so the joint and gut symptoms are the clues that a cognitive decline might have a reversible infective cause. The cardinal features worth carrying are few:

- polyarthralgia, often long preceding the neurological illness;
- abdominal complaints; and
- in a minority, the pathognomonic ocular and masticatory movement described below.

The reason Whipple's disease earns a place in a psychiatry curriculum out of all proportion to its rarity is that it is one of the few dementing illnesses that can be arrested, and even reversed, once it is recognised. When a cognitive or behavioural decline is accompanied by unexplained joint and abdominal symptoms, the diagnosis should be actively considered rather than left to a specialist to raise, because the whole value of knowing about it lies in thinking of it. The formal nosology of the dementia syndrome it enters belongs to the Dementias and neurocognitive disorders notes; what this section owns is the infective cause and its one unmistakable sign.

22.6 Oculomasticatory myorhythmia: the pathognomonic sign

The sign that makes Whipple's disease examinable is **oculomasticatory myorhythmia**, and it repays precise description, because vague versions lose the marks. It consists of acquired pendular vergence oscillations of the eyes together with concurrent contraction of the muscles of mastication: a smooth, rhythmic convergence of the eyes cycling at about **1 Hz** and then diverging, accompanied by synchronous rhythmic elevation and depression of the jaw. Two

properties seal its identity. The movement persists during sleep and is unaltered by external stimuli, which together set it apart from the many oscillations that vary with attention or arousal.

The sign rarely travels alone. Patients may also show paralysis of vertical gaze, progressive somnolence and intellectual deterioration, a combination that points firmly at the brainstem and diencephalon. What gives the movement its examination value is its specificity: this distinct movement disorder has been recognised only in Whipple's disease, which is to say it is pathognomonic. A slow, rhythmic convergence of the eyes locked to a rhythmic chewing movement in a patient with cognitive decline is therefore not a sign to weigh among others but a diagnosis to act on, and it should trigger the work-up for Whipple's disease directly.

> Oculomasticatory myorhythmia, the slow pendular convergence of the eyes locked to rhythmic contraction of the muscles of mastication, has been recognised only in Whipple's disease: it is pathognomonic, and it flags a treatable dementia.

22.7 Progressive multifocal leukoencephalopathy and the wider differential

The last of the chronic neuroinfections to name here is **progressive multifocal leukoencephalopathy (PML)**, a demyelinating disease caused by the JC virus infecting oligodendrocytes. It is set beside SSPE and Whipple's disease because it too is a slowly evolving white-matter infection that can present with cognitive and behavioural change, but its clinical detail, its association with immunosuppression and its management belong with the CNS opportunistic infections of HIV and are taught there rather than reproduced here. Named alongside it, and likewise owned by other parts of these notes, are the syphilitic infection of the nervous system, taught in full with the account of neurosyphilis and general paresis, and the endemic parasitic and arboviral infections of the Indian subcontinent, taught with the endemic neuroinfections of India. Setting them side by side is useful only as a differential: the chronic infections that present to psychiatry share a habit of slow cognitive or behavioural decline, and they reward the clinician who keeps an infective cause on the list.

Within the group this section owns, three conditions are best held apart on a few shared axes, which the accompanying comparison sets out.

CONDITION	CAUSE	SIGNATURE CLINICAL CLUE	KEY INVESTIGATION
SSPE	Persistent measles morbillivirus	Myoclonus and dementia in a child or adolescent	Raised CSF measles antibody titre; periodic sharp-wave EEG
CNS tuberculoma	Tuberculosis	Focal seizures, often in an endemic-area patient	CT and MRI
Whipple's disease	Systemic infection	Oculomasticatory myorhythmia with arthralgia and gut symptoms	Directed systemic and neurological work-up

22.8 Excluding the treatable masqueraders: a clinical synthesis

What ties this heterogeneous group together is not a shared organism but a shared clinical trap and a shared reward. Each can present to psychiatry with cognitive decline, behavioural change or psychosis, and in each the diagnosis is made by the clinician who thinks of it. The stakes differ across the group. SSPE, once established, is progressive and fatal, so recognition changes prognosis and counselling rather than cure; the tuberculoma and Whipple's disease are treatable, so recognition changes the outcome outright. That asymmetry is the argument for keeping the whole set in mind, because the cost of missing the treatable members is a reversible illness allowed to run.

RULE **Before an atypical dementia or a late-onset psychosis is called primary, the treatable chronic neuroinfections must be actively excluded.** Whipple's disease is a treatable cause to keep in mind in the demented patient, and it, along with the tuberculoma and the infections owned elsewhere in these notes, will not announce itself unless it is sought. A degenerative or primary-psychiatric label is safe only once these have been thought of and set aside.

GOOD TO REMEMBER

When cognitive or behavioural decline does not fit a primary psychiatric illness or a common neurodegenerative pattern, screen deliberately for the treatable chronic infections. Look for the systemic clues of Whipple's disease, the polyarthralgia and abdominal complaints and above all the oculomasticatory myorhythmia; image early where the tuberculoma is endemic; and remember that a childhood-onset myoclonic dementia points at SSPE. The unifying action is simple: put an infective cause on the list before settling on a degenerative one.

The clinical habit these conditions teach is worth more than any single fact about them. A slowly failing intellect, a new movement disorder and a systemic clue in the history are, taken together, an invitation to look for a chronic infection of the nervous system, and the reward for looking is occasionally a patient who gets better.

Multiple sclerosis and psychoneuroimmunology

23 · Multiple sclerosis: psychiatric manifestations and the effect of disease-modifying therapy

For the psychiatrist, multiple sclerosis is one of the most psychiatrically loaded of the neurological diseases. A demyelinating illness that strikes the young adult brain, it produces mood disorder, suicide, cognitive decline and a distinctive treatment-induced psychopathology out of all proportion to its physical disability, and it does so through lesions that fall preferentially on the very white matter a stable mind depends on. The marks cluster here for reasons worth stating plainly. Depression in this disease is commoner than in comparably disabling illnesses elsewhere in medicine, its suicide risk is among the highest in clinical neurology, and its own therapies, the interferons and above all the corticosteroids, generate psychiatric syndromes that a consultant is repeatedly asked to manage. What follows sets out the

disease a psychiatrist must recognise, then works disorder by disorder through its depressive, suicidal, manic, psychotic and cognitive consequences, and closes on the psychiatric effect of disease-modifying and adjunctive treatment.

23.1 The disease a psychiatrist must recognise

Before its psychiatry can be read correctly, the disease itself has to be placed. Multiple sclerosis is a disorder of young adults, and the two standard references quote materially different central-tendency figures for its onset, a divergence worth carrying rather than smoothing over. Kaufman's Clinical Neurology for Psychiatrists gives a mean age of onset of 33 years, with 70 percent of cases arising between 21 and 40 years, and a female excess of three to four times; the Companion to Psychiatric Studies instead gives a median onset of 24 years and a female excess of about twice. Either way this is a woman's disease of early adult life, arriving at the age when identity, career and family are being built, which is part of why its psychiatric toll is so heavy.

Susceptibility is familial without being Mendelian. Compared with the general population, the disease appears 20 to 40 times more often in first-degree relatives of an affected person, with concordance of 25 percent in monozygotic and 5 percent in dizygotic twins; the Companion frames the same signal as a 30 to 50-fold familial increase. No single mutation is necessary or sufficient, so this is a polygenic, part-environmental illness rather than a single-gene disorder. Its course sorts into recognisable patterns. The relapsing-remitting form is the commonest, and here too the sources part company: Kaplan and Sadock's Comprehensive Textbook of Psychiatry puts it at 85 to 90 percent of cases while Kaufman reports it at about 80 percent at onset, with most eventually evolving to a secondary progressive phase and a smaller primary progressive minority.

FEATURE	FIGURE	SOURCE
Mean age of onset	33 years, 70% aged 21 to 40	Kaufman's Clinical Neurology for Psychiatrists
Median age of onset	24 years	Companion to Psychiatric Studies
Female predominance	3 to 4 times	Kaufman's Clinical Neurology for Psychiatrists
Female predominance	about twice	Companion to Psychiatric Studies
Relapsing-remitting share	about 80% at onset	Kaufman's Clinical Neurology for Psychiatrists
Relapsing-remitting share	85 to 90%	Kaplan and Sadock's Comprehensive Textbook

23.2 Confirming the diagnosis, and where the old teaching has moved

The diagnosis rests on demonstrating that lesions are separated in space and in time, which is the enduring core of the **McDonald criteria**. Their two chief demands have remained constant: dissemination of focal deficits in time, meaning distinct attacks separated by a period of at least a month and each lasting a minimum of 24 hours, and dissemination in space, meaning distinct

central nervous system lesions, together with the exclusion of other causes. The 2017 revision, grounded here on Kaplan and Sadock's textbook and since updated by a 2024 revision these sources do not yet carry, loosened how each may be shown: dissemination in time can now be met by a further clinical attack, by new lesions on imaging, or by the presence of central-nervous-system-specific oligoclonal bands, and dissemination in space now counts both symptomatic and asymptomatic lesions and treats cortical lesions as equivalent to juxtacortical ones.

This is exactly where a stale figure trips candidates. An older revision set a fixed imaging threshold, requiring one gadolinium-enhancing lesion or nine T2-hyperintense lesions (Kaufman); the 2017 criteria abandon the fixed nine-lesion threshold, so the frequently memorised nine-lesion rule is now obsolete and should be flagged as pre-2017 wherever it appears. Laboratory support comes from the cerebrospinal fluid, which in Kaufman's account contains **oligoclonal bands** in about 90 percent of patients or shows increased intrathecal immunoglobulin G synthesis, though these bands are nonspecific and also appear in lupus, neurosyphilis, sarcoidosis and other inflammatory disease; slowed or absent visual and somatosensory evoked potentials add support by exposing subclinical, disseminated lesions. On imaging the plaques are disseminated through the white matter but characteristically periventricular, mostly in the frontal periventricular white matter, and on sagittal magnetic resonance imaging they produce the relatively specific **Dawson fingers** radiating from the ventricles. Overall lesion load, and periventricular demyelination in particular, correlate most closely with cognitive impairment.

23.3 Depression and the psychiatric burden of the disease

Depression is the signature psychiatric consequence of multiple sclerosis and the one that carries most of the mortality. It is the most common psychiatric comorbidity of the disease, classified in DSM-5, when judged a direct physiological consequence of the disease, as a **Depressive Disorder due to another medical condition** and mapped in ICD-11 as a secondary mood syndrome; the primary nosology and pharmacotherapy of depressive illness itself belong to the Mood disorders: pharmacotherapy notes. Its frequency is striking. Major depression affects **25 to 50 percent** of patients across the lifetime, and, tellingly, it develops more often than in most other chronic, equally disabling non-neurological illnesses such as rheumatoid arthritis, which argues that the depression is not merely a reaction to being ill.

25-50%	Up to 7x	Up to 80%	45-65%
LIFETIME MAJOR DEPRESSION	SUICIDE RATE VERSUS AGE PEERS	AFFECTED BY FATIGUE OR LASSITUDE	WITH COGNITIVE DEFICITS ON TESTING

The shape of this depression is instructive. Its genetic contribution is negligible, the rate in relatives of depressed patients being considerably lower than in relatives of depressed people without the disease, and unlike primary depression it affects men and women equally. It is a disease of the brain rather than the cord: depressive symptoms are commoner when the cerebrum rather than only the spinal cord is involved, and when imaging shows cerebral atrophy and a large total lesion burden. A history of depression and premorbid trait anxiety further raise the risk.

RULE **Depression is the commonest psychiatric consequence of multiple sclerosis and exceeds the rate seen in comparably disabling illnesses elsewhere in medicine.** Because it develops more often than in chronic non-neurological disease of similar severity, and because its risk tracks cerebral rather than spinal involvement, it reflects the brain disease itself and not merely an understandable reaction to disability, and should be screened for actively.

23.4 The elevated risk of suicide

The clinical urgency of the depression is that it kills. The suicide rate among patients attending multiple sclerosis clinics runs **up to seven times** that of comparably aged people, a magnitude that largely reflects the high incidence of depression in the disease and that places this illness among the most lethal in outpatient neurology. That single figure should reset the threshold for asking about suicidal thoughts in any patient with the disease.

The risk is not spread evenly, and the profile of the patient who attempts or completes suicide is worth knowing precisely because it is partly counter-intuitive. Those affected have tended to be younger than 30 and symptomatic for less than a year, so it is the newly diagnosed rather than the long-disabled who are most exposed. Their histories carry depression in themselves or their families, alcohol misuse, and limited psychosocial support. The point examiners press hardest is the negative one: cognitive impairment from the disease is not a risk factor for suicide, so a patient's forgetfulness should never falsely reassure the clinician who is weighing risk.

MNEMONIC

Young, newly diagnosed, drinking, depressed, alone

The highest-risk profile: **young**er than 30, **newly diagnosed** and symptomatic under a year, a personal or family history of **depression**, alcohol misuse, and thin psychosocial support. Note what is absent from the list. Disease-related cognitive impairment is explicitly not a suicide risk factor, so it must not be used to downgrade concern.

23.5 Mania, euphoria and pathological affect

The elevated pole is less prominent but diagnostically richer. Bipolar disorder occurs at about twice the general-population rate in these patients, yet frank mania rarely develops, and when it does the first move is to consider a side effect of steroid treatment, which is a ready cause of a manic picture in this population. Distinct from bipolarity is **MS-induced euphoria**, an elevation of mood clearly inappropriate to the patient's disability. It is not happiness but a sign of brain disease: it tracks physical deterioration, chronicity and at least subtle intellectual impairment, is linked to steroid treatment, and usually reflects extensive cerebral involvement, so that even where psychological factors seem to explain it a diseased brain generally underlies it. It has been reported in as many as a quarter of patients, although that figure is thought to represent substantial over-reporting except in those receiving intravenous steroids, and it may relate to reduction in global grey matter volume. The classic mood-disorder eponym sometimes attached to this state is not attested in the clean reference sources and is deliberately not used here.

Closely related, and easily conflated with euphoria, is **pseudobulbar affect**, the pathological laughing and crying that is common in the disease and that in Kaufman's account is explained by pseudobulbar palsy; it may respond to serotonergic treatment. Its full phenomenology, pathophysiology and pharmacological management belong to the Stroke, TBI, delirium and focal brain syndromes notes and are named here rather than reproduced, the point for this chapter being simply that it occurs in multiple sclerosis and must be distinguished from a genuine mood disorder before either is treated.

23.6 Psychosis, and a live controversy

Psychosis is the striking exception to the disease's psychiatric reputation. On the classical teaching, and unlike depression, the prevalence of psychosis is not significantly greater in these patients than in unaffected people, and is in fact lower than in most other neurological illnesses, including Alzheimer disease, Parkinson disease, head trauma and epilepsy. Except in scattered case reports the disease does not open with psychosis, so a first psychotic episode in a young adult is far more likely to be a primary psychotic illness, whose nosology belongs to the Schizophrenia: management, antipsychotics and adverse effects notes, than a manifestation of demyelination.

TRAP **Do not state flatly that multiple sclerosis carries no excess of psychosis.** The long-standing orthodoxy, that its psychosis rate is not raised above the background population and is lower than in other neurological disease, has been challenged by a well-conducted population study reporting a modest increase concentrated in the youngest adults. The two positions genuinely disagree, and a stem can be built on either, so the examinable point is the discordance itself rather than a single number. The specific percentages from the population study are not carried in the reference sources used here and are therefore not quoted.

23.7 Cognitive impairment and fatigue

Cognitive change is common, under-recognised and characteristic in pattern. The disease produces a **subcortical dementia**, in which cortical symptoms from grey-matter injury come late if at all; memory and new learning are impaired early, while language is comparatively spared. The hallmark is slowed processing speed with impaired attention, executive deficits are common, and procedural and implicit memory are generally preserved. The most sensitive bedside-adjacent measure is the **Paced Auditory Serial Addition Test**, and characteristically the speed of test completion is more impaired than accuracy. On demanding neuropsychological testing, deficits that may be clinically silent are found in 45 to 65 percent of patients in Kaufman's account, with prevalence studies converging on 40 to 65 percent. The standardised cognitive instruments used to screen for such change are owned by the Psychotherapies, clinical assessment, MSE and nosology notes and are named here only as tools; the disease-specific point is that the deficit they detect tracks the disease's white-matter lesion burden and cerebral atrophy, in keeping with its subcortical pattern.

Overlapping with all of this is fatigue. An inexplicable, constant tiredness that neurologists call **lassitude** affects **up to 80 percent** of patients. It is entirely subjective, does not track age or degree of weakness, and intensifies both the depression and the cognitive impairment, which is

why it matters so much to the psychiatrist. Crucially, antidepressants do not relieve it, so it cannot be treated as though it were a somatic symptom of depression.

PITFALL

Reaching for an antidepressant to lift the fatigue. Because lassitude and low mood travel together, the tiredness is easily read as a depressive symptom, yet antidepressants do not alleviate the fatigue of the disease, and the reflexive prescription adds risk without benefit: selective serotonin reuptake inhibitors may increase spasticity, and antidepressants with anticholinergic action may precipitate urinary retention. Treat the depression on its own indication and address the fatigue by other means.

23.8 Treating mood, and the interferon question

Managing mood in this disease is as much about avoiding harm as about achieving benefit. Well-controlled studies have failed to prove that antidepressants improve mood in these patients, and the same agents carry the spasticity and urinary-retention hazards already noted, so an agent is chosen with these neurological adverse effects in mind. When a depression is severe enough to demand somatic treatment, the reassuring point is that the disease itself does not close off the most effective option, as the accompanying note sets out.

The disease-modifying drugs raise a separate and heavily examined question. One disease-modifying agent used in the disease is **interferon-beta**, and although early reports suggested it caused or worsened depression, that link was ultimately unsubstantiated, with recent systematic reviews finding no association; many neurologists nonetheless still avoid it in patients with a depressive history. Its near-namesake behaves entirely differently. Interferon-alpha, an innate-immune cytokine once widely used for hepatitis C and still used in some cancers, is a potent and reliable inducer of major depression in **up to 50 percent** of those treated, together with anhedonia, fatigue and cognitive impairment, and antidepressant pretreatment can lower that risk.

AGENT	TYPICAL INDICATION	DEPRESSION LINK
Interferon-beta	disease-modifying therapy for multiple sclerosis	initially reported but unsubstantiated on systematic review; cautious avoidance persists in patients with a depression history
Interferon-alpha	hepatitis C and cancer, not multiple sclerosis	a reliable inducer of major depression in up to 50 percent

TRAP **The interferon that causes depression is not the interferon used in multiple sclerosis.** The disease-modifying agent is interferon-beta, whose reported depression link is unsubstantiated on systematic review, while the reliable depressant is interferon-alpha, given for hepatitis C and cancer. A stem that offers an interferon and asks for the drug that induces major depression is testing whether the two forms have been kept apart; answer beta and you have walked into it.

GOOD TO REMEMBER

When a patient with the disease has a severe depression that needs somatic treatment, the cerebral lesions are not a contraindication to electroconvulsive therapy, which may be given with only the usual precautions. Do not let the diagnosis of multiple sclerosis, by itself, veto a treatment the depression genuinely warrants.

23.9 Corticosteroids: iatrogenic psychiatry and its management

The steroids used to treat relapses are the most reliable psychiatric offenders of all. Steroid treatment is a dependable source of psychiatric disturbance across a spectrum of syndromes, and because brain damage from the disease increases vulnerability, high-dose treatment can readily produce mental changes fulfilling DSM-5 criteria for delirium, medication-induced psychotic disorder or medication-induced depressive disorder. Glucocorticoids such as prednisone and dexamethasone are more apt to induce psychosis than mineralocorticoids such as fludrocortisone. The range runs from the mild to the severe:

- anxiety, as the mildest and commonest disturbance;
- euphoria, especially with intravenous dosing;
- mania, the picture that should prompt suspicion of a steroid effect;
- depressive symptoms, which may deepen an existing low mood;
- frank psychosis, at the severe end of the spectrum.

The dose relationship is quantified and worth carrying. The incidence of steroid psychosis, which usually begins 1 to 4 days after starting treatment, is about 4 percent in patients receiving less than 40 mg of prednisone daily and rises to 20 percent in those receiving more than 80 mg daily; once the steroid is stopped the disturbance recedes within 6 weeks in 90 percent of patients. Management follows the mechanism. If treatment cannot be interrupted, prophylactic lithium may prevent the psychosis; if it emerges, first- or second-generation antipsychotics may suppress it, whereas antidepressants may exacerbate it and should be avoided. In one reported case, **glatiramer acetate** was chosen as the disease-modifying agent considered least likely to disturb mood. Above all, because steroids are not life-saving in this disease and chronic use may raise the risk of suicidal behaviour, they should be reduced or discontinued as soon as the relapse allows.

In multiple sclerosis, depression is the commonest psychiatric burden and drives a suicide rate up to seven times that of age peers, while the disease's own treatments split cleanly: interferon-beta's depression link is unsubstantiated, whereas interferon-alpha and the corticosteroids genuinely cause psychiatric illness, so steroids are tapered as soon as the relapse allows.

24 · Psychoneuroimmunology and the immune hypothesis of psychiatric disorders

Why the marks are here. **Psychoneuroimmunology** is the study of how the immune system and the nervous system read the same threats, talk to each other, and between them shape mood,

cognition and behaviour. Two examinable ideas sit inside it. The first is the machinery of immune-brain communication: how a peripheral immune signal reaches the brain at all, and how the brain writes back to the immune system. The second is the immune or inflammatory hypothesis of psychiatric disorders, which asks whether low-grade inflammation contributes to depression and, more cautiously, to psychosis. Hold onto one framing throughout: inflammation here is a dimensional lens laid across common disorders, not a diagnostic test and not a disease in its own right. It is also distinct from the discrete antibody-mediated encephalitides, in which a single autoantibody produces a defined neuropsychiatric syndrome; psychoneuroimmunology is instead about graded, subthreshold inflammation nudging the risk and the colour of otherwise common disorders. That framing is also where candidates lose marks, because the biomarker data are real but far less specific than they first appear.

RULE **Immune-brain signalling runs both ways.** The immune system can shape behaviour to promote healing and recovery, and neuronal activity can in turn alter the immune response inside the brain. Any model that treats the brain as merely downstream of a peripheral immune signal, or the immune system as a passive effector of central commands, has drawn only half the circuit.

24.1 Two systems, one conversation

The immune and nervous systems are the body's two great surveillance-and-response networks, and psychoneuroimmunology begins by noticing how alike they are. Both detect and neutralise threats and work to maintain homeostasis; both perceive the internal and external environment and deploy specific receptors to monitor ambient stimuli. What the field adds is that the two are coupled rather than parallel. On one side, the immune system can control behaviour in a manner that promotes healing and recovery, the phenomenon that later becomes sickness behaviour. On the other, neuronal activity can alter the immunologic response within the brain, with microglia sensing spillover neurotransmitters through their surface receptors and adjusting their state accordingly. So the traffic is genuinely bidirectional, and the rest of this topic simply follows the signal in each direction: outward from a stressed brain to the marrow and lymphoid organs, and inward from an inflamed body to mood and thought. The symmetry is not merely rhetorical; it means a brain state can be read off the immune compartment, and an immune state can be read off behaviour, which is exactly what the biomarker and sickness-behaviour literatures later exploit. Keeping the loop in view matters clinically, because it suggests that addressing only one arm, calming the mind while inflammation smoulders, or damping cytokines while chronic stress persists, may fall short, an idea that motivates combined approaches rather than a proven treatment rule.

24.2 How the immune signal reaches the brain

The brain was long taught to be immune-privileged; the modern account is regulated access, not exclusion. Resident immune cells, the microglia, sit mostly in the parenchyma, while trafficking immune cells are stationed in specialised niches, chiefly the meninges and the choroid plexus. The blood-brain barrier tightly regulates the flow of peripheral immune molecules into the central nervous system, and the usual site of blood-brain interchange is the fenestrated capillaries

of the **circumventricular organs**. A further conduit is the **glymphatic system**, the brain's lymphatic route, which carries cytokines from the meningeal compartment through cerebrospinal fluid and the perivascular (Virchow-Robin) spaces into the parenchyma. It is worth reducing all of this to three routes, which the accompanying figure sets out: a humoral route for soluble mediators, a cellular route for trafficking leukocytes, and a neural route that the next subtopic develops.

ROUTE	WHERE IT OPERATES	WHAT IS CARRIED
Humoral	Fenestrated capillaries of the circumventricular organs; glymphatic and perivascular flow	Soluble cytokines from the periphery and meningeal compartment
Cellular	Meninges and choroid plexus niches	Trafficking immune cells sampling the interface
Neural	Vagal afferents and dorsal root ganglion sensory neurons	Immunologic signals read by Toll-like and cytokine receptors

24.3 The neural and autonomic interface

The neural route deserves its own account because it is fast and specific. Both the sensory afferent fibres of the autonomic nervous system, the vagal afferents, and the peripheral sensory neurons of the dorsal root ganglia display immune receptors, namely Toll-like receptors and cytokine receptors, and they transmit immunologic signals to the brain. When these receptors are stimulated the neurons become more sensitive to pain and itch, which drives behavioural change such as avoidance, so the afferent arm is not just a wire but a behaviour-shaping input in its own right. Traffic in the other direction is autonomic. Sympathetic nervous system fibres innervate the reticuloendothelial organs, the bone marrow, thymus, spleen and lymph nodes, while efferent input from the vagal and recurrent laryngeal nerves supplies parasympathetic counter-regulation. The immune cells themselves are wired to listen: the adrenergic receptor on T and B lymphocytes was one of the first identified, followed by receptors for noradrenaline, dopamine, acetylcholine, serotonin and glutamate on immune cells including microglia. Timing is everything with these mediators. Norepinephrine boosts immune activity during antigen recognition but suppresses it during the effector phase, so the same signal helps or hinders depending on when, and at what dose, the cell meets it. The practical corollary is that the autonomic state a patient inhabits, sympathetically aroused or parasympathetically settled, biases the immune response they can mount, which is one concrete channel through which sustained stress leaves an immune signature.

24.4 From stress to inflammation

The cascade that turns a stressor into measurable inflammation is the mechanistic hinge of the whole topic. Noradrenaline released by activated sympathetic fibres stimulates the bone marrow to produce myeloid cells. Endogenous danger signals and microbial signals, the DAMPs and MAMPs, then switch on two inflammatory pathways: NF-kappa-B and the **NLRP3 inflammasome**. The inflammasome activates caspase-1, which matures IL-1-beta and IL-18 and cleaves the glucocorticoid receptor, contributing to **glucocorticoid resistance**, the state in which

immune cells stop heeding cortisol's usual restraining signal. NF-kappa-B, for its part, drives the release of TNF and IL-6. These cytokines, IL-1-beta, IL-18, TNF and IL-6, then access the brain by the humoral and neural routes already described. This is why a psychological stressor can end as a rise in circulating IL-6 and TNF, and why chronic stress and depression are so often associated with a blunted cortisol brake rather than a simple excess or deficiency of cortisol. The link back to the hypothalamic-pituitary-adrenal axis is direct: a receptor that has been cleaved cannot transmit feedback.

24.5 Acute versus chronic stress

Stress does not do one thing to immunity; its direction depends on duration, and confusing the two is a common conceptual error. Acute stress boosts leukocyte activity, recruiting cells from the bone marrow and driving infiltration and proliferation. That acute enhancement is a sympathetic effect, and the suppression that follows once the stressor resolves is a parasympathetic one. Chronic or severe stress does the reverse and more. It shifts the balance away from proinflammatory Th1 towards anti-inflammatory Th2, suppressing interferon-gamma and IL-2; it lowers natural killer cell activity and lymphocyte proliferation; and it decreases the sensitivity of monocytes to endogenous cortisol, which loops straight back into glucocorticoid resistance. The clinical reading is that acute and chronic stress are not two points on one line but qualitatively different immune states, which is why a brief challenge and a grinding adversity produce different immune and behavioural pictures. It also resolves an apparent paradox, that stress is described as both proinflammatory and immunosuppressive at once. The acute, sympathetically driven phase amplifies innate inflammatory activity, while the sustained phase suppresses cell-mediated defence through the Th1 to Th2 shift and falling interferon-gamma, yet simultaneously leaves the innate inflammatory tone poorly restrained because monocytes no longer respond fully to cortisol. The two halves are sequential rather than contradictory, and depression tends to sit at the chronic end, where the cortisol brake has failed.

DIMENSION	ACUTE STRESS	CHRONIC OR SEVERE STRESS
Net effect on immunity	Enhancement	Suppression and dysregulation
Leukocytes	Recruitment, infiltration, proliferation	Reduced lymphocyte proliferation
Natural killer cells	Not the primary change	Decreased activity
T-helper balance	Not the primary change	Th1 to Th2 shift; IFN-gamma and IL-2 suppressed
Autonomic basis	Sympathetic drive, then parasympathetic suppression on resolution	Sustained sympathetic and HPA drive with glucocorticoid resistance
Cortisol sensitivity	Not the primary change	Monocytes less sensitive

24.6 Sickness behaviour: the bridge to depression

Everything so far becomes clinically legible through **sickness behaviours**. Coincident with the physiologic immune changes, animals given an immune challenge reduce a recognisable cluster of

behaviours.

- reduced general activity;
- reduced exploration of novel objects;
- reduced social interaction;
- reduced food and water intake; and
- reduced sexual behaviour.

The same link appears in humans. Healthy volunteers develop anxiety and depression in response to low-dose cytokines, and even people with the common cold show sickness behaviours such as fatigue, loss of interest, low mood and cognitive impairment. Tricyclic antidepressants reduce lipopolysaccharide-induced sickness behaviour in animals, an early pharmacological hint that this pathway overlaps with the pathway of depression. The concept earns its place because it is the translational bridge: it explains how a proinflammatory signal is converted into a depressive phenotype, and it reframes the vegetative symptoms of depression as an evolved, cytokine-driven programme rather than an incidental accompaniment of low mood.

PITFALL

The overlap cuts both ways at the bedside. The fatigue, anhedonia, poor concentration and low mood of an acute systemic infection can closely mimic a depressive episode, because sickness behaviour and the vegetative symptoms of depression share a cytokine-driven substrate. Reading transient sickness behaviour as a new primary depression, and starting an antidepressant on the strength of it, is a real and avoidable error; a picture that lifts as the infection clears usually reflects transient sickness behaviour rather than a primary mood disorder, though the judgement rests on the full syndrome and course.

24.7 How cytokines produce depression

If inflammation contributes to depression, it does so through three converging mechanisms, and holding all three together is what the examiners reward. Proinflammatory cytokines, including the type I and type II interferons, IL-1-beta and TNF, act on the monoaminergic, tryptophan and glutamatergic systems at once. First, they reduce the availability of the monoamines serotonin, dopamine and noradrenaline, both by increasing the expression and function of presynaptic reuptake transporters through MAPK pathways and by depleting tetrahydrobiopterin, the cofactor for monoamine synthesis. Second, they activate **indoleamine 2,3-dioxygenase**, the enzyme that diverts tryptophan down the kynurenine pathway; microglia then convert kynurenine to **quinolinic acid**, which activates extrasynaptic NMDA receptors. Third, together with a cytokine-induced fall in astrocytic glutamate reuptake, the result is excess glutamate, reduced brain-derived neurotrophic factor and excitotoxicity. The elegance for revision is that a single upstream signal, inflammation, converges on the monoaminergic, tryptophan and glutamatergic systems at once, overlapping the monoaminergic and glutamatergic targets that existing antidepressants act on, while the kynurenine arm remains mainly an investigational one.

MNEMONIC

Starve the monoamines, hijack the tryptophan, flood the synapse

Three routes from cytokine to low mood: monoamines are **starved** by raised reuptake and lost tetrahydrobiopterin; tryptophan is **hijacked** down the kynurenine pathway to quinolinic acid; and the synapse is **flooded** with glutamate as astrocytic reuptake falls, lowering BDNF and driving excitotoxicity.

24.8 Inflammatory biomarkers and longitudinal risk in depression

From mechanism to measurement. Individuals with depressive disorders show elevated levels of several pro- and anti-inflammatory cytokines, including IL-2, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, interferon-gamma, C-reactive protein and TNF. From that broad set, the most robust and consistent associations are with CRP, IL-6, IL-1 and TNF. A meta-analysis of 82 studies found peripheral IL-6 and TNF-alpha elevated and interferon-gamma lower in major depression, with TNF-alpha, IL-6 and IL-1b tracking the severity of depressive and cognitive symptoms. The relationship is prospective as well as cross-sectional: raised CRP and IL-6 predict later depression, and in a large Danish population cohort the risk of mood disorder rose by **45%** after a diagnosis of autoimmune disorder and by **62%** after hospitalisation for an infectious disease. IL-6 carries particular weight: it predicts the chronicity and follow-up severity of depression and is associated with increased suicide risk, the highest levels correlating with the most violent suicide attempts, and autopsies of suicide victims show raised cytokine concentrations in the orbitofrontal and dorsolateral prefrontal cortex. That combination, a prospective marker of chronicity and a correlate of violent self-harm with a tissue-level footprint, is why IL-6 recurs across the whole immune literature rather than sitting as one cytokine among many. None of this makes inflammation the diagnosis. The primary nosology and management of depression belong to the Mood disorders: pharmacotherapy notes; what the immune lens adds is an inflammatory subgroup and a set of state markers.

GOOD TO REMEMBER

In depression that is proving treatment-resistant, a coexisting autoimmune or infective illness, or a prospective rise in CRP and IL-6, is worth noting as a group-level correlate of severity and chronicity and a prompt to look for a treatable medical contributor. It does not by itself establish causation or a diagnosis, but it flags the patient in whom the mood disorder and the body are moving together.

24.9 The immune lens on schizophrenia

The immune story is weaker and more cautious in psychosis than in depression, and that caution is itself examinable. Increased inflammation is generally not associated with the development of positive psychotic symptoms, and circulating immune markers do not distinguish schizophrenia from affective disorders. What the data do support is modest. A meta-analysis of over 85,000 people found small but reliable increases in CRP among people with schizophrenia, paralleling positive but not negative symptom severity, and a first-episode meta-analysis comparing 3,453

drug-naive first-episode patients with 4,152 controls reported raised IL-6, IL-8 and TNF. Elevated IL-6, TNF, soluble IL-2 receptor and IL-1 receptor antagonist appear across acute schizophrenia, bipolar mania and major depression alike, which underlines the non-specificity. Two further strands complete the picture. A Danish National Registry analysis linked prior illness to later schizophrenia, and the developmental hypothesis of **maternal immune activation** ties prenatal rubella, influenza and toxoplasmosis to schizophrenia; maternal IL-8 is significantly raised in pregnancies that lead to schizophrenia, with fetal exposure associated with increased ventricular cerebrospinal fluid and reduced left entorhinal cortex and right posterior cingulate volumes, raised maternal TNF has been linked to later illness, and blocking IL-1, IL-6 and TNF reduces schizophrenia-like deficits in animal models. As with mood disorder, the primary nosology and treatment sit in the Schizophrenia: management, antipsychotics and adverse effects notes.

29%	60%	125%
HIGHER SCHIZOPHRENIA RISK AFTER AUTOIMMUNE DISORDER	AFTER HOSPITALISATION FOR INFECTION	WHEN AUTOIMMUNITY AND INFECTION COMBINE

TRAP **Raised inflammatory markers are not a psychosis-specific finding.** Candidates read an elevated CRP or IL-6 as evidence that inflammation is driving the hallucinations and delusions, or as a marker that separates schizophrenia from mood disorder. Neither holds: inflammation is generally not tied to the development of positive psychotic symptoms, and the same circulating markers rise across acute schizophrenia, bipolar mania and depression. The lens describes a shared vulnerability, not a diagnostic signature.

IN INDIA

When a new depressive or psychotic presentation coincides with a systemic infection or an autoimmune illness, the raised prospective risk shown above is a reason to take a deliberate infective and autoimmune history and to look for an active inflammatory process before settling on a primary psychiatric diagnosis. That discipline earns its keep wherever infective and autoimmune illness routinely share the psychiatric differential, and it keeps a treatable contributor from being missed.

Immune-brain signalling is bidirectional, and subthreshold inflammation is both a state marker and, in some patients, a probable contributor across mood and psychotic illness: a lens on severity and vulnerability, never a diagnosis in itself.

Degenerative, neuromuscular and functional neurology

25 · Atypical parkinsonism and the hereditary ataxias

Two families of neurodegeneration bring a patient to psychiatric attention long before anyone has thought of a psychiatrist. The first is the group of atypical parkinsonian, or Parkinson-plus, syndromes, which borrow the outward signs of Parkinson disease but run a faster

course, resist dopaminergic treatment, and carry cognitive and behavioural change from early in the illness. The second is the hereditary cerebellar ataxias, in which a genetically determined degeneration of the cerebellum and its connections produces not only incoordination but a substantial and frequently unrecognised psychiatric burden. Marks cluster here because each of these disorders is first misread as something else: a Parkinson-plus syndrome as ordinary Parkinson disease, an ataxia as a primary depression or a personality change. Recognising the atypical features, and knowing which signs separate one syndrome from the next, is what the examination rewards.

25.1 The Parkinson-plus class and where it departs from Parkinson disease

Parkinson-plus diseases are a group of related neurodegenerative illnesses that share many of the physical signs of Parkinson disease, yet other features set them apart from it and from one another. The single most useful class-level discriminator is that, compared with Parkinson disease, they follow a more rapid course and respond less well to dopaminergic medication. A patient whose parkinsonism advances quickly, spreads symmetrically, and fails to improve convincingly on levodopa is telling you the diagnosis is probably not idiopathic Parkinson disease.

A second early signpost is the timing of dementia. In several illnesses characterised by parkinsonism, among them dementia pugilistica, the Parkinson-plus disorders themselves, and dementia with Lewy bodies, dementia may appear as the first or the most prominent symptom, whereas in Parkinson disease cognitive decline is a comparatively late development. Dementia with Lewy bodies, the one-year rule that separates it from Parkinson disease dementia, and its neuroleptic sensitivity are taught in the Dementias and neurocognitive disorders notes and are only named here. The point to carry forward is that early, prominent cognitive or behavioural change in a parkinsonian patient argues against simple Parkinson disease.

RULE **A parkinsonism that progresses rapidly, carries early atypical features, and responds poorly to levodopa is a Parkinson-plus syndrome until proven otherwise.** Idiopathic Parkinson disease is asymmetric at onset, evolves slowly, and answers to dopaminergic treatment; symmetry at onset is not a class-level rule but varies by syndrome, being typical of progressive supranuclear palsy yet absent in the characteristically asymmetric corticobasal degeneration. Each of the three degenerative Parkinson-plus syndromes then adds a signature of its own: a vertical gaze palsy, autonomic or cerebellar failure, or an apraxic alien limb.

25.2 Progressive supranuclear palsy: axial rigidity, early falls and the vertical gaze palsy

Progressive supranuclear palsy presents with parkinsonism but rarely with the resting tremor that typifies Parkinson disease. Its rigidity is predominantly axial, forcing the head, neck and spine to remain overly upright and unnaturally straight, in pointed contrast to the flexed neck and stooped kyphosis of Parkinson disease. Postural instability and falls occur early, often within the first year of onset, and the parkinsonism progresses with symmetric bradykinesia and axial rigidity rather than the asymmetric picture of Parkinson disease. It becomes manifest in affected individuals over the age of 40 years, and levodopa does not significantly correct it.

The most characteristic feature is a loss of the ability to look voluntarily in the vertical plane, the **vertical supranuclear gaze palsy**, which characteristically impairs downward gaze first and can make descending stairs treacherous. It is named supranuclear for a reason that also supplies the bedside test: the lesion sits above the ocular motor nuclei, so the oculocephalic, or doll's eye, vertical reflex is preserved even when voluntary vertical gaze is lost. This sign may not appear until **3 years** after the parkinsonism begins, so its absence early does not exclude the diagnosis. Progressive supranuclear palsy is a tauopathy, and MRI may show the hummingbird sign of rostral midbrain atrophy.

MNEMONIC

Look down, stand straight, fall back

The clinical spine of progressive supranuclear palsy: impaired voluntary **down**gaze, an unnaturally **straight** and upright axial posture, and early **backward** falls from postural instability, none of which behaves like idiopathic Parkinson disease.

PITFALL

Being reassured by intact reflex eye movements. Because the deficit is supranuclear, the doll's eye vertical reflex is preserved while *voluntary* vertical gaze is lost, so the eyes can look normal on passive testing. Ask the patient to look up and down to command; a normal oculocephalic response does not exclude the palsy.

25.3 The subcortical dementia and neuropsychiatry of progressive supranuclear palsy

Cognitive change in progressive supranuclear palsy is common and follows a frontal-subcortical pattern rather than the cortical one of Alzheimer disease. Roughly 10% of patients present with cognitive symptoms, and up to **70%** develop a frank dementia over the course of the illness. Neurocognitive assessment shows psychomotor slowing, poor working memory and executive dysfunction, the profile of a disease that disrupts the frontal circuits from below. The classic cortical triad of aphasia, apraxia and agnosia is not the story here, which is one of the features that separates it from Alzheimer disease and, as the next sections show, from corticobasal degeneration.

Progressive supranuclear palsy also produces pseudobulbar signs, the disinhibition of brainstem motor programmes that in its affective form yields pathological laughing and crying. That syndrome in full, its phenomenology, pathophysiology and treatment, is taught in the Stroke, TBI, delirium and focal brain syndromes notes and is named here only as one of the neuropsychiatric accompaniments of the disease. Retropulsion, the tendency to lose balance in a backward direction, is often prominent and compounds the falls that already mark the illness from its onset. Taken together, the slowing, the executive failure and the brainstem release give the disease a characteristic frontal-subcortical texture that becomes diagnostically useful when it is set against the cortical picture of corticobasal degeneration.

25.4 Multiple system atrophy: two subtypes and the levodopa wall

Multiple system atrophy is a family of Parkinson-plus disease with two classic subtypes a candidate is expected to name. One is a cerebellar subtype, historically called olivopontocerebellar degeneration, notable for ataxia; the other is a subtype dominated by pronounced autonomic dysfunction, historically called Shy-Drager syndrome. Naming the disease by the system that fails first, cerebellum or autonomic nervous system, is the practical way to hold its presentations together.

Like Parkinson disease, multiple system atrophy is a synucleinopathy; unlike Parkinson disease, it responds poorly to levodopa, and any response is usually incomplete or unsustained, which is a large part of what marks it as atypical. The autonomic failure of the dysautonomic subtype expresses itself as orthostatic intolerance, disturbed bladder control and other signs of a nervous system that can no longer regulate its own housekeeping, and it is frequently the autonomic collapse, rather than the parkinsonism, that disables the patient and brings them to attention. The cerebellar subtype, by contrast, stands at the border of the second half of this section, because its ataxia raises exactly the differential that the hereditary cerebellar degenerations occupy, and a middle-aged patient with a progressive ataxia plus autonomic failure and a levodopa-resistant parkinsonism is describing this disease.

25.5 Corticobasal degeneration: the asymmetric apraxic limb

Corticobasal degeneration has as its core clinical syndrome a progressive asymmetric rigidity and apraxia together with signs of both cortical and basal-ganglia dysfunction. It was first identified in 1967 in three individuals with a progressive asymmetrical akinetic-rigid syndrome and apraxia. It is largely sporadic and, like progressive supranuclear palsy, is a tauopathy; more precisely it is a sporadic four-repeat tauopathy, with deposition of hyperphosphorylated four-repeat tau in neurons and glia as astrocytic plaques. Because the living clinical picture and the histopathology do not always coincide, the term corticobasal syndrome is often used for the clinical presentation, reserving the label corticobasal degeneration for the pathological diagnosis.

The clinical signs cluster on one side of the body and betray the cortex as much as the basal ganglia:

- asymmetric rigidity and limb apraxia;
- the **alien limb phenomenon**, in which a limb behaves as if it has a will of its own;
- cortical sensory loss;
- myoclonus; and
- postural instability.

The neuropathology matches the asymmetry of the signs. Imaging shows asymmetric frontoparietal atrophy with subcortical hypometabolism contralateral to the more clinically affected side, and tau inclusions are found in the substantia nigra, the basal ganglia and along the dentatorubrothalamic tracts. The laterality is not incidental; it is the anatomical signature of a

disease that attacks one hemisphere ahead of the other, and it mirrors the one-sided apraxia and alien limb at the bedside.

25.6 The neuropsychiatry of corticobasal degeneration and its contrast with progressive supranuclear palsy

The neuropsychiatric hallmarks of corticobasal syndrome are cortical in character, which is what most sharply separates it from progressive supranuclear palsy. Its clinical signatures are a lateralised ideomotor and ideational apraxia and the alien hand syndrome, and on cognitive testing parietal-lobe dysfunction shows itself as sensory or visual neglect and visuospatial impairment, alongside measurable deficits in social cognition. Where progressive supranuclear palsy disrupts the frontal circuits from below and produces a slowed, subcortical picture, corticobasal degeneration attacks the parietal and frontal cortex directly and produces the apraxic, neglecting profile of a cortical disease. That localising difference is the deeper reason the two tauopathies feel so unlike each other at the bedside despite sharing a four-repeat tau pathology.

GOOD TO REMEMBER

When two akinetic-rigid, levodopa-poor patients differ in mood, the affective colour can support the distinction the motor signs already draw: depression is much more common in corticobasal degeneration, whereas apathy is the hallmark of progressive supranuclear palsy. It corroborates rather than leads; the side-to-side asymmetry and apraxia of the one and the axial, gaze-palsied posture of the other remain the diagnostic anchors, with the affective colour a genuine supporting clue rather than an incidental comorbidity.

Set side by side, the three degenerative Parkinson-plus syndromes separate cleanly on a handful of axes, as summarised in the accompanying comparison.

FEATURE	PSP	MSA	CBD
Signature motor sign	Axial rigidity, early falls	Ataxia or autonomic failure	Asymmetric akinesia, apraxia
Giveaway sign	Vertical supranuclear gaze palsy	Autonomic or cerebellar failure	Alien limb, cortical sensory loss
Symmetry	Symmetric	-	Asymmetric
Levodopa	Poor response	Poor or unsustained response	Poor response
Pathology	Tauopathy	Synucleinopathy	Four-repeat tauopathy

TRAP **Pushing the levodopa dose ever higher when a "Parkinson disease" patient will not respond.** In the Parkinson-plus syndromes the poor response to dopaminergic medication is not undertreatment, it is the diagnosis. Multiple system atrophy responds poorly, if at all, to levodopa, and progressive supranuclear palsy responds poorly; a parkinsonism that will not answer escalating doses should prompt a rethink of the diagnosis, not a bigger prescription.

25.7 Medication-induced parkinsonism: the mimic on the prescription pad

Medication-induced parkinsonism is the most common and most reversible of the Parkinson disease mimics, and it belongs in every differential because its cause sits in the drug chart. Typical and most atypical antipsychotic agents, to a greater or lesser degree, block D2 receptors and so routinely cause parkinsonism. So do several non-psychiatric D2 blockers prescribed for nausea and vertigo:

- metoclopramide;
- prochlorperazine; and
- promethazine.

Tetrabenazine produces the same picture by a different route, depleting dopamine rather than blocking its receptor. The resemblance to idiopathic Parkinson disease is close enough that clinical examination cannot reliably tell them apart; the most useful single clue is symmetry. Medication-induced parkinsonism usually causes symmetric, bilateral signs from the onset, whereas Parkinson disease tends to begin asymmetrically and stays asymmetric throughout. Once the offending drug is stopped the syndrome usually resolves over weeks, but a minority does not: about 10% of persistent cases turn out to harbour Parkinson disease or a Parkinson-plus syndrome that the medication had merely unmasked.

> **IN INDIA**
>
> In any patient presenting with new, symmetric, bilateral parkinsonism, review the drug chart before diagnosing Parkinson disease. D2-blocking antiemetics such as metoclopramide and prochlorperazine, and antipsychotics of every class, are common precipitants; withdraw the offending agent and reassess over the following weeks. The mimic is common and usually reversible, and the price of missing it is months of unnecessary antiparkinsonian treatment for a problem the prescription created.

25.8 The hereditary ataxias: inheritance, prevalence and age of onset

The second half of this section turns from the basal ganglia to the cerebellum. The hereditary ataxias are genetically heterogeneous, but an important group of them, including Friedreich ataxia and many spinocerebellar ataxias, are trinucleotide-repeat disorders, and the first thing to fix is the pattern of inheritance. **Friedreich ataxia** follows an autosomal recessive pattern and is the most common autosomal recessive cerebellar ataxia, while the **spinocerebellar ataxias** follow an autosomal dominant pattern; the same trinucleotide-repeat mechanism, working in different genes, also underlies the autosomal dominant Huntington disease and the sex-linked fragile X syndrome, which are named here only to place the ataxias within their family. The spinocerebellar ataxias themselves form a large numbered series, running to types 1 to 42 and beyond.

Prevalence gives a second anchor. Taken separately, the recessive cerebellar degenerations (primarily Friedreich ataxia), the dominant ones, and the sporadic cerebellar neurodegenerations each run at about **2 per 100,000**. Age of onset then separates the two hereditary groups at the

bedside: Friedreich ataxia declares itself in childhood, whereas the spinocerebellar ataxias typically begin in middle age. That single discriminator, a child with a progressive ataxia against an adult with one, does much of the early diagnostic work before any genetic test is sent, and it maps onto the recessive-versus-dominant split that structures the whole group. The specific repeat unit and causative gene of each disorder belong with the individual disease and are not asserted where the available sources do not cleanly supply them.

25.9 The psychiatric burden of the cerebellar degenerations

For the psychiatrist the important truth about these disorders is that the cerebellum is not merely a motor structure, and its degeneration carries a heavy and often silent psychiatric load. In degenerative disorders predominantly limited to the cerebellum, most patients develop one or more psychiatric syndromes within the first decade and a half of the illness, and depression dominates that picture.

about 75%	about one-third	about 25%
DEVELOP A PSYCHIATRIC SYNDROME WITHIN 10 TO 15 YEARS OF ONSET	HAVE AN EPISODE OF MAJOR DEPRESSION	DEVELOP PERSISTENT PERSONALITY CHANGE

Beyond the patients who reach the threshold for major depression, roughly as many again experience other depressive states, from brief recurrent and minor depression to dysthymia, so that depressive illness of one form or another comes close to being the rule. The persistent personality change resembles that seen in Huntington disease and, as in Huntington disease, is not confined to those who have gone on to cognitive decline. Where extra-cerebellar structures degenerate as well, the neuropsychiatric picture widens: **spinocerebellar ataxia type 2**, a late-onset autosomal dominant disorder in which loss extends to the inferior olive, pontocerebellar nuclei, substantia nigra and motor neurons, adds executive dysfunction, impaired memory, apathy, depression and potentially psychosis to the cerebellar signs.

Suicidality can be striking, and one figure is worth carrying. In **spinocerebellar ataxia type 3**, also called Machado-Joseph disease, the rate of suicidal ideation has been reported as high as **65%**. That number, from The Clinical Research Consortium for Spinocerebellar Ataxias, is specific to type 3 and stated as an upper bound rather than a general figure for the ataxias, but it is a stark reminder that these are not benign motor disorders.

TRAP **Waiting for a cerebellar-degeneration patient to complain of low mood.** Depression is common in these disorders, yet self-awareness of it is frequently absent, so a clinician who screens only by asking the patient will miss it. Depression here must be sought actively and corroborated with an informant, and the high figures for suicidal ideation make that active screening a safety matter rather than a courtesy.

Atypical parkinsonism is a rapid, symmetric, levodopa-poor parkinsonism with a signature sign for each disease, a vertical gaze palsy in progressive supranuclear palsy, autonomic or cerebellar failure in multiple system atrophy, an apraxic alien limb in corticobasal degeneration, while the hereditary ataxias carry a heavy and frequently unrecognised psychiatric burden that must be sought and not awaited.

26 · Motor neuron disease: cognitive, behavioural and end-of-life neuropsychiatry

Motor neuron disease was for a long time taught as a pure disorder of movement, and that is exactly why its psychiatry catches candidates out. The illness that supposedly spares the mind is now understood to reach the frontal and temporal lobes, to overlap with a dementia syndrome, to generate a disinhibited disorder of affective display, and to force some of the hardest end-of-life decisions in clinical medicine onto a patient whose intellect may itself be quietly eroding. The marks here reward the psychiatrist who can hold two facts at once: that the motor picture is the diagnosis, and that cognition, behaviour and mood belong to the same disease and shape everything from capacity to survival. What follows sets out the disease a psychiatrist must recognise, then works through its cognitive overlap with frontotemporal degeneration, its genetic and behavioural links, the pathological affect it produces, the drugs that modify and palliate it, and the prognostic frame within which every psychiatric decision has to be made.

26.1 The disease a psychiatrist must recognise

The commonest form of motor neuron disease is **amyotrophic lateral sclerosis**, long regarded as a very rare condition though its frequency is far from negligible. On the account in Kaplan and Sadock's Comprehensive Textbook of Psychiatry it is uncommon rather than vanishingly rare, a distinction that matters because a psychiatrist working a busy neurology liaison service will meet it. Its diagnostic signature is the coexistence, in the same patient, of two families of physical sign that are usually thought of as opposites. The lower motor neuron signs are weakness, muscle atrophy and fasciculations, the last being **fasciculations**, painless spontaneous discharges of motor units seen as rapid involuntary twitches in limb or trunk muscles, while the upper motor neuron signs are spasticity, loss of dexterity, hyperreflexia and pseudobulbar palsy. It is that combination, upper and lower motor neuron signs together, that classically makes the clinical diagnosis.

SIGN CLASS	CLINICAL FEATURES
Lower motor neuron	weakness, muscle atrophy and fasciculations (painless spontaneous discharges of motor units, seen as involuntary twitches in limb or trunk muscles)
Upper motor neuron	spasticity, loss of dexterity, hyperreflexia and pseudobulbar palsy

~2 / 100,000	6 / 100,000	5-20%	within 3 years
ANNUAL INCIDENCE	POINT PREVALENCE	FAMILIAL CASES	TYPICAL SURVIVAL

26.2 Where the degeneration falls

The psychiatry of this disease is legible only once its pathology is placed, because the lesions that produce the mind symptoms are not where the classical teaching looks. The degeneration is multi-level: it consumes the motor neurons of the spinal cord, that is the anterior horn cells, together with the motor neurons of the brainstem and the upper motor neurons of the cerebrum. So far this is the map of a movement disorder. The critical addition for a psychiatrist is cortical. In the same disease there is gliosis and neuronal loss in the superficial layers of the dorsomedial neocortex of the frontal lobes, and this may extend into the hippocampal and parahippocampal regions of the temporal lobes.

That frontal and temporal cortical involvement is not incidental. It is the anatomical substrate of everything the rest of this topic describes: the executive and language changes, the behavioural syndromes, and the overlap with a frontotemporal dementia. A disease whose pathology reaches the dorsomedial frontal neocortex and the medial temporal structures is, on anatomical grounds alone, a disease that should be expected to disturb cognition and social behaviour, and the reason the older teaching missed this is simply that the motor signs are so much louder that the cortical ones went unexamined. Reading the pathology this way turns the neuropsychiatric findings from a surprise into a prediction.

26.3 The amyotrophic lateral sclerosis and frontotemporal degeneration spectrum

The single most important conceptual shift in this field is that **frontotemporal degeneration** and amyotrophic lateral sclerosis lie on one spectrum rather than standing as two wholly separate diseases. There is increasing recognition of the neuropsychiatric aspects of the motor disease, most notably its association with frontotemporal degeneration, and careful examination shows cognitive decline in patients who present with otherwise classic motor symptoms; either condition may develop first, so the dementia may emerge in someone with established motor disease or the motor disease in someone already carrying the dementia diagnosis. The two share much of their molecular pathology, the ubiquitin-positive neuronal cytoplasmic inclusions found in lower motor neurons, hippocampus and neocortex, staining in most cases for the protein TDP-43, the pathological thread that lets them be understood as one disease spectrum rather than two unrelated illnesses. The standalone account of frontotemporal dementia as a primary neurocognitive disorder belongs to the Dementias and neurocognitive disorders notes and is named here, not reproduced.

Quantified, the overlap is substantial rather than anecdotal. Between **one-third to one-half** of patients perform poorly on formal neuropsychological testing against matched controls, and the pattern is a frontal one, distinct from the amnestic and apraxic profile of Alzheimer disease. Its recognisable components are worth carrying:

- mild memory loss, rather than the dense amnesia of a cortical dementia;
- word-finding difficulty and reduced semantic fluency;
- executive dysfunction, the frontal signature of the disease;

- impaired recognition of facial emotion, a social-cognition deficit that patients and families feel long before it is tested.

The reason this matters clinically, and not only diagnostically, is prognostic: the presence of cognitive impairment is associated with shorter survival. The standardised cognitive instruments used to detect such change are owned by the Psychotherapies, clinical assessment, MSE and nosology notes and are named here only as tools.

RULE **Motor neuron disease is not a pure disorder of movement.** It lies on a continuum with frontotemporal degeneration, and a substantial minority of patients carry a frontal-executive cognitive syndrome that the loud motor signs conceal. Because that impairment predicts a shorter survival and erodes the very faculties a patient needs to make end-of-life decisions, cognition and behaviour must be assessed as part of the diagnosis, not left until they declare themselves.

GOOD TO REMEMBER

Screen cognition and behaviour at diagnosis, before the motor decline dominates the consultation. Doing so is not academic: because cognitive impairment is linked to decreased survival time and may impair a patient's capacity to weigh decisions about ventilation and feeding, though such impairment does not by itself establish incapacity and capacity must be assessed for the specific decision with appropriate communication support, an early baseline lets you tell later change from long-standing deficit and lets the difficult conversations happen while the patient can still fully participate.

26.4 The genetics and the C9ORF72 behavioural phenotype

Most disease is sporadic, but a meaningful minority is inherited, and the genes involved are where the motor and psychiatric ends of the spectrum are physically joined. About 5 to 20 percent of cases are familial, and several genes have been implicated, among them SOD1, C9ORF72, VCP, TARDBP, FUS, CHMP2B and ATXN2. One of these deserves separate teaching because it is the gene that most concerns a psychiatrist. Carriers of the **C9ORF72** mutation, an expanded hexanucleotide repeat, a six-base repeat rather than the trinucleotide repeat expansions that underlie Friedreich ataxia and several of the spinocerebellar ataxias described elsewhere in this chapter, may present with behavioural syndromes, especially psychosis and agitation. The same repeat sits on both the motor disease and the frontotemporal dementia, which is precisely why a single gene can produce weakness in one relative and a psychiatric presentation in another.

The clinical consequence is a differential trap in reverse. A middle-aged adult who presents with new psychosis, agitation or a change in social conduct, and who on careful examination has subtle wasting or fasciculations, may be showing the behavioural face of a C9ORF72-related disease rather than a primary psychiatric illness. The primary nosology and management of psychosis itself belong to the Schizophrenia: management, antipsychotics and adverse effects notes; the point owned here is only that this disease can announce itself through the mind before the limbs, and that the family history and the motor examination are the clues that most help separate the

two, though neither, when absent, rules out a C9ORF72-related disease. The corpus does not state a numeric repeat-size threshold for pathogenicity, and none is asserted here.

26.5 Pseudobulbar affect: recognition and its traps

The most distinctive affective disturbance of the disease is **pseudobulbar affect**, a syndrome of disinhibited affective display in which the patient produces inappropriate and exaggerated laughing or weeping in response to environmental stimuli, and it may affect **up to 50 percent** of patients. Its two discriminating features are what an examiner will press. First, the behaviour is not usually associated with any disturbance of the underlying mood, so the weeping patient is not necessarily sad and the laughing patient is not elated. Second, the display tends to be stereotyped for each patient, taking much the same form each time and often disproportionate to or independent of the apparent trigger. The full phenomenology, pathophysiology and management of pseudobulbar affect under any name belong to the Stroke, TBI, delirium and focal brain syndromes notes; what this chapter owns is that it occurs in this disease and must be distinguished from a mood disorder before either is treated.

TRAP **Reading the affective display as the mood.** A patient weeping in the clinic is assumed to be depressed and one laughing to be euphoric, and an antidepressant or a mood stabiliser follows. The defining clue is that in pseudobulbar affect the display is dissociated from the underlying mood and is stereotyped, so the question to ask is not what the tears look like but whether the patient reports the corresponding feeling. Get this wrong and you treat a phantom mood while missing a treatable disorder of affective control.

PITFALL

Confusing two terms that share a prefix. **Pseudobulbar palsy** is the motor sign of upper motor neuron dysfunction in the corticobulbar tracts supplying the bulbar muscles, one of the physical findings listed above, whereas pseudobulbar affect is the emotional syndrome of pathological laughing and crying. They can coexist in this disease and are easily elided, but one is a disorder of the tongue and swallow and the other a disorder of affective display, and only the second answers to the treatments in the next section.

26.6 Treating pseudobulbar affect

Recognising pseudobulbar affect is worthwhile because, unlike much in this disease, it can be treated, and treated on its own indication rather than as though it were the mood disorder it mimics. Successful treatment has been reported with tricyclic compounds or with selective serotonin reuptake inhibitors, used off-label, which makes a low-threshold trial reasonable once the diagnosis is secure. The one agent developed specifically for the syndrome is a combination of dextromethorphan and quinidine, marketed as Nuedexta, which is effective in many cases and is the only agent approved by the United States Food and Drug Administration for pseudobulbar affect. The reference source states these as treatment facts and quotes no milligram doses for them, so none is given here; the fuller pharmacology of the syndrome sits with the Stroke, TBI, delirium and focal brain syndromes notes. For the psychiatrist the practical teaching is compact: name the syndrome correctly, separate it from mood, and reach first for a serotonergic agent or

the approved combination rather than escalating an antidepressant against a depression that is not there.

26.7 Disease-modifying and symptomatic drug treatment

Two established drugs modify the disease itself, and both matter to the psychiatrist for reasons that go beyond survival. The first is **riluzole**, which blocks glutamate release and prolongs survival by about **3 months** in clinical studies. Two details earn their place in a psychiatry chapter. One is that an oral suspension, Tiglutik, exists to avoid the problems of crushing tablets, which is directly relevant in a disease whose bulbar involvement makes swallowing tablets unsafe. The other is a liaison caution: riluzole in overdose may cause agitation, so a disturbed patient on this drug is one in whom the agitation may be pharmacological rather than psychiatric.

The second disease-modifying agent is **edaravone**. Given for amyotrophic lateral sclerosis, in its intravenous formulation it is infused at 60 mg on an initial cycle of daily dosing for 14 days followed by a 14-day drug-free period, and thereafter in cycles of daily dosing on 10 of every 14 days with 14-day drug-free periods between them; an oral suspension formulation also exists. Its benefit in the trials was read on the **ALS Functional Rating Scale-Revised, a twelve-item rating scale spanning fine motor, gross motor, bulbar and respiratory function**, the instrument the reader will meet as the standard functional endpoint in this disease. Neither drug is curative, and both are best understood by the psychiatrist as tools that buy time and function rather than reverse the illness, which keeps the therapeutic conversation honest.

26.8 Prognosis and the end-of-life frame

Every psychiatric decision in this disease is made against a foreshortened prognosis, and stating it plainly is part of the clinician's duty. Death, from respiratory failure or aspiration, typically occurs within 3 years of diagnosis. The one course-modifying decision the source records is the patient's own: the course may occasionally be prolonged, particularly where the patient decides to accept respiratory support. That single fact is what makes advance discussion of ventilation unavoidable rather than optional, and it must be had while cognition allows, because the same disease that shortens survival can, through its frontal involvement, impair the very capacity a valid decision requires.

The wider end-of-life psychiatric care of these patients, the systematic attention to mood and to the psychological weight of a foreseeable death, the formal assessment of decisional capacity as the illness advances, and advance care planning for ventilation and for feeding, is real and important, but it rests on general palliative and psychiatric principles and on the primary management of depressive illness set out in the Mood disorders: pharmacotherapy notes rather than on any figure specific to this disease. Where the numbers are not there to be quoted, the honest teaching is to name the task and treat the patient, not to invent a prevalence. The psychiatrist's contribution across these final years is to keep the mind in view in a disease everyone else is watching for its muscles.

Motor neuron disease is not a pure disorder of movement: in amyotrophic lateral sclerosis, one-third to one-half show frontal-executive cognitive change on the frontotemporal degeneration spectrum, and up to half develop a pseudobulbar affect that is dissociated from mood; cognitive impairment is associated with shorter survival in a disease whose own course is short, with death typically within 3 years of diagnosis.

27 · The functional neurological disorder spectrum and its positive signs

A psychiatrist is often the clinician who recognises this disorder and helps demonstrate the positive signs that establish it. Functional neurological symptom disorder is the modern name for what was long called conversion disorder: genuine neurological symptoms - limb weakness, tremor, seizure-like attacks, visual loss, gait failure - that are real and disabling but arise from a disorder of nervous-system functioning rather than from structural damage to the nervous system. It earns its marks because the whole diagnostic logic has been rewritten in the current classifications, and because the signs that establish it are elegant, reproducible at the bedside, and perfectly suited to a viva. The old teaching treated the disorder as a diagnosis of exclusion, reached once investigations came back clear; the current teaching treats it as a positive, rule-in diagnosis established by specific clinical signs. This section works through those positive signs across the spectrum, then closes on how the diagnosis is explained to the patient and treated.

27.1 A rule-in diagnosis, not a diagnosis of exclusion

The single most examined point in this topic is a change in how the diagnosis is reached. Under DSM-5-TR, **functional neurological symptom disorder**, historically termed conversion disorder, rests on clinical findings that show clear evidence of incompatibility between the symptom and recognised neurological disease. The diagnosis is explicitly not one of exclusion. It is not made simply because investigations are normal, and it is not made because a symptom looks bizarre or defies an anatomical explanation on first impression. What establishes it is positive evidence, a demonstration that the nervous system remains capable of the movement or the perception that the patient cannot voluntarily produce.

The idea at the heart of most positive signs is **internal inconsistency**: a physical sign elicited by one method of examination is no longer present when the same function is tested a different way, or when the patient's attention is drawn elsewhere. Positive signs demonstrate incompatibility through inconsistency or incongruence with recognised neurological disease, and internal inconsistency is one important route rather than a property of every sign; that idea generates much of the bedside repertoire. It also carries a clinically liberating corollary. Because the diagnosis is made on positive signs rather than on the absence of disease, it can be made even in a patient who also has a structural neurological disorder such as epilepsy or multiple sclerosis, according to DSM-5-TR. Functional and organic symptoms coexist in one patient far more often than the older either/or framing allowed. The manual adds a single safeguard against over-reading any one test: the diagnosis should rest on the overall clinical picture and not on a solitary finding.

RULE **Functional neurological disorder is a positive, rule-in diagnosis demonstrated by internal inconsistency, and it can be made alongside genuine neurological disease.** The examiner is testing whether you have absorbed the shift from the exclusion model to the positive-sign model. The presence of a real neurological illness does not exclude a functional overlay, and normal investigations do not establish one.

TRAP **Labelling a symptom functional because the scan is normal or because the presentation looks bizarre.** DSM-5-TR states plainly that the diagnosis is not made on normal investigations and not made because a symptom is bizarre. A normal image does not establish a functional disorder and does not by itself exclude every organic one, and strange-looking symptoms occur in organic disease too. The call is made on a demonstrated incompatibility sign, never on the strangeness of the story or the emptiness of the report.

MNEMONIC

Present one way, absent the other

Every functional positive sign is a demonstration of **internal inconsistency**: the deficit is present when the function is tested directly and absent when the very same function is recruited automatically or through distraction. If you can show the movement returning by another route, you have your rule-in evidence.

27.2 Functional limb weakness: Hoover's sign and the hip abductor sign

Functional limb weakness is the commonest presentation of the disorder and the one with the most reliable signs. The best known is **Hoover's sign**, described by Kaufman for suspected psychogenic weakness of one leg. It exploits the reflex that hip extension in one leg is coupled to hip flexion in the other. When a patient with genuine paresis tries to raise the sound leg, the affected leg presses down; the functional patient, by contrast, fails to press down with the sound leg when raising the weak one, yet unconsciously presses down with the weak leg when attempting to raise the sound one. Elicited formally, weakness of hip extension in the affected leg returns to normal strength when the opposite hip is flexed against resistance, according to DSM-5-TR.

The accompanying figure sets these positive signs out across the spectrum, so that the reader can see how each one turns a claimed deficit into a demonstrable inconsistency.

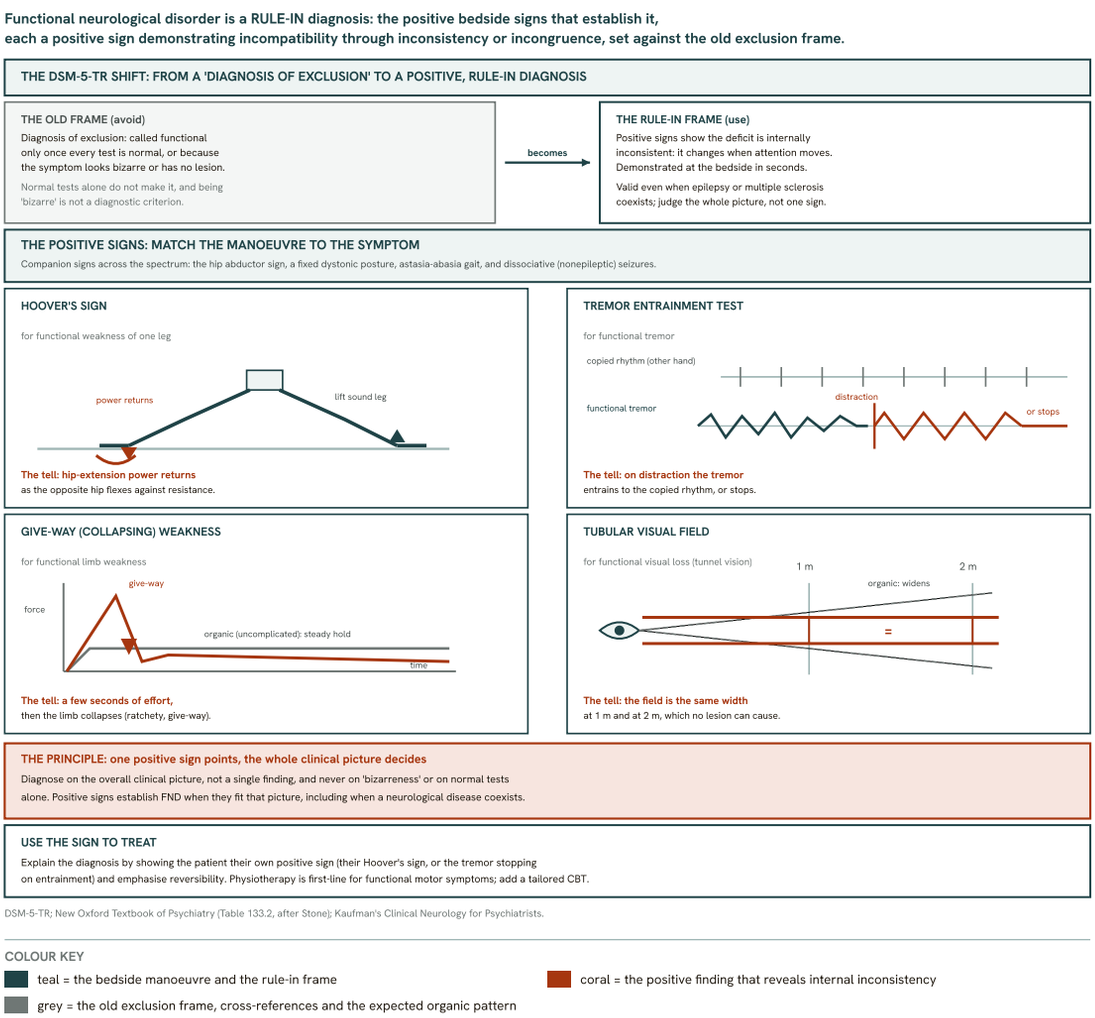


Fig 35.10 **Functional neurological disorder: the positive signs that rule it in.** DSM-5-TR reframes functional neurological symptom disorder as a rule-in diagnosis demonstrated by internal inconsistency, not a diagnosis of exclusion, and it can be made even when a neurological disease such as epilepsy or multiple sclerosis coexists. Four bedside manoeuvres are shown: Hoover's sign (hip-extension power returns as the opposite hip flexes against resistance), the tremor-entrainment test (the tremor locks to a copied rhythm or stops on distraction), give-way or collapsing weakness (a few seconds of effort then collapse), and a tubular visual field (the same width at 1 m and at 2 m). Base the diagnosis on the whole clinical picture and not a single sign, then use the sign to explain the diagnosis, with physiotherapy first-line for functional motor symptoms and a tailored CBT. (DSM-5-TR; New Oxford Textbook of Psychiatry, Table 133.2; Kaufman's Clinical Neurology for Psychiatrists.)

Its companion is the **hip abductor sign**, in which weakness of thigh abduction returns to normal when the opposite hip is abducted against resistance, on the same reflex logic that Hoover exploits for extension. The related discrepancy worth eliciting is a mismatch between two tasks that use the same muscles: weakness of ankle plantar flexion tested on the couch set against a preserved ability to walk on tiptoes, per DSM-5-TR. The value of these manoeuvres is that they compare a voluntary movement against an automatic one and let the automatic movement betray the intact pathway, though they still require adequate comprehension and contralateral effort and must be read alongside pain and cognition rather than as tests of the patient's honesty. That is why they are trusted where an assessment of effort alone would not be.

27.3 Give-way weakness, the face-hand test and the global pattern

Beyond the reflex signs, several patterns in the way weakness behaves point to a functional origin. Kaufman describes the **give-way** or collapsing effort, in which the patient produces a brief exertion of several seconds before the limb returns to an apparently paretic position; sustained organic weakness holds more steadily, whereas this intermittent, ratchety collapse, once pain and fatigue are accounted for, supports a fluctuating and probably psychogenic deficit that is weighed with the other signs rather than read alone. The paired bedside test is the **face-hand test**: the supposedly paralysed hand is held over the patient's own face and released, and a functional patient momentarily exerts enough strength to deflect the falling hand so that it does not strike the face, a preserved protective response that supports, rather than proves, a functional origin.

A further clue is the absence of functional impairment despite the appearance of profound weakness, such as the patient who walks on heels and then on toes even though manual testing seemed to show marked ankle weakness, again per Kaufman. The New Oxford Textbook of Psychiatry adds a distributional sign: weakness that is global, affecting extensors and flexors of a limb equally, rather than following the pyramidal pattern in which extensors of the arm and flexors of the leg give way first. A global, whole-limb pattern can support a functional origin when it is incongruent with the neurological examination, but organic disease can also weaken a limb globally, so the pattern is a pointer to weigh rather than proof on its own.

> **PITFALL**
>
> The commonest clinical error here is to make the call on impression rather than on neuroanatomy. A patient who seems anxious, whose story is inconsistent, or whose weakness feels non-organic to the examining hand has not thereby been shown to have a functional disorder. DSM-5-TR is explicit that the diagnosis is not made because a symptom is bizarre, and that it rests on the overall picture rather than a single impression. Elicit an incompatibility sign, or reserve judgement; a psychogenic label pinned on a gestalt is how genuine disease gets missed.

27.4 Functional tremor and functional dystonia

Functional movement disorders carry their own rule-in tests, and the most powerful is the **tremor entrainment test** for functional tremor. The patient is asked to copy the examiner in making a rhythmical movement with the contralateral hand or foot, which loads the same motor-timing resource the tremor is drawing on. The test is positive, per DSM-5-TR, when the tremor takes up the imposed rhythm, when it is suppressed altogether, or when the patient simply cannot copy a simple rhythmical movement at all. Additional supportive features of a functional limb tremor are variability in its frequency or in its direction, neither of which is characteristic of the organic tremors it mimics, whose frequency is comparatively fixed.

The other cardinal functional movement disorder is **functional dystonia**. Its typical presentation, per DSM-5-TR, is a fixed inverted position of the ankle, a clenched fist, or a unilateral contraction of the platysma, characteristically with sudden onset. The New Oxford Textbook of Psychiatry describes the same picture as a fixed dystonic posture, most often of the

hand with flexion of the fingers, wrist and elbow, or of the ankle with plantar flexion and inversion. The abrupt onset and the fixed, non-mobile quality of the posture distinguish it from most organic dystonias, which tend to be mobile, task-specific and gradual in evolution. Fatigable or fluctuating weakness of a limb should also raise the neuromuscular-junction and dystrophic disorders that enter this differential, which are taken up elsewhere in these notes rather than here.

27.5 Functional (dissociative) seizures and the duration question

Attacks that resemble epileptic seizures or syncope are among the most important and most litigated presentations of the disorder. They carry several names for the same thing, **functional or dissociative seizures**, also called non-epileptic seizures or attacks, and the terminology itself signals that they are not driven by epileptic discharge. The positive features that suggest a functional origin, according to DSM-5-TR, include persistent eye closure during the attack, sometimes with active resistance to having the eyes opened, bilateral motor movements occurring with preserved awareness, and a duration of the event longer than the norm for an epileptic seizure. The New Oxford Textbook of Psychiatry adds ictal weeping, crying during or immediately after the attack, the ability afterwards to recall the experience of being in a generalised shaking attack, and ictal hyperventilation, since respiration ceases in a generalised epileptic seizure but commonly speeds up during a non-epileptic one.

These features must be combined rather than used singly, and they may be supported by a normal simultaneous ictal electroencephalogram, though DSM-5-TR cautions that a normal ictal recording alone does not exclude every form of epilepsy or of syncope. Duration is the classic quantified clue, and it is also the classic source of examination error.

TRAP **Treating a single attack-duration cut-off as diagnostic, and assuming the standard references agree on it.** DSM-5-TR gives the suggestive feature as a duration **longer than 5 minutes**. The New Oxford Textbook of Psychiatry sets the long-duration threshold appreciably shorter, so the two authorities a candidate is likely to have read give different numbers for the same construct. Both stress that duration is only supportive and must be combined with other features. The safe answer names the disagreement and refuses to let any single duration stand as proof.

IN INDIA

Functional and dissociative attacks can coexist with epilepsy, and where epilepsy and endemic seizure-causing infections such as neurocysticercosis are common, the pull toward settling every atypical attack as one or the other is strong. The clinical decision is to diagnose the functional attack on its own positive signs, ideally captured on simultaneous electroencephalography, and never to assume that finding a genuine seizure disorder excludes a functional one, nor that a functional diagnosis excludes coexisting epilepsy. Both can be present, and each is treated on its own terms.

27.6 Functional gait and the value of distraction

Gait is where a functional disorder is often most visible, and its signature is a mismatch between apparent danger and actual safety. The most readily identifiable pattern, per Kaufman, is **astasia-abasia**, from the Greek for an inability to stand and an inability to walk. The patient staggers, balances momentarily and appears to be in great danger of falling, yet catches themselves at the last moment by grabbing railings, furniture and even the examiner, and never actually injures themselves. That preserved postural control under apparent chaos, the fall that is always averted, is the giveaway, because it demonstrates an intact balance system working automatically beneath a gait that is failing on demand. The New Oxford Textbook of Psychiatry describes a related dragging gait in which the forefoot stays in contact with the ground and the hip is held externally or internally rotated, a pattern that supports a functional gait when it is inconsistent or incongruent with the examination, though organic disease can drag the forefoot too.

Distraction is the examiner's most useful single tool across this spectrum, and it is nowhere more telling than in gait and stance. In the New Oxford description, a patient with an apparently positive Romberg's test is asked to guess numbers traced on their back or to perform a complex motor task, and the sway settles; in a functional gait problem, balance improves significantly once attention is diverted from the act of standing. The principle is the same one that runs through every positive sign: engage automatic motor control, take conscious attention off the failing function, and the function returns. Distraction does not trick the patient so much as reveal the pathway that voluntary effort could not access.

27.7 Functional visual and speech symptoms

The sensory and speech domains complete the spectrum, and they too are diagnosed on internal inconsistency rather than on a normal structural examination. In functional speech, the positive sign is an internal inconsistency in articulation and phonation, per DSM-5-TR: a whispering dysphonia or a stutter that shifts or resolves when the patient is off guard, coughs normally, or is engaged in unselfconscious speech. In the visual domain, the hallmark is a **tubular visual field**, or tunnel vision, together with tests that show internal inconsistency in visual acuity. The New Oxford Textbook of Psychiatry gives the operational definition that exposes it: a tubular field has the same width at **1 m as at 2 m**, which is geometrically impossible for a genuine field defect, since a real constricted field widens as the target moves further from the eye.

Acuity is probed with the fogging test, per DSM-5-TR, in which the patient reads a chart with both eyes open while the good eye is progressively fogged with lenses, so that any letters still read must be the work of the supposedly blind eye. The table below consolidates the positive signs across the whole spectrum, since the examinable core is not any one sign but the shared logic that binds them.

DOMAIN	POSITIVE RULE-IN SIGN	WHY IT IS INCOMPATIBLE WITH ORGANIC DISEASE
Limb weakness	Hoover's sign; the hip abductor sign	Power returns via the contralateral reflex the patient cannot suppress
Weakness pattern	Give-way effort; face-hand test; global weakness	Collapsing, whole-limb weakness ignores the pyramidal distribution
Tremor	Tremor entrainment; variable frequency	Tremor entrains or stops when the timing resource is loaded
Dystonia	Fixed inverted ankle or clenched fist, sudden onset	Fixed, abrupt posture unlike the mobile organic dystonias
Seizures	Eye closure with resistance; preserved awareness	Retained awareness during bilateral shaking; a normal ictal EEG supports but does not prove it
Gait	Astasia-abasia; improvement on distraction	Balance is intact automatically but fails on demand
Vision	Tubular field; fogging test	A field that does not widen with distance cannot be organic

27.8 Explaining and treating the disorder

The first therapeutic act is the diagnosis itself. Management, according to the New Oxford Textbook of Psychiatry, should usually be multi-disciplinary, and its foundation is a plausible and agreed explanation of the diagnosis followed by effective triage to the right therapy. The explanation is not a reassurance script. It has recognisable components, and they are what a viva answer on this topic is expected to name.

- Take the problem seriously.
- Give the patient a positive diagnostic label rather than a list of the things they do not have.
- Demonstrate the rationale for the diagnosis, by showing them their own positive Hoover's sign or how their tremor stops during the entrainment test.
- Emphasise potential reversibility, often through the metaphor that the trouble lies in the running of the system rather than in its structure.
- Provide written information the patient can take away.

GOOD TO REMEMBER

Showing the patient the sign is both the proof of the diagnosis and the start of the treatment. When a patient watches their own leg regain power as the opposite hip flexes, or their tremor dissolve the moment they tap a rhythm with the other hand, the demonstration does what no reassurance can: it makes the reversibility credible from the inside. Build the explanation around the sign you elicited, not around a scan that was normal.

On the specific therapies, the New Oxford Textbook of Psychiatry holds that physiotherapy should be a first-line treatment for functional movement disorders and limb weakness, provided the patient has some confidence in the diagnosis and is motivated to change. The physiotherapy has to be the tailored, functional-disorder kind; generic physiotherapy of the sort delivered for stroke may in fact be counterproductive here, because it reinforces the very abnormal patterns the treatment is trying to unlearn. Alongside it, a tailored cognitive behavioural therapy delivered as an informed guided self-help programme was found to be better than treatment as usual, and a specific form of cognitive behavioural therapy has been developed for dissociative seizures. The three pillars to carry are therefore a credible explanation, targeted physiotherapy and a tailored psychological therapy.

over 5 min ATTACK DURATION THAT FLAGS A FUNCTIONAL SEIZURE (DSM-5-TR)	**1 m = 2 m** TUBULAR FIELD: EQUAL WIDTH NEAR AND FAR

Functional neurological disorder is diagnosed by positive signs of internal inconsistency, not by normal scans, and the sign you demonstrate to the patient is the first step of the treatment.

28 · Myasthenia gravis, mitochondrial and muscular dystrophy neuropsychiatry

Three very different diseases meet here for one reason: each disturbs muscle, nerve terminal or mitochondrion, yet each reaches the psychiatric clinic wearing a mental disguise. Myasthenia gravis produces a fluctuating fatigable weakness that is repeatedly mistaken for a functional disorder or for depressive exhaustion; the mitochondrial disorder MELAS can open with a psychosis years before its neurology declares itself; and myotonic dystrophy carries an almost inescapable cognitive decline and a flattening of personality. The marks in this topic sit at two junctions the examiner returns to: the point where an organic neuromuscular illness is misread as psychiatric, and the point where a psychotropic drug becomes hazardous in a person whose muscles, heart or metabolism are already compromised. This account works through myasthenia first, then the mitochondrial and dystrophic disorders, keeping to what the primary neurology and prescribing sources state and flagging, at each step, the confidently remembered number that is not safe to assert.

28.1 The neuromuscular-junction lesion, and the mind it leaves untouched

Myasthenia gravis is the classic disorder of the neuromuscular junction. Circulating antibodies to the **nicotinic acetylcholine receptor** block the binding of acetylcholine on the postsynaptic membrane, so repeated stimulation fails to sustain contraction and the muscle fatigues. The distribution is characteristic: the extraocular, facial, neck and proximal limb muscles bear the brunt, and it is weakness spreading to the respiratory muscles that threatens life. The single fact a psychiatrist must hold above all others is where these antibodies do not act. They attack the muscle-type nicotinic receptors of the junction, they do not cross the blood-brain barrier, and they ordinarily do not reach or attack central cholinergic receptors, so the disease itself does not

directly disturb consciousness or cognition. Extraocular muscles weaken while the intraocular pupillary muscles stay strong, and bladder, bowel and sensory function are all preserved. The antibodies do, however, cross the placenta, which is why an affected mother can transmit a transient neonatal myasthenia to her infant. This split, a peripheral postsynaptic lesion with an intact central nervous system, is the whole reason myasthenia belongs in a psychiatric account: it is dramatic weakness without a single central sign.

RULE **Myasthenia gravis weakens the body and spares the mind.** Profound, even ventilator-dependent weakness coexists with an entirely normal mentation and level of consciousness, because the antibody is confined to the peripheral nicotinic junction. A patient who is weak and also drowsy, confused or cognitively altered has something else, or something in addition, going on. That dissociation between striking weakness and a clear sensorium is the feature that separates myasthenia from both a primary psychiatric disorder and a central neurological one.

28.2 The fatigable, diurnal signature and how the diagnosis is secured

The hallmark of myasthenia is **fatigable weakness**: strength that is present at rest and drains with use, so power is worst after sustained effort and recovers with rest and sleep. The pattern is almost diurnal, mild in the morning and heaviest in the late afternoon and evening, and it fluctuates from one day to the next. The eyes usually announce the disease. Almost **90%** of patients, typically young women or older men, present first with diplopia and ptosis. Facial and neck involvement follows, giving a nasal, dysarthric speech and a snarling grimace on attempting to smile, and progression to the neck, shoulder, swallowing and respiratory muscles produces a bulbar palsy and, at its most severe, respiratory distress. The important clinical texture is that the weakness is asymmetric and variable rather than fixed, which is exactly why it is so easily doubted.

Diagnosis rests on the bedside and the laboratory rather than on clinical impression, and several tests are used together:

- The **Tensilon (edrophonium) test** and the ice-pack test, both of which briefly reverse a ptosis.
- Serum antibody assays, for acetylcholine-receptor and, in seronegative cases, muscle-specific-kinase antibodies.
- Repetitive nerve stimulation showing a decremental response as the junction fatigues.

28.3 Serology, the thymus and the treatment ladder

The majority of patients are seropositive for acetylcholine-receptor antibodies; of the seronegative remainder, about half carry antibodies to **muscle-specific kinase (MuSK)**, and a smaller group are seronegative on current assays. The disease also keeps company with the thymus and the thyroid, and both associations are worth carrying because treating them can improve the myasthenia itself.

~80%	10%	5%
SEROPOSITIVE FOR ACHR ANTIBODIES	HAVE A MEDIASTINAL THYMOMA	HAVE UNDERLYING HYPERTHYROIDISM

Treatment follows two logics that are worth keeping distinct. The first raises acetylcholine at the junction: the cholinesterase inhibitor pyridostigmine is the mainstay, with parenteral neostigmine when a patient cannot swallow. The second restores the receptor by damping the immune attack, using corticosteroids, other immunosuppressants, plasmapheresis or intravenous immunoglobulin, and, in refractory disease, the anti-CD20 monoclonal antibody rituximab. The division matters to the psychiatrist because it is the immunomodulatory arm, and corticosteroids above all, that carries the psychiatric hazard taken up below.

28.4 The organic illness most often mistaken for a functional one

This is the reason myasthenia earns a place in a psychiatry syllabus at all. A patient may present with the abrupt onset of dysarthria, dysphagia and diplopia and be labelled, wrongly, with a conversion disorder. Everything about the surface presentation invites the error. The weakness fluctuates and is relieved by rest, so it looks inconsistent; the objective signs are often transient or subtle, as they are in multiple sclerosis, focal seizures and small strokes, so a purely history-based assessment can mislead; exacerbations usually arise spontaneously but can be precipitated by an intercurrent illness or by psychological stress, which invites a psychogenic reading; and, because mentation is untouched, nothing in the mental state points away from a primary psychiatric cause. The functional neurological disorder spectrum and its positive signs are taken up separately in these notes; the point to hold here is the discipline of excluding myasthenia before that label is applied.

TRAP **Reading fatigable, stress-sensitive, evening-worse weakness as conversion or as depressive fatigue.** Fluctuation, relief by rest and provocation by stress are typical of myasthenia, not evidence against it, and a normal sensorium removes the one reassurance a clinician might reach for. The safe rule is that new bulbar or ocular fatigable weakness earns antibody testing and repetitive nerve stimulation before it earns a functional or a depressive label, because the price of missing myasthenia is a preventable respiratory crisis.

28.5 Prescribing in myasthenia: steroids, sedation and neuromuscular safety

Two prescribing problems converge in myasthenia. The first is that its own immunotherapy is psychoactive. Corticosteroids, a mainstay of treatment, cause depression, anxiety, psychosis and mania; short courses tend toward euphoria or mania and long courses toward depression; onset is usually rapid, within one to two weeks and by one review a median of about **11.5 days**; and the incidence is dose-related. Compared with others who have the same underlying illness, patients on glucocorticoids are almost twice as likely to become depressed, four times as likely to become manic and five times as likely to become delirious, and withdrawal, especially if rapid, can itself precipitate symptoms. The dose relationship, from the Boston Collaborative Drug Surveillance Program, is worth carrying as a table.

PREDNISONE DOSE	ACUTE PSYCHIATRIC REACTION
Under 40 mg daily	1.3%
40 to 80 mg daily	4.6%
More than 80 mg daily	18%

The second problem is that several psychotropics are unsafe in a disease of respiratory-muscle weakness. Because the bulbar and respiratory muscles can fail, drugs that depress respiration are hazardous, and benzodiazepines and the Z-drug hypnotics such as zopiclone are listed as contraindicated in myasthenia gravis for exactly that reason. Other agents worsen neuromuscular transmission directly: propranolol may aggravate myasthenic weakness, and the anticholinergic action of quinidine can do the same. The general choice and adverse-effect profile of antipsychotics and hypnotics belongs to the Schizophrenia: management, antipsychotics and adverse effects notes; what this topic adds is that the neuromuscular disease reorders those safety priorities.

PITFALL

Reaching for a benzodiazepine or a Z-drug hypnotic to settle anxiety or insomnia in a known myasthenic. In a disease whose danger is respiratory-muscle failure, a respiratory depressant is precisely the wrong sedative, and the caution holds even when the request seems minor. Where sedation or anxiolysis is genuinely needed, it is the neuromuscular risk, not habit, that should drive the choice of agent.

28.6 MELAS: the commonest mitochondrial disorder and its genetics

MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes, is the most common of the mitochondrial disorders and the one most likely to surface in a psychiatric differential. Its genetics are maternal, because mitochondria are inherited through the egg, and about **80%** of cases arise from a single A3243G point mutation in the tRNA-Leu(UUR) gene; a further tenth involve other regions of that same gene and the remainder involve other mitochondrial genes. Maternal transmission also helps explain why severity and family history are so variable, since the mutant load carried by different tissues need not be equal.

The clinical core is in the name. The **stroke-like episodes** are the defining event, and their crucial feature is that the lesions do not conform to arterial territories and may involve grey or subcortical white matter, which is what marks them out from a true ischaemic stroke. Onset is usually in childhood, after a period of normal development, though a first presentation in early adulthood is well described. The syndrome is multisystem:

- Short stature, migraine, recurrent vomiting and seizures.
- An elevated lactate, whose level has been correlated with the burden of neurological symptoms.
- Over time, deafness, diabetes, retinopathy and cardiac abnormalities, in a course that ranges from a single episode to a relentless accumulation of strokes.

28.7 Where the lesions fall, the psychosis that comes first, and treatment

The stroke-like lesions favour the posterior brain. They fall in the temporo-parieto-occipital cortex, and also in the basal ganglia, brainstem and cerebellum, and the posterior, parieto-occipital emphasis explains the hemianopia and cortical blindness that punctuate the illness, while hemiparesis follows involvement of the motor cortex and descending motor pathways. For

the psychiatrist the more treacherous fact is what can come first. MELAS has been reported to present with a schizophrenia-like psychosis, often in the third decade, several years to a decade before the neurological diagnosis is made, and cases resembling depression, obsessive-compulsive disorder, bipolar disorder and borderline personality disorder are described. In each the course runs atypically, and a retrospective look frequently turns up previously unremarked short stature, diabetes or unexplained somatic complaints; it is usually the later neurological signs, cognitive decline and strokes on imaging that finally reveal the diagnosis.

TRAP **Taking an atypical early-adult psychosis at face value when it sits on a mitochondrial background.** A psychosis in the third decade with an unusual course, set against short stature, sensorineural deafness, diabetes or a maternal line of similar illness, should prompt thought of MELAS rather than a purely primary psychosis. The mental picture can precede the strokes by years, so it is the somatic clues, not the mental state alone, that open the door to the diagnosis.

There is no proven disease-modifying treatment. A study of 13 patients given L-arginine during acute stroke-like episodes reported a reduction in their frequency and severity without altering the overall trajectory, and care is otherwise symptomatic: cochlear implants for deafness, anticonvulsants for seizures, antipsychotics for psychosis, and treatment of the diabetes.

GOOD TO REMEMBER

Because MELAS itself predisposes to diabetes, an antipsychotic with a high risk of glucose intolerance, such as olanzapine, is best avoided or used with caution when psychosis complicates the disorder. The reasoning generalises: in any disease that already loads the metabolic dice, the metabolic profile of the antipsychotic should weigh more heavily than usual in the choice.

28.8 Myotonic dystrophy: an autosomal dominant channelopathy

Myotonic dystrophy is the most frequent myopathy of adult life, usually declaring itself between 20 and 25 years and affecting both sexes equally. Its lesion is an excessive CTG trinucleotide repeat in the DMPK gene on chromosome 19. Because the expansion disturbs ion channels in the membranes of muscle and other cells, the disease is classed as a **channelopathy**; it is transmitted as an autosomal dominant trait and, like other unstable-repeat disorders, shows **anticipation**, appearing earlier and more severely down the generations. The distinct type 2 disease, proximal myotonic myopathy, instead carries a four-nucleotide repeat, shows no genotype-phenotype correlation and does not anticipate.

The clinical signature is named for its cardinal sign. **Myotonia** is an involuntary, prolonged muscle contraction that delays release of the grip for several seconds after a handshake, and percussion of the thenar eminence produces a visible sustained contraction. Weakness and wasting are distal and facial, and atrophy of the face and temples gives the characteristic **hatchet face** with ptosis and a prominent forehead. The disorder is multisystem, with cataracts, cardiac conduction disturbance and endocrine failure, testicular atrophy, diabetes and infertility, running alongside the muscle disease. This distal, myotonic picture is the mirror image of the proximal weakness and pseudohypertrophy of Duchenne muscular dystrophy.

FEATURE	MYOTONIC DYSTROPHY	DUCHENNE MUSCULAR DYSTROPHY
Weakness distribution	Distal and facial	Proximal
Hallmark muscle sign	Myotonia, grip and percussion	Pseudohypertrophy
Cognitive course	Progressive, increases with age	Non-progressive

MNEMONIC

Grip, Face, Lens, Heart, Gland

The multisystem reach of myotonic dystrophy: a sustained **grip** and percussion myotonia, the hatchet **face**, cataracts in the **lens**, conduction disease in the **heart**, and endocrine **gland** failure. Each element is drawn from the disease as described here and none is added to it.

28.9 Cognition and personality in myotonic dystrophy

The neuropsychiatric heart of myotonic dystrophy is easy to overlook beside the striking muscle signs, yet it is what most shapes the patient's life and the psychiatrist's involvement. Cognitive impairment is almost uniform and, unlike the fixed deficit of Duchenne, it increases with age, so the picture is one of slow decline rather than a stable baseline. Alongside it runs a characteristic change in personality: a lack of initiative and a progressive blandness, an apathetic flattening of drive and affect that families often notice before any formal testing does. The combination, an age-related cognitive decline with apathy and emotional blunting, can be mistaken for a primary depressive disorder or for an independent dementia, and it is better read as part of the multisystem disease than as a separate psychiatric illness. Formal cognitive assessment and support, and attention to the apathy as a source of disability in its own right, are the practical response, and they are what a psychiatrist most often adds to the care of these patients.

In myasthenia gravis the antibody spares the mind while the body fails, so fatigable weakness must be excluded before a functional or depressive label; MELAS can open with a third-decade psychosis years before its stroke-like episodes; and myotonic dystrophy pairs an age-increasing cognitive decline with an apathetic, bland personality.

Consolidate and apply

29 · Worked vignettes

A vignette is where recall becomes clinical judgement. The examiner rarely asks a candidate to define a disease of the brain; far more often a short stem describes a patient, plants one or two features that mark the presentation as something other than a primary psychiatric disorder, and waits to see whether the candidate reads them. This closing section teaches no new disease. It takes the syndromes assembled across this chapter and rehearses them as **recognition signatures**, the compact clinical gestalts that let a reader move from a paragraph of history to the right family of disease under examination time pressure.

The skill being tested is discrimination, not enumeration. Two stems can share a headline symptom, a first psychotic episode or a low mood, and diverge on a single detail that changes the whole answer. Learning the chapter as a set of paired look-alikes, each separated by the one feature that changes the answer, is worth more marks than a longer catalogue of associations, because it mirrors what the clinician actually does at the bedside.

29.1 Read the stem for its planted discriminator

The first task with any case stem is to decide whether the psychiatric picture might be a **secondary neuropsychiatric syndrome**, the mental-state expression of a systemic or neurological disease, rather than a primary disorder in its own right. The chapter's diseases share a small set of tells, and an efficient reader scans for them before committing. Four axes carry most of the discriminating information.

Tempo	Company	Atypia	Background
HOW FAST IT CAME	THE SIGN BESIDE THE SYMPTOM	WRONG FOR A PRIMARY DISORDER	EXPOSURE AND HEREDITY

Tempo asks how quickly the change arrived and whether it fluctuates; an abrupt or subacute course, or a waxing and waning conscious level, is unusual for most primary disorders. Company asks what neurological sign sits beside the psychiatric symptom: a movement disorder, a seizure, a focal deficit or autonomic instability. Atypia asks whether any feature is simply wrong for the diagnosis being entertained, such as a first psychotic episode in later life, visual rather than auditory hallucinations, or failure to respond to adequate standard treatment. Background asks what the patient carries into the illness, an infective or immune exposure, or a movement disorder running through the family tree. The single feature that reorganises the differential is the **discriminator**, and good stems are written around it.

TRAP **Diagnostic overshadowing: attributing new organic symptoms to a psychiatric label the patient already carries.** When a stem opens with a known diagnosis, the tempting move is to read every later feature as part of it, so a new movement disorder becomes a medication effect and a subacute confusion becomes relapse. **Diagnostic overshadowing** is an important way a secondary cause is missed, and examiners plant a pre-existing diagnosis precisely to test whether the candidate keeps the differential open.

29.2 The hyperkinetic case: chorea and its neuropsychiatric tail

A **hyperkinetic** stem leads with excess movement, and chorea is the movement that most often carries a neuropsychiatric tail into the examination. The archetype is a progressive chorea with personality change, irritability and cognitive decline, often with a family history reaching back through affected parents; this pattern points to Huntington disease, whose genetics and psychiatric features are developed in full within this chapter. Against it sits a usually self-limiting chorea in a child or adolescent after a streptococcal illness, sometimes with emotional lability and obsessive features, which points instead to Sydenham chorea. Age, tempo, heredity and whether the course remits separate the two.

Wilson disease enters the same differential from a different door: a young patient with a movement disorder, its characteristic systemic and ophthalmological signs, and psychiatric or behavioural change. Its movement-disorder and neuropsychiatric presentation belongs to this chapter's hyperkinetic overlap, while the hepatic and metabolic disease is developed in the Endocrine and metabolic psychiatry notes. Tics are the other hyperkinetic pattern a stem may use as a distractor; the archetypal tic disorder, Tourette syndrome, and its diagnostic criteria belong to the Child behavioural, emotional and other disorders notes, and recognising a tic as a tic keeps it out of the chorea differential. The recognition point is that a young patient with an involuntary movement disorder and a psychiatric change deserves a search for a defined neurological or metabolic cause before the psychiatric label is fixed.

29.3 The hypokinetic case: parkinsonism with a mental-state change

A **hypokinetic** stem leads with slowness, rigidity and tremor, and the neuropsychiatric question is which parkinsonian syndrome the picture represents and what its mental-state features signify. In established Parkinson disease, the classic examination trigger is well-formed visual hallucinations with initially preserved insight, the presentation of Parkinson disease psychosis, where management turns on antipsychotic selection that does not worsen motor function; that treatment is set out within this chapter's Parkinson disease sections. A slowly accruing dysexecutive and visuospatial decline late in the disease course points instead to Parkinson disease dementia, also developed here.

The discriminator the examiner most often plants is timing and drug response. When cognitive impairment and visual hallucinations arrive around the onset of the motor syndrome rather than well after it, the temporal rule that separates dementia with Lewy bodies from Parkinson disease dementia becomes the issue, and that rule, with the neuroleptic sensitivity that accompanies it, belongs to the Dementias and neurocognitive disorders notes. When parkinsonism responds poorly to dopaminergic therapy, or is joined early by falls, autonomic failure, gaze restriction or asymmetric limb apraxia, the stem is steering away from idiopathic disease toward atypical parkinsonism, which this chapter develops among the degenerative syndromes. Reading a parkinsonian stem is therefore a matter of placing the mental-state change in the sequence of motor, cognitive and autonomic events.

29.4 The subacute encephalopathy: new psychosis with neurological company

Some of the highest-yield stems describe a previously well adult who develops, over a subacute course, a new psychosis or severe behavioural change accompanied by seizures, a movement disorder, autonomic instability or a fluctuating conscious level. This **subacute encephalopathy** pattern is the signature of the autoimmune and infective encephalitides. Anti-NMDA receptor encephalitis is the archetype, often opening with prominent psychiatric features before the neurological picture declares itself; the antibody-mediated limbic encephalitis spectrum and the viral encephalitides, herpes simplex chief among them, produce overlapping pictures and are each developed in full within this chapter.

RULE **One brain, one diagnosis first.** When a new psychiatric syndrome keeps company with a movement disorder, seizures, autonomic instability or a focal neurological sign, the parsimonious reading is a single disease of the brain producing both, not two coincident illnesses. Coincident illness is the less parsimonious reading, weighed in parallel while the unifying organic cause is pursued first.

The examination trap in this territory is that the encephalitides can produce catatonic and psychotic phenomena that mimic a primary disorder. Catatonia phenomenology, its structured rating and the lorazepam challenge belong to the Other psychotic disorders, delusional syndromes and catatonia notes, and the distinction between an antibody-mediated encephalitis and a primary catatonia is developed within this chapter's autoimmune-psychosis discussion. The primary nosology of schizophrenia and of mood disorder, against which these secondary syndromes are read, belongs to that same Schizophrenia notes and to the Mood disorders: pharmacotherapy notes. The recognition point is tempo with company: a psychosis that arrives quickly, alongside a neurological sign, earns investigation for an encephalitis rather than a reflexive primary diagnosis.

29.5 The chronic infection: reading the stem in Indian practice

Endemic exposure rewrites the differential. A stem describing insidious personality change, cognitive decline, mood disturbance or new psychosis on the background of a chronic infection is a recurring examination pattern, and the causes that matter most in Indian practice are not always those a Western textbook lists first. Neurosyphilis, presenting as general paresis of the insane, remains a classic cause of a dementing and disinhibited picture and must stay in the differential of a progressive neuropsychiatric decline. Neurocysticercosis is a leading cause of adult-onset seizures in endemic regions, so seizures with behavioural or psychotic features should raise it. Japanese encephalitis and cerebral malaria produce acute encephalopathic illness and later neuropsychiatric sequelae, and subacute sclerosing panencephalitis presents in a child or adolescent with cognitive and behavioural decline, myoclonus and progressive deterioration. Central nervous system tuberculosis underlies a proportion of subacute meningoencephalitic presentations. Each is developed in full within this chapter.

IN INDIA

Where these infections are endemic, keep them at the front of the differential rather than at the end. In an adult with new-onset seizures and behavioural change, pursue neuroimaging for neurocysticercosis before settling on a primary psychiatric explanation. In a child or adolescent with declining school performance, personality change and myoclonus, hold subacute sclerosing panencephalitis in view. In a progressive dementing syndrome with disinhibition, retain neurosyphilis as a treatable cause worth testing for. The decision that changes management is to investigate the endemic infection early, because several are treatable and the rest still alter supportive care, prognosis and counselling, and each is missed when the presentation is read as psychiatric first.

29.6 The HIV case: an ordinary presentation with an extraordinary differential

A stem that supplies HIV status, or the risk factors for it, invites the candidate to think through the neuropsychiatry of HIV rather than to treat the psychiatric syndrome in isolation. Cognitive slowing, apathy and executive difficulty on this background raise the spectrum of HIV-associated neurocognitive disorders, whose classification and the effect of antiretroviral therapy are developed in full within this chapter. New focal deficits, seizures or a declining conscious level raise the central nervous system opportunistic infections, including the opportunistic viral leukoencephalopathy that this chapter owns among them, progressive multifocal leukoencephalopathy. Depression, mania, psychosis, anxiety and an elevated suicide risk are all recognised psychiatric comorbidities, and the direct neuropsychiatric effects of the antiretroviral agents themselves belong to the chapter's discussion of drug interactions and adverse effects.

> **GOOD TO REMEMBER**
>
> When a psychiatric syndrome and a treatable disease of the brain appear in the same patient, treating one is not an alternative to treating the other. The examination answer, and the clinical one, is **two-front**: correct the underlying disease and manage the psychiatric syndrome in parallel, because a mood or psychotic disturbance driven by an active brain disease seldom settles on psychiatric treatment alone.

Bedside cognitive testing frames the recognition but does not make the diagnosis; the standardised cognitive instruments used to quantify impairment belong to the Psychotherapies, clinical assessment, MSE and nosology notes, and here they serve only to flag that a cognitive syndrome is present and to track its course. The recognition point is that HIV converts an ordinary psychiatric presentation into a differential that must include neurocognitive disorder and opportunistic infection before it is called primary.

29.7 The demyelinating, neuromuscular and functional case

Relapsing neurological events separated in time and space, joined by mood disturbance, cognitive change or pathological affect, describe multiple sclerosis, whose psychiatric manifestations and the effect of disease-modifying therapy are developed in full within this chapter. Multiple sclerosis and motor neuron disease can both produce pseudobulbar affect, the pathological laughing and crying whose full phenomenology, mechanism and treatment belong to the Stroke, TBI, delirium and focal brain syndromes notes; here it is named as a feature these diseases carry. Motor neuron disease itself, through the amyotrophic lateral sclerosis and frontotemporal dementia spectrum, brings behavioural and cognitive change alongside progressive weakness and the end-of-life questions this chapter addresses.

Two neuromuscular tells reward recognition. Weakness that fatigues through the day and recovers with rest, sometimes with the psychiatric consequences of a chronic disabling illness, points toward myasthenia gravis and its neuromuscular-junction cautions, developed here among the neuromuscular syndromes. Weakness, sensory loss or movement that is internally inconsistent and incongruent with neuroanatomy, and that is confirmed by **positive signs** rather

than by exclusion, points toward functional neurological disorder, whose positive-sign diagnosis this chapter develops in full.

PITFALL

Diagnosing functional neurological disorder on impression, because the presentation seems atypical or the patient distressed, rather than on the positive signs that establish it. A functional diagnosis reached by exclusion is unsafe: it both mislabels genuine neurological disease and denies the patient a confident, rule-in diagnosis that carries its own treatment. The call rests on demonstrable incongruence and specific positive signs, not on the clinician's impression.

29.8 Look-alikes and the master recognition spine

Consolidation is easiest as pairs. The table below sets the chapter's most confusable presentations against the single feature that separates them, and the accompanying figure arranges the same discriminators along the recognition axes.

PRESENTATIONS THAT GET CONFUSED	THE DISCRIMINATING FEATURE	POINTS TOWARD
Usually self-limiting chorea after infection in the young against relentless chorea with cognitive decline and family history	Course and heredity	Sydenham chorea against Huntington disease
New psychosis with seizures, a movement disorder or autonomic instability against new psychosis alone	Neurological company and tempo	Antibody-mediated encephalitis against a primary psychotic disorder
Asymmetric parkinsonism responsive to dopaminergic therapy against parkinsonism with early falls, autonomic failure or poor response	Drug response and early red-flag signs	Idiopathic Parkinson disease against atypical parkinsonism
Visual hallucinations and cognitive decline arriving around the onset of parkinsonism against well after established motor disease	The temporal sequence	Dementia with Lewy bodies against Parkinson disease dementia
Fatigable weakness worse through the day against fixed weakness	Fatigability	Myasthenia gravis against a fixed structural cause
A deficit incongruent with neuroanatomy with positive signs against a deficit that respects it	Internal consistency	Functional neurological disorder against a structural lesion
Cognitive-behavioural decline with myoclonus in a child against chronic disinhibited decline in an adult	Age and the associated sign	Subacute sclerosing panencephalitis against neurosyphilis

MNEMONIC

Course, Leading sign, Unusual features, Exposure and endowment, Systemic and cognitive signs

The recognition spine for any neuropsychiatric stem: **C**ourse and tempo of onset with any fluctuation; the **L**eading neurological sign standing beside the mental-state change; features **U**nusual for the primary disorder being considered; the **E**xposure and inherited endowment the patient brings; and the **S**ystemic and cognitive examination findings a primary formulation would not explain. Read together they spell CLUES, and each is a door back to a treatable disease.

With the pattern recognised, a marks-winning answer follows four moves.

- Name the syndrome and state explicitly that it may be secondary rather than primary.
- Identify the companion neurological sign and use it to localise or to name the likely disease.

- Choose the targeted investigation that answers the specific question, not a reflexive screen.
- Treat on two fronts, the underlying disease and the psychiatric syndrome together.

> In any psychiatric presentation with a neurological companion sign, exclude the treatable disease of the brain before settling on a primary psychiatric diagnosis.

30 · Consolidation and quick review

A chapter that has been read is not yet a chapter that can be retrieved. Reading builds recognition, the comfortable sense that each disease is familiar when its name appears on the page. The examination asks for something harder and less forgiving, which is **free recall**: the ability to generate the right disease, the discriminating feature and the plan from a blank sheet, under time pressure, with the stem giving nothing away. The distance between recognising a syndrome when it is prompted and producing it cold is where marks are won and lost, and it is the distance this closing section is built to close.

Consolidation is the work of turning a read chapter into a small number of durable, retrievable structures. It teaches no new disease. The dedicated sections have already supplied the mechanisms, the investigations and the treatment for each illness in full; the task here is to compress that material into scaffolds that can be reconstructed from memory, and to practise retrieving them so the knowledge survives the weeks between revision and the examination hall. **Consolidation**, in the sense used here, is both the cognitive process by which a memory is stabilised and the deliberate revision method that drives it.

30.1 Why retrieval, not rereading, consolidates this chapter

The single most important decision in revising a dense chapter is how the hours are spent, and memory research and examination experience agree on the answer: memory is built by **retrieval practice**, the act of producing an answer from memory, far more than by rereading the material again. Each time a fact is retrieved with effort, the memory trace that carries it is strengthened and made easier to find next time. Rereading, by contrast, smooths the text into familiarity without building the retrieval route the examination will demand. This asymmetry, that testing a memory improves it more than restudying it, is the **testing effect**, and it is the reason a chapter as long as this one rewards self-testing over passive review.

The practical consequence is to convert reading into questioning at every opportunity. Close the section and state the mechanism, the syndrome and the plan aloud before checking; cover the table and rebuild it; turn each heading into a question and answer it cold. Retrieval that is effortful, and even retrieval that partly fails, consolidates better than fluent rereading, provided the answer is checked and corrected soon afterwards. The discomfort of struggling to recall is not a sign that the method is failing; it is the sensation of the memory being strengthened.

Retrieve	Check	Space	Interleave
GENERATE IT COLD	CORRECT AGAINST THE SOURCE	RETURN AFTER A GAP	MIX THE DISEASES

RULE **You keep what you retrieve, not what you reread.** Plan revision around generating answers from memory and checking them, not around passing your eyes over the text a further time. The chapter is consolidated when each disease can be reconstructed from a blank page, not when it feels familiar on the printed one.

30.2 One retrieval card for every disease: the RECALL template

The chapter contains many diseases, but it asks the same questions of every one of them. That regularity is the reader's advantage, because a single **retrieval template** can be applied to each illness in turn, and the same few prompts will reconstruct any of them. Rather than memorising each disease as an unstructured block, the reader learns one card and fills it repeatedly, which both reduces the memory load and guarantees that no limb of an answer is dropped under pressure.

The template is captured by the word RECALL, chosen because the act it names is exactly the act being practised. Each letter is a prompt to be answered from memory for the disease in hand, and a disease is consolidated when all of them can be produced without the book. The accompanying figure sets the card beside the shared clinical axes as a single revision map.

MNEMONIC

Route, Expression, Clue to organicity, Assessment, Link the treatments, Limit

For any disease in this chapter, retrieve: **R**oute to the brain, the mechanism that carries the disease to the mind, whether direct, immune, infective, systemic and metabolic, or iatrogenic; **E**xpression, the psychiatric and cognitive syndrome the patient shows; **C**lue to organicity, the discriminating red flag that marks the picture as secondary rather than primary; **A**ssessment, the targeted investigation that answers the question the case raises; **L**ink the treatments, the two-front plan that treats the disease and the mind together; and **L**imit, the boundary of what this chapter owns and what it hands to another. Read together they spell RECALL: one card, six prompts, every disease.

The card also disciplines an answer. A candidate who has retrieved all six prompts for the disease in front of them has, without further effort, produced a structured response: the mechanism, the presentation, the reason for suspecting organicity, the investigation, the management and the boundary. The examiner reads that as a formulation rather than a list, which is the difference the marking scheme rewards.

30.3 Retrieve across the mechanisms, not down a list

A list learned in the order it was read is fragile, because recall then depends on starting at the top and running down. Durable retrieval comes from organising the same diseases along more than one axis, so that any entry point reaches the whole set. The first reorganisation is by mechanism. The chapter's diseases reach the mind by a small number of recurring routes, direct involvement of neural tissue, immune and inflammatory injury, infective and post-infective processes,

systemic and metabolic disturbance, and iatrogenic effects of treatment, and retrieving the diseases route by route rather than name by name forces the deeper and more useful connection.

This is **interleaving**: deliberately mixing the diseases during practice instead of studying one to exhaustion before moving to the next. Interleaving feels harder and slower than working through a single disease at a time, and that difficulty is precisely why it works, because it trains the discrimination the examination tests. Retrieving all the diseases that reach the brain by immune injury, or all those that do so by chronic infection, builds the cross-connections that let a reader move sideways from a presentation to its differential rather than only forwards from a name to its facts.

Worked as a drill, this means posing the route as the question. Asked for the immune and inflammatory route, the reader should be able to reach the antibody-mediated encephalitides, the demyelinating disease of multiple sclerosis and the immune hypothesis of psychiatric disorders, each taught in full in its own section. Asked for the chronic infective route, the reader should recover neurosyphilis, the endemic neuroinfections and the subacute and rare chronic infections. The value is not the list itself but the practised movement from a mechanism to the diseases that express it, which is the movement a viva demands.

30.4 Retrieve by the shared clinical axis

The examiner starts from a presentation, so the reader must be able to as well. The second reorganisation runs along the clinical surface, the presenting picture that several diseases share. A stem does not announce a disease; it describes a patient, and the efficient response is to hold the small set of diseases that produce that presentation and then sort them by the single feature that separates them. Retrieving by shared axis rehearses exactly this move. The table below is a retrieval index rather than a teaching table: for each shared presenting axis it names the diseases to be recalled and the prompt that unlocks the discrimination, with the full teaching for each disease living in its own section.

PRESENTING AXIS TO RETRIEVE FROM	DISEASES TO BRING TO MIND	THE PROMPT THAT SORTS THEM
Excess movement with psychiatric change	Huntington disease, Sydenham chorea, the movement lens of Wilson disease, and tics	Course, heredity and age
Slowness and rigidity with a mental-state change	Parkinson disease psychosis and Parkinson disease dementia, and atypical parkinsonism	Drug response, and the timing of cognition and hallucinations
Subacute new psychosis with neurological company	Anti-NMDA receptor encephalitis, the limbic-encephalitis spectrum, and the viral encephalitides	Tempo and the companion neurological sign
Chronic treatable infection presenting psychiatrically	Neurosyphilis, the endemic neuroinfections, and the subacute and rare chronic infections	Exposure, systemic clues and the associated sign
Cognitive, affective or psychotic change on an HIV background	The HIV-associated neurocognitive spectrum, the opportunistic infections, psychiatric comorbidity and drug effects	Which of the four is producing the change
Demyelinating, neuromuscular or functional presentation	Multiple sclerosis, motor neuron disease, myasthenia gravis, and functional neurological disorder	The relapsing course, fatigability or positive signs

Practised in both directions, from an axis to its diseases and from a single disease back to the axis it shares, this index turns the chapter from a sequence of sections into a network that any clue can enter.

30.5 Retrieve the diagnostic boundary

Consolidating this chapter includes consolidating its edges, because a disciplined answer is defined as much by what it hands over as by what it teaches. The **diagnostic boundary** is the set of constructs this chapter names but does not own, and retrieving the boundary cleanly keeps an answer on the disease question actually asked rather than drifting into a neighbouring syndrome and losing time. Each of the following should be recalled as an interface, named where it touches the case and then handed to its owning chapter.

- Pseudobulbar affect, the pathological laughing and crying seen in multiple sclerosis and in motor neuron disease, is named in those diseases but taught in full in the Stroke, TBI, delirium and focal brain syndromes notes.
- Dementia with Lewy bodies, and the temporal rule that separates it from Parkinson disease dementia, belong to the Dementias and neurocognitive disorders notes, while the Parkinson-disease side of that boundary is taught here.
- The diagnostic criteria of Tourette syndrome belong to the Child behavioural, emotional and other disorders notes; the chapter names it as the archetypal tic disorder and teaches the acquired choreas itself.

- Catatonia phenomenology, its structured rating and the lorazepam challenge belong to the Other psychotic disorders, delusional syndromes and catatonia notes, and the chapter teaches only how an antibody-mediated encephalitis is separated from catatonia.
- The primary nosology of depression belongs to the Mood disorders: pharmacotherapy notes; the hepatic and metabolic disease of Wilson disease belongs to the Endocrine and metabolic psychiatry notes; and the standardised cognitive instruments belong to the Psychotherapies, clinical assessment, MSE and nosology notes.

Retrieving these as a short, rehearsed set means the handover sentence arrives ready-made in the examination: name the neighbouring construct, say why it matters to the case, point to its owner, and return to the disease in hand.

30.6 The revision habits that only feel like learning

Several common revision habits produce a strong feeling of progress while building little durable memory, and recognising them is part of consolidating well. The most seductive is the **fluency illusion**: rereading a section until it feels effortless and mistaking that fluency for mastery, when what has actually been trained is recognition of the text, not the ability to generate it from memory. Highlighting, recopying notes and passively watching a topic being explained share the same flaw, feeling productive while leaving the retrieval route unbuilt.

A second habit is massing all the revision of a topic into a single long session close to the examination. Cramming can carry a fact into a test the next morning, but it fades quickly and leaves little for the papers that follow, because memory laid down all at once is denied the spacing that makes it durable. The sense of a productive marathon is real; the retention it buys is not.

> **PITFALL**
>
> Judging readiness by how familiar the material feels rather than by whether it can be produced from a blank page. Familiarity is built by exposure and is a poor predictor of recall; the only honest test of readiness is a cold retrieval attempt with the book closed. A candidate who feels fluent after rereading but cannot reconstruct the RECALL card for a disease has confirmed the illusion, not disproved it, and the remedy is to test earlier and more often, not to reread once more.

TRAP **Confusing recognition on the page with recall in the hall.** Being able to pick the right disease when the material is in front of you is a far weaker skill than generating it from a bare stem, and revision that only ever recognises never trains the harder skill the examination demands. Many candidates discover the gap for the first time in the examination itself, when a syndrome they thought they knew will not come. Practise by producing answers cold, not by reviewing answers already written.

30.7 Space the retrieval and follow the weakness

If retrieval is the engine, **spaced retrieval** is the schedule that makes it last: returning to each topic after a deliberate gap rather than in one continuous block. Spacing works because a memory retrieved just as it begins to fade is strengthened more than one retrieved while still fresh, so allowing a topic to cool a little between attempts is a feature of the method rather than

neglect. Across a revision period, the gaps between visits to a secure topic can lengthen while a shaky one is returned to sooner, so effort follows weakness rather than comfort.

Interleaving and spacing work best together. A practical session mixes several diseases from different parts of the chapter rather than drilling one to exhaustion, and revisits the set after a gap of days rather than minutes. The diseases that fail the retrieval test are flagged and brought forward; the ones that come easily are spaced further out. This concentrates the limited hours of revision on the specific gaps the reader actually has, which no amount of rereading a comfortable section can achieve.

GOOD TO REMEMBER

Build the week around a short daily cold-retrieval test of a mixed handful of diseases, checked and corrected the same afternoon, rather than a long weekly reread. The habit that changes an outcome is closing the book and producing the RECALL card for a handful of diseases from memory, then reviewing only what came out wrong.

30.8 Weight retrieval to the diseases you will meet, and carry the frame in

Not every disease in the chapter carries the same weight at the bedside you will actually work at. Consolidation is finite, so the last decision is where to spend the retrieval that remains, and the honest answer is to weight it toward the diseases that are both common in local practice and dangerous to miss. In much of Indian practice the treatable endemic infections of the nervous system are exactly those diseases, and they reward being retrieved first and most often.

IN INDIA

Where neurocysticercosis, Japanese encephalitis, cerebral malaria, central nervous system tuberculosis, HIV and neurosyphilis remain part of everyday practice, put these treatable causes at the front of the retrieval queue, so that a new psychiatric or cognitive presentation carrying neurological or systemic signs prompts them early rather than late. The clinical decision the weighting protects is to investigate the endemic, potentially treatable disease before settling on a primary psychiatric diagnosis, because several have effective disease-directed treatment while the rest still change supportive care and prognosis, and each is missed when the presentation is read as psychiatric first.

Carried into the examination, the frame collapses to a sequence that survives when detail fails. Meet the stem, decide from its red flags whether the picture is secondary, run the RECALL card for the leading disease, and sort the differential along the shared clinical axis. What consolidation buys is not more facts but faster and more reliable access to the facts already learned, so that under pressure the chapter arrives as a method rather than as a set of half-remembered associations.

Consolidate by retrieval, not rereading: learn one card, RECALL, apply it to every disease, retrieve across mechanism and shared axis, and space the practice until the chapter can be rebuilt from a blank page.

Sources and further reading

The clinical specifics in this chapter are grounded in the standard texts below; where two sources set different thresholds, both are named in the text as a conflict rather than reconciled. Instrument content (the cognitive screens and rating scales) is described and cross-referred, never reproduced.

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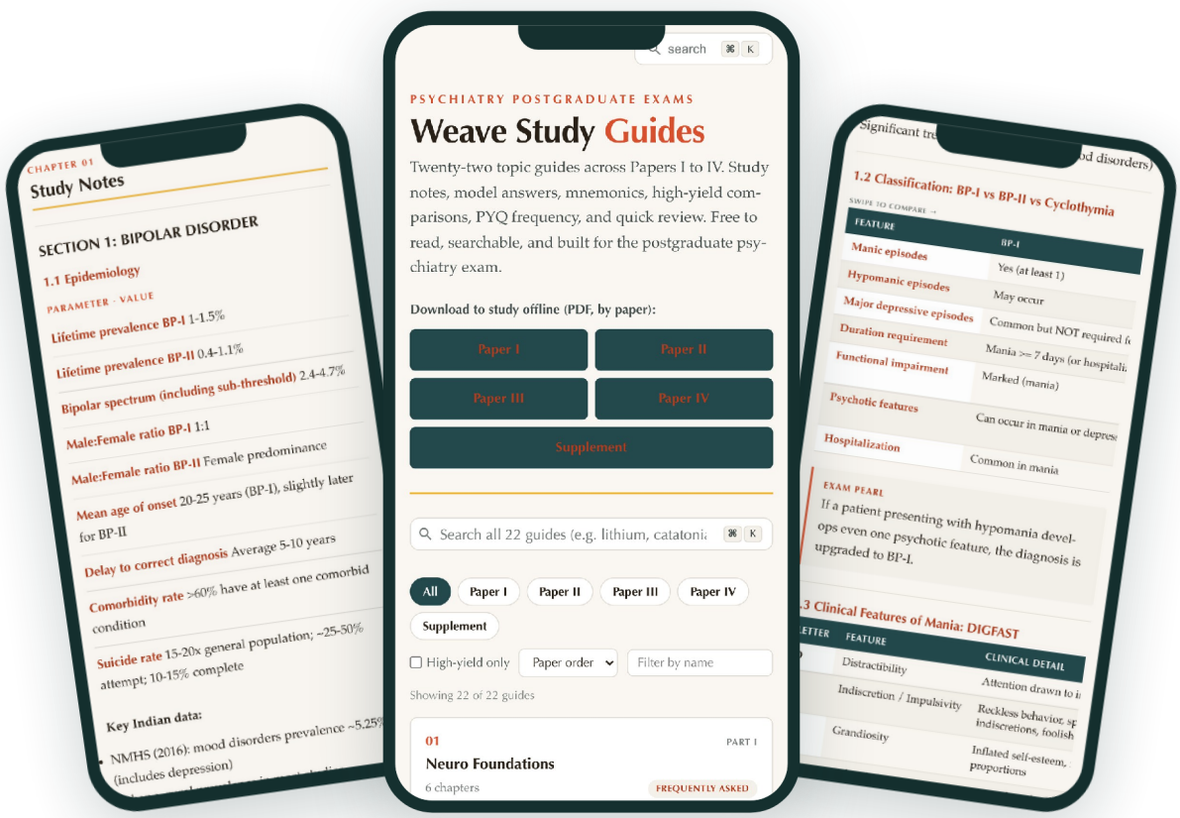
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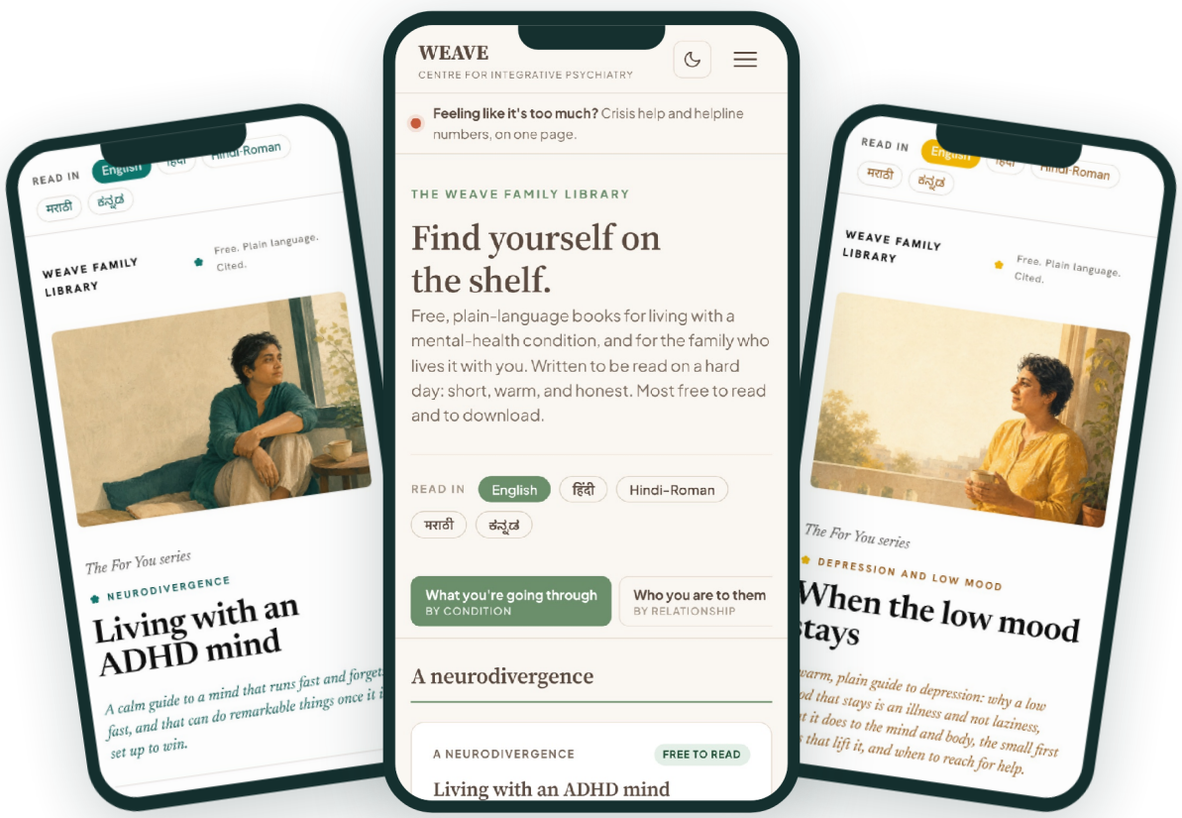
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