WEAVE SPRINT . PAPER IV

Neuropsychiatry of systemic and neurological disease

The systemic and neurological diseases a psychiatrist must recognise, investigate and treat: HIV and its neurocognitive spectrum with the psychiatric comorbidity and antiretroviral interactions that come with it, the neuropsychiatry of Parkinson disease and the movement disorders, Huntington disease with its genetics and predictive testing, the autoimmune and infective encephalitides that present first as psychosis, neurosyphilis and the endemic CNS infections that still reach an Indian clinic, multiple sclerosis and the psychoneuroimmunology behind the immune hypothesis, and the degenerative, neuromuscular and functional neurology that reaches us before it reaches the neurologist.

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Dr. Wilfred D'souza . Dr. Niharika Reddy

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Concept / rule Key number Trap

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.

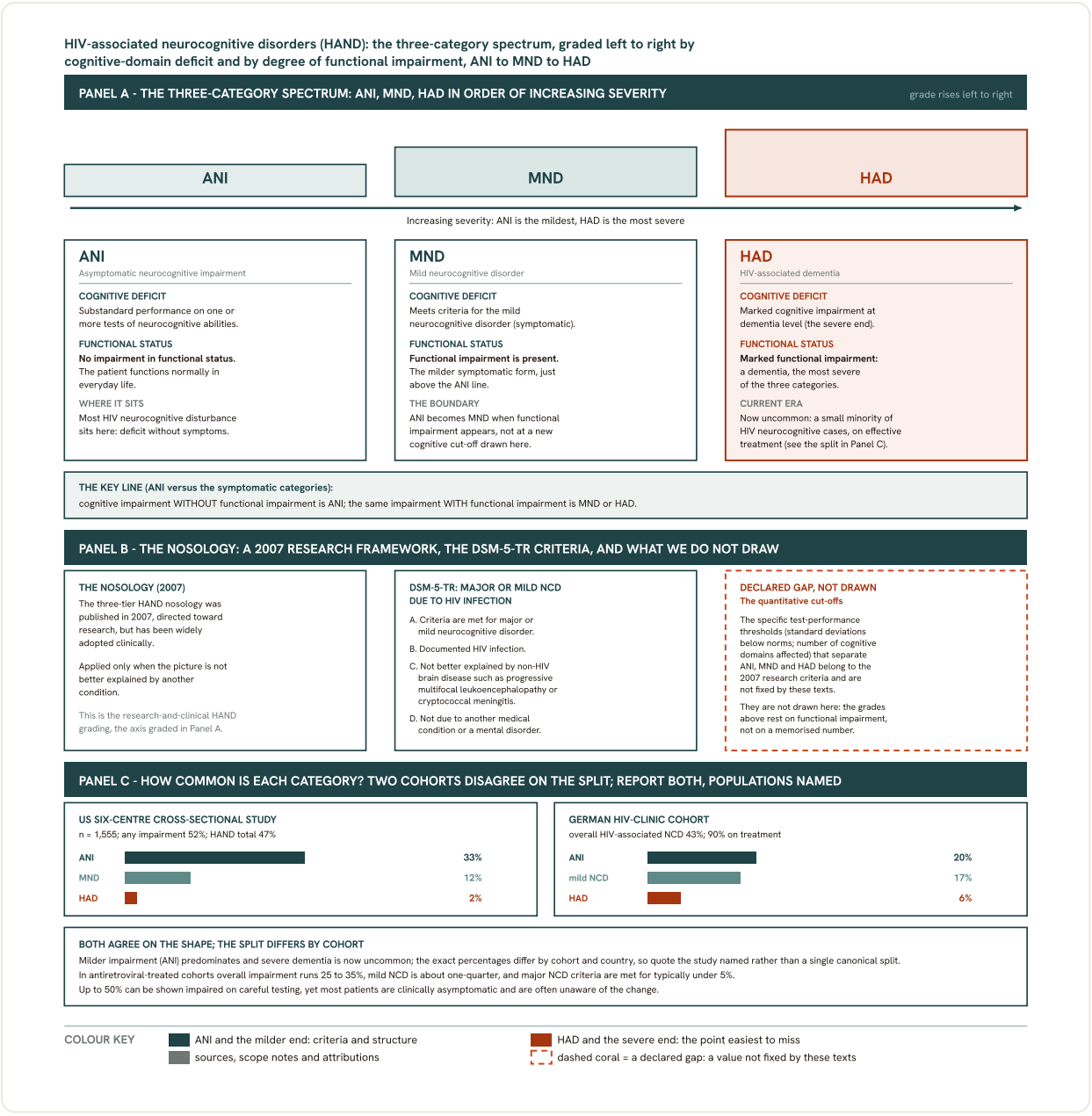

Fig 35.1 HIV-associated neurocognitive disorders (HAND): the three-category spectrum. Most authors grade HAND by increasing severity into asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD); the boundary from ANI to the symptomatic categories 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.

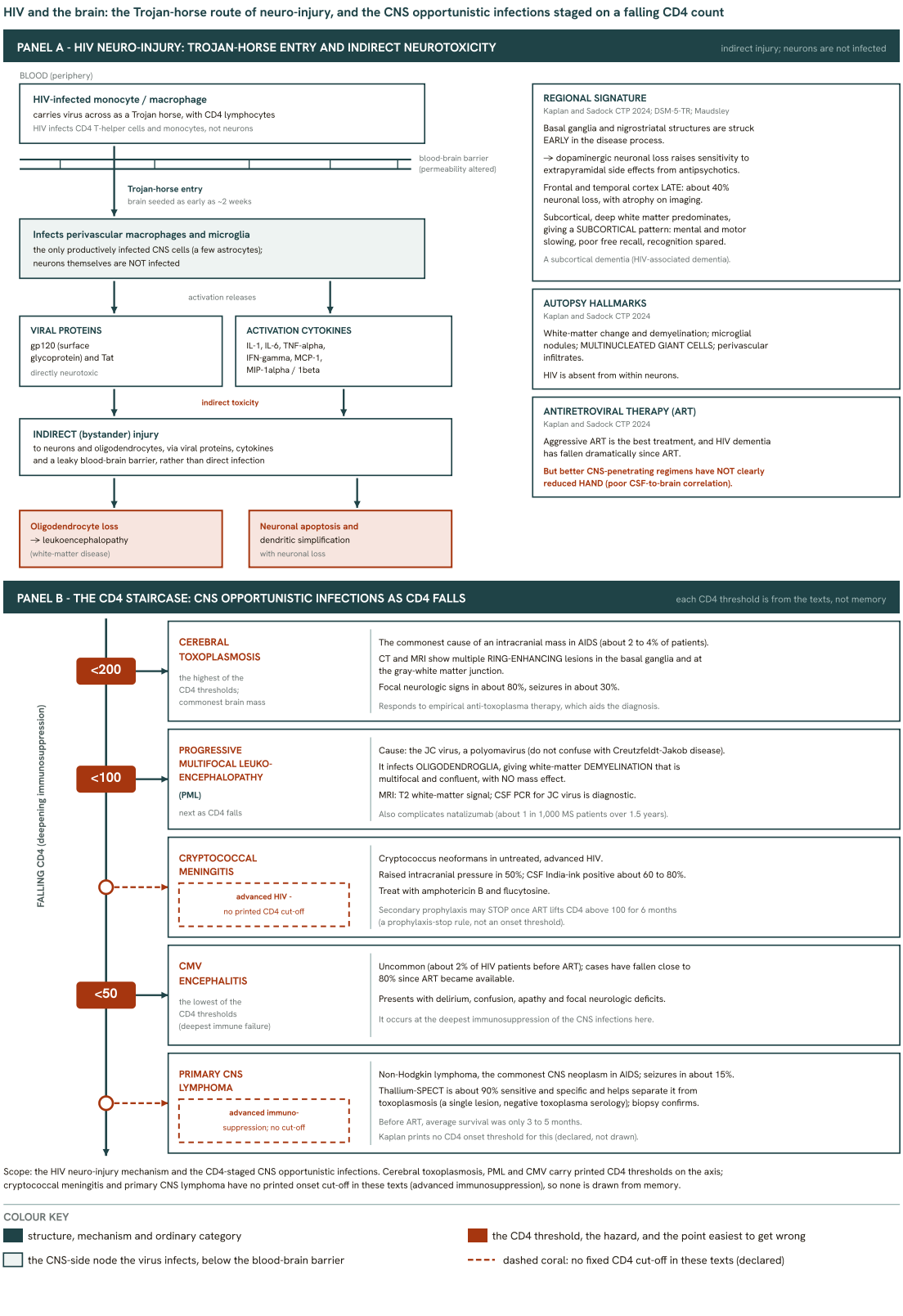

Fig 35.2 HIV neuro-injury and the CD4-staged CNS opportunistic infections. Panel A: the Trojan-horse route into the brain and indirect neurotoxicity that injures neurons without productively infecting them, with the regional and treatment signatures. Panel B stages toxoplasmosis, PML and CMV encephalitis 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% OF PD PATIENTS AFFECTED OVER THE DISEASE COURSE	**25-36 mg/day** MEAN CLOZAPINE DOSE FOR PSYCHOSIS IN PD	**40 mg/day** PIMAVANSERIN, PIVOTAL PDP TRIAL	**2016** 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.

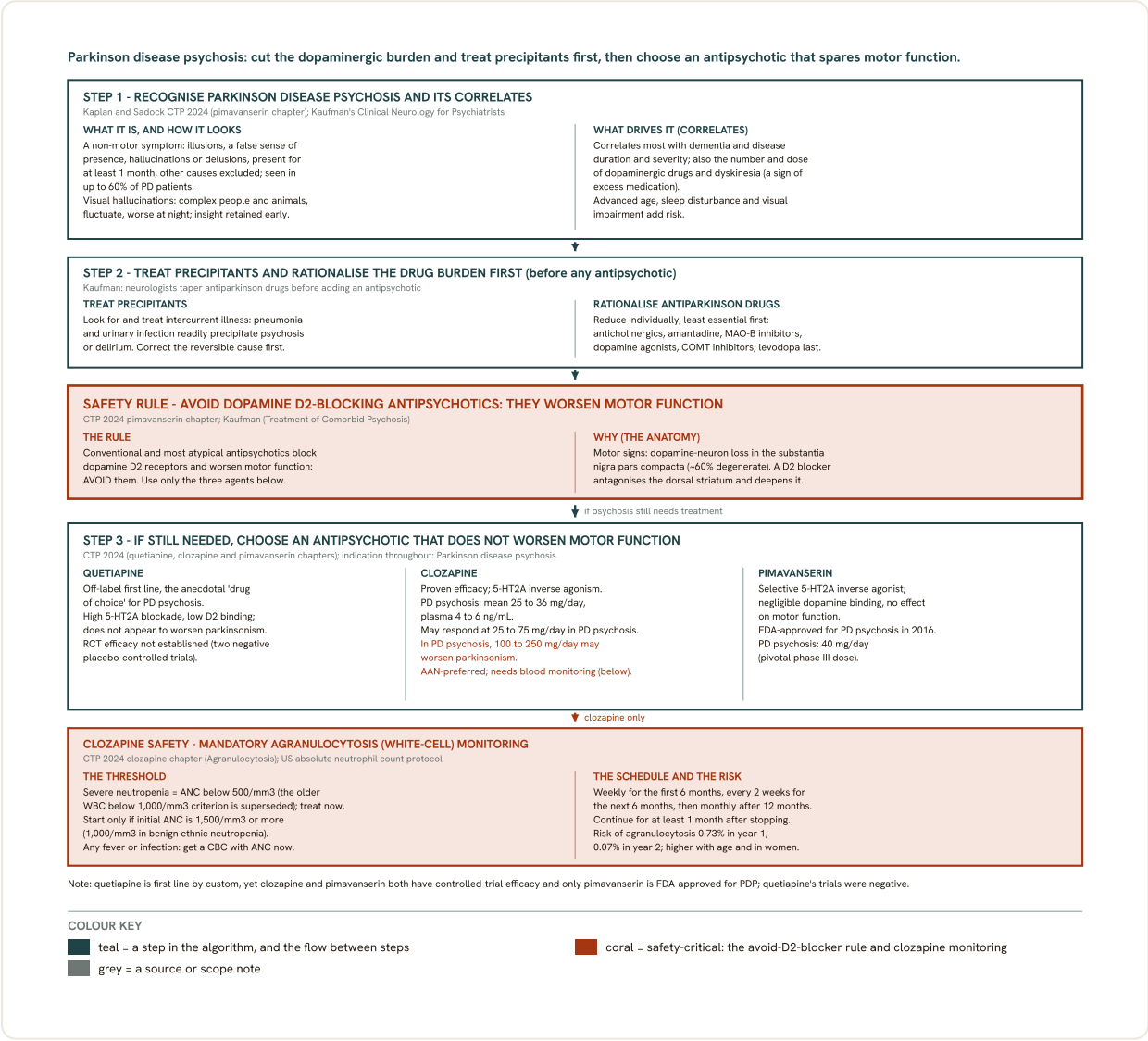

Fig 35.3 **Parkinson disease psychosis: the antipsychotic-choice algorithm.** Because dopaminergic drugs and disease severity drive the psychosis, the path first treats intercurrent precipitants and rationalises the antiparkinson burden, and only then reaches for a drug; the salient rule is that conventional 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.

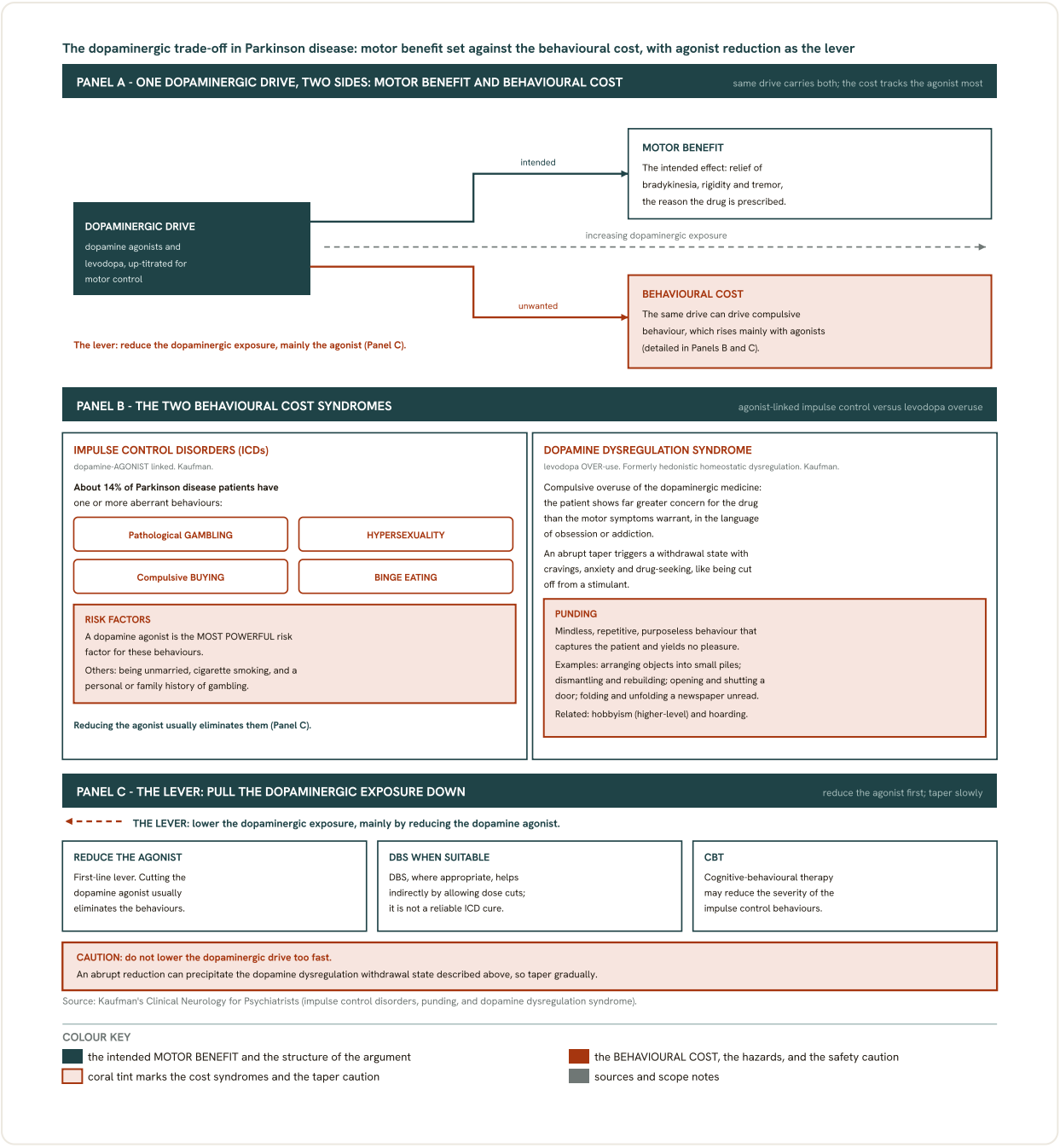

Fig 35.4 The dopaminergic trade-off in Parkinson disease. The same dopaminergic drive that relieves bradykinesia, rigidity and tremor also carries a behavioural cost: dopamine-agonist-linked impulse control disorders (pathological gambling, hypersexuality, compulsive buying and binge eating, affecting 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.

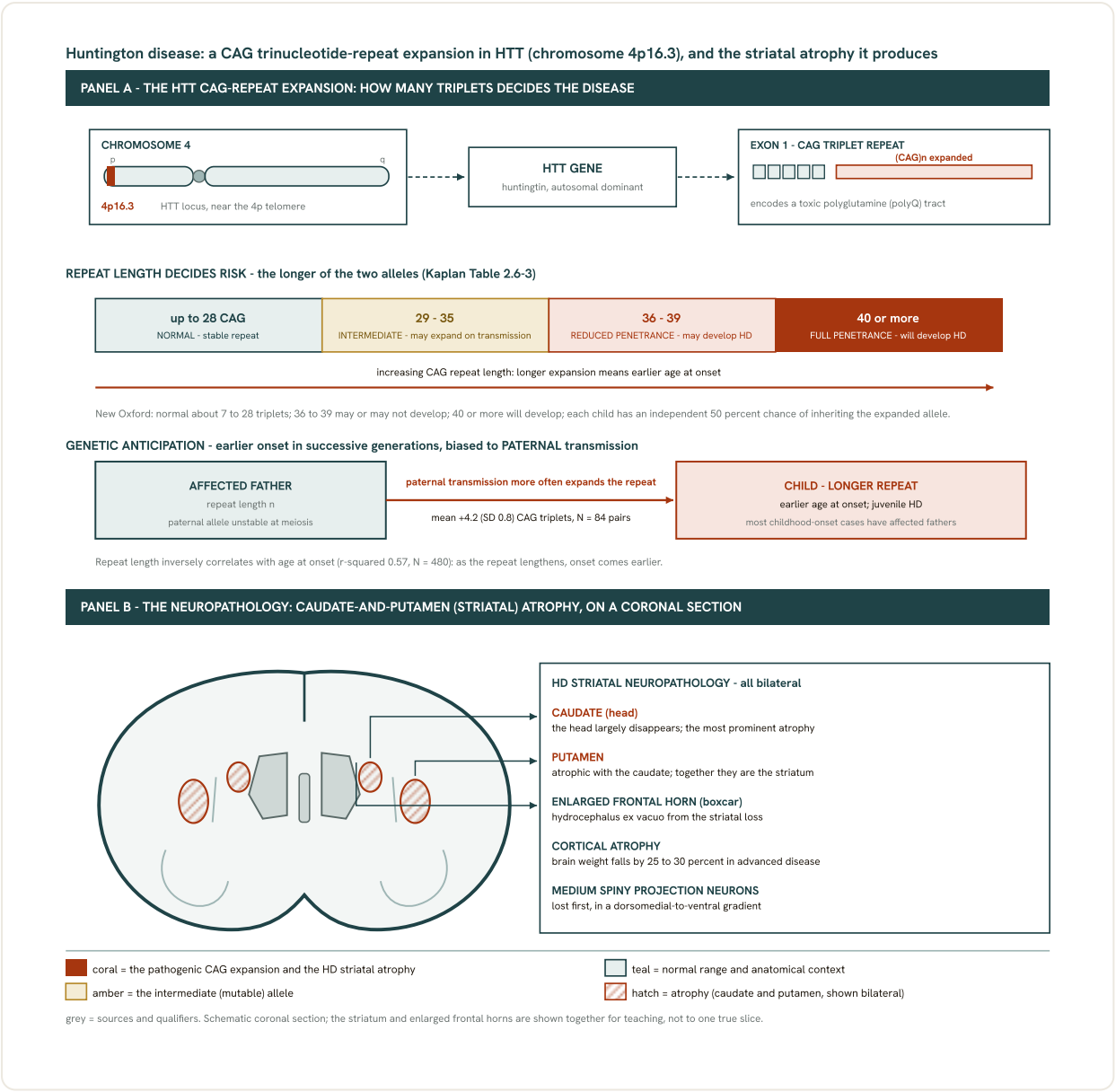

Fig 35.5 **Huntington disease genetics and neuropathology.** HD is an autosomal dominant disorder caused by a CAG trinucleotide-repeat expansion in the first exon of HTT at 4p16.3; the longer of the two alleles decides risk (up to 28 normal, 29 to 35 intermediate, 36 to 39 reduced penetrance, 40 or more 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% DEVELOP A NONCOGNITIVE PSYCHIATRIC DISORDER DURING THE ILLNESS	**11% to 13%** LIFETIME PREVALENCE OF PSYCHOTIC PHENOMENA	**30% to 40%** DEVELOP MAJOR DEPRESSION	**up to 10%** 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.

IN INDIA

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.

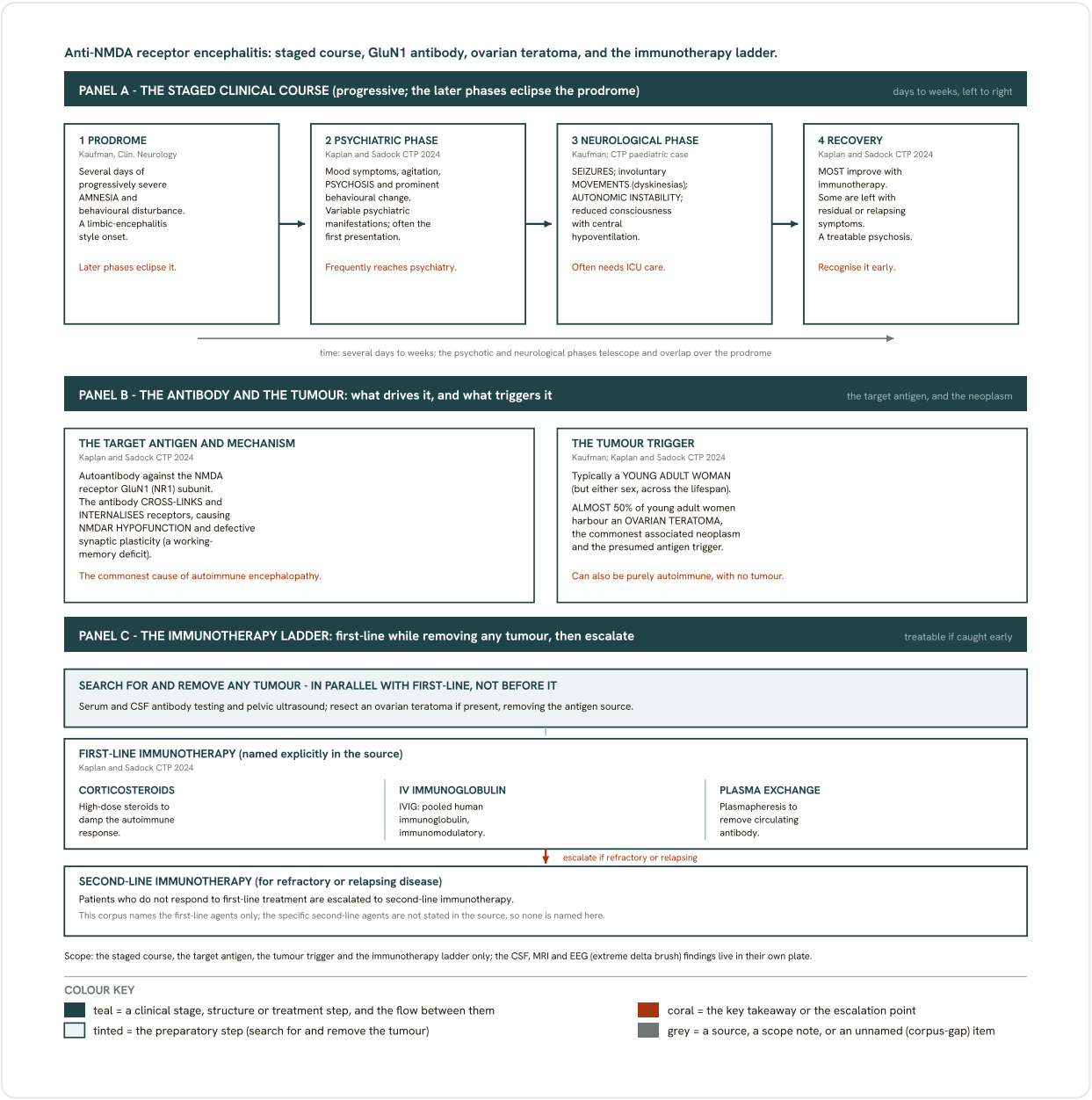

Fig 35.6 Anti-NMDA receptor encephalitis: the staged course and the treatment ladder. An autoantibody against the NMDA receptor GluN1 (NR1) subunit cross-links and internalises the receptor, producing NMDAR hypofunction; the illness runs a staged course from a prodrome of progressive amnesia and behavioural 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.

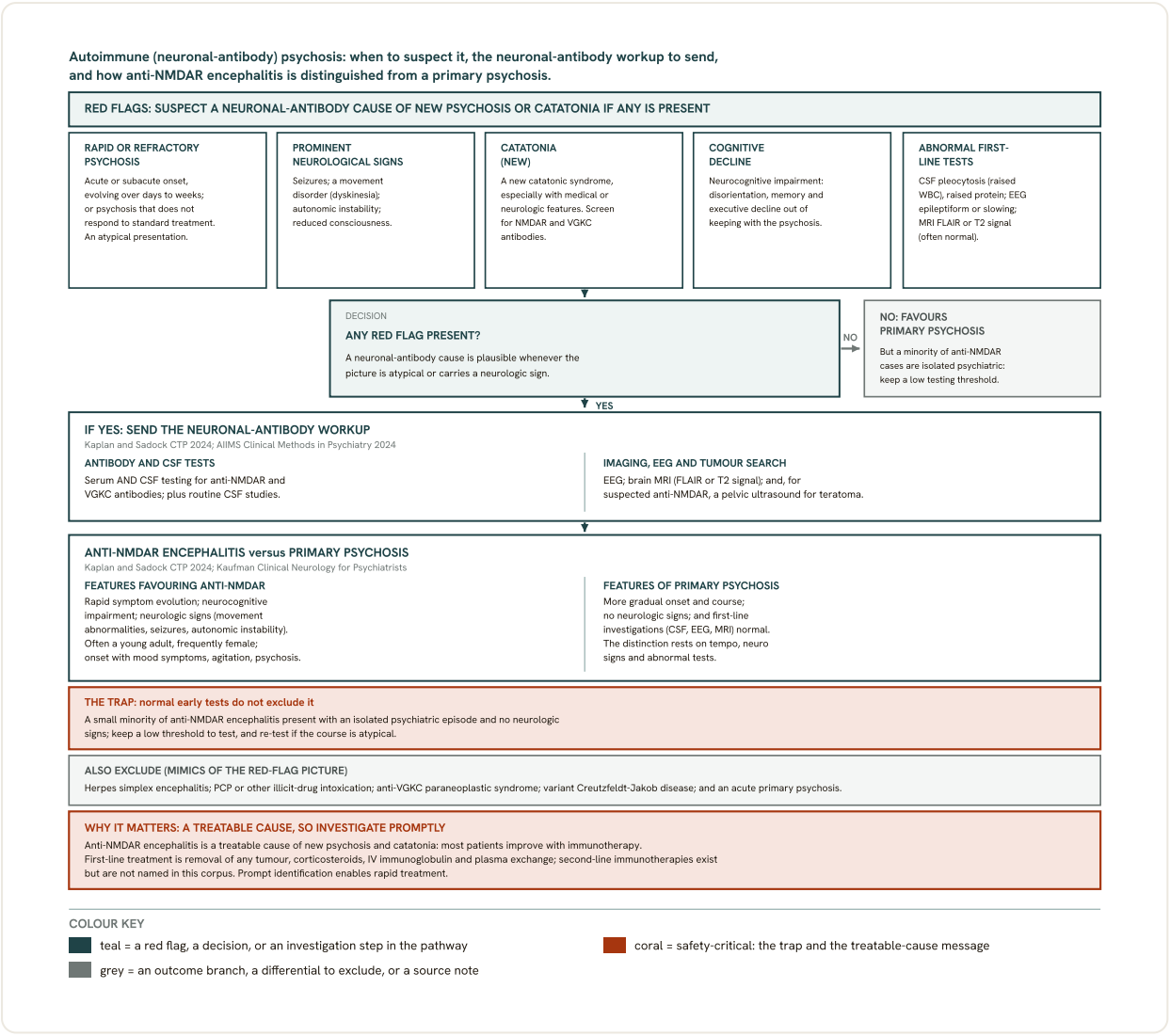

Fig 35.7 Autoimmune (neuronal-antibody) psychosis: the red-flag panel that prompts a neuronal-antibody search. New psychosis or catatonia that is rapid or treatment-refractory, carries neurologic signs (seizures, a movement disorder, autonomic instability, reduced consciousness), shows cognitive decline, 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.

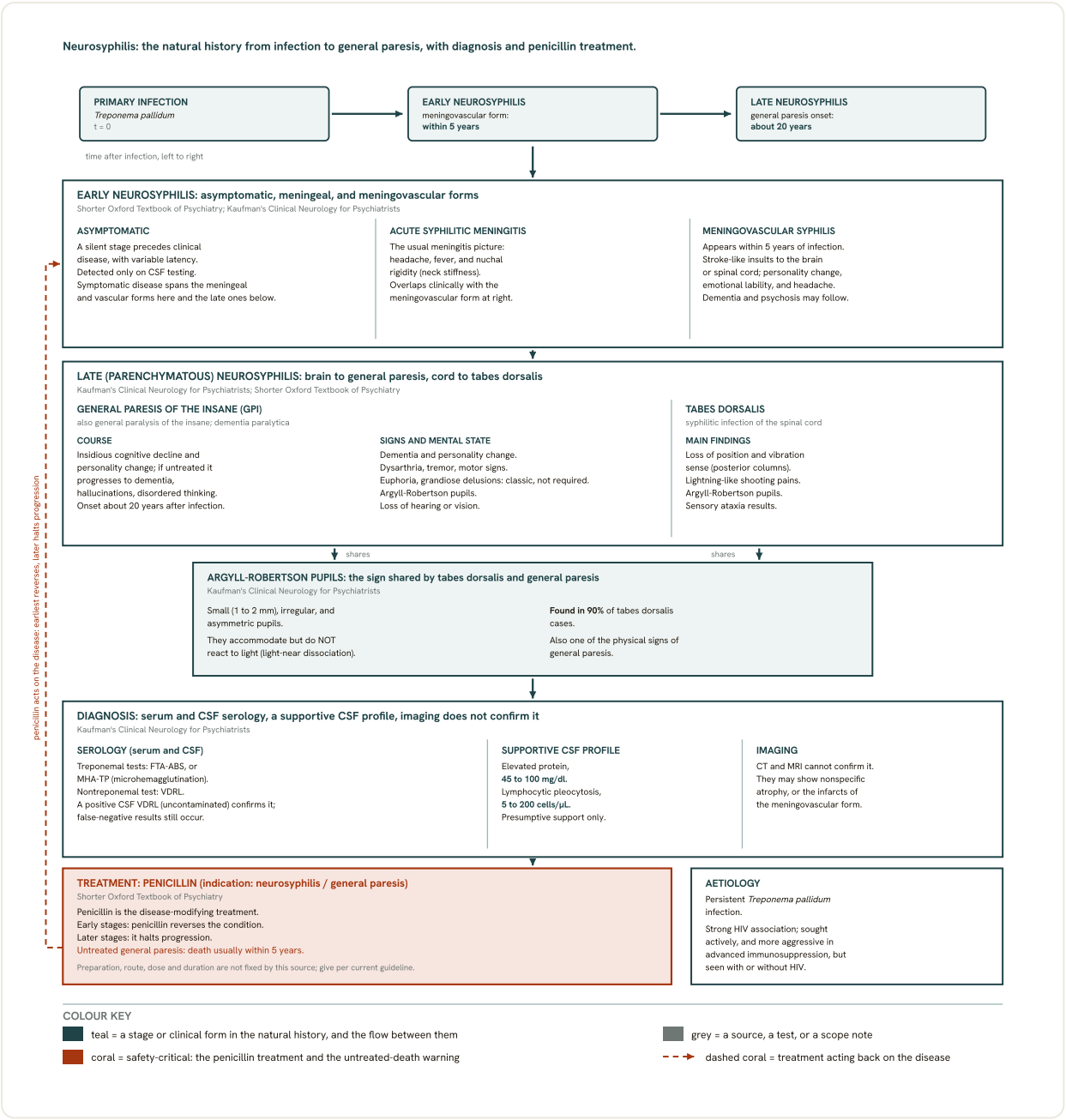

Fig 35.8 **Neurosyphilis across the natural history of syphilis.** Persistent Treponema pallidum infection runs from an asymptomatic stage through early neurosyphilis (acute syphilitic meningitis and meningovascular syphilis, the latter within 5 years) to late parenchymatous disease, in which brain involvement 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.

Neuroinfections that reach the Indian psychiatrist: reading the clinical clue to the diagnosis.

Five endemic CNS infections, told apart by their clue, their neuropsychiatric picture, and the test that confirms them.

NEUROINFECTION	THE CLUE THAT REACHES YOU	NEUROPSYCHIATRIC PICTURE	HOW TO CONFIRM
NEURO-CYSTICERCOSIS (NCC) the calcified granuloma	Endemic across the Indian subcontinent. A parenchymal cyst at the grey-white junction, a few mm to 1-2 cm, then calcifies. About 30% of the epilepsy in endemic zones is attributed to it.	Seizures are the usual presentation and subside over years; psychosis usually complicates the epilepsy. A 4th-ventricle cyst gives Bruns syndrome: positional headache, vertigo, drop attacks.	CT screens, MRI characterises; serology for difficult cases. Over 50% relapse of seizures off medication; calcification predicts it. Antiseizure drug for seizures; antiparasitic and steroid if viable.
JAPANESE ENCEPHALITIS (JE) Asian encephalitis	A major encephalitis problem across Asia.	Encephalitic. Its impact is set beside measles encephalitis; survivors carry developmental and sensory sequelae.	Declared gap. This corpus gives no JE virology, vector, MRI signature or movement sequelae.
CEREBRAL MALARIA P. falciparum	Plasmodium falciparum. Retinal haemorrhages in 30-40% of cases.	An encephalopathy: impaired consciousness, delirium, or seizures.	Blood-smear microscopy; low CSF glucose favours it over viral encephalitis. Untreated usually fatal; treated mortality 15-20%. IV artesunate is first-line.
CNS TB the tuberculoma	Intracerebral tuberculomas, especially in the Indian subcontinent and in AIDS.	A mass lesion. On the subcontinent, one of the commonest causes of focal seizures, and may underlie new epilepsy in recent migrants.	CT or MRI can detect a tuberculoma even when the clinical picture does not suggest it. Declared gap: TB-meningitis syndrome and CSF profile.
SSPE measles, years later	A late measles complication, 7-10 years after infection; 85% present at a mean of 12 years, 15% as adults.	Behavioural change over weeks to years, then myoclonus (the hallmark), then dementia and akinetic mutism. Fatal: most die in 1-2 years, 95% within 5.	EEG: periodic sharp-wave complexes or burst-suppression. Raised CSF measles-antibody titre. Cowdry intranuclear inclusions on histology.

THE INDIAN-SUBCONTINENT READ (grounded in the body, not the health system) Kaplan and Sadock 2024; Kaufman

Neurocysticercosis is endemic here, and about 30% of the epilepsy in endemic zones is attributed to it; and on the Indian subcontinent, tuberculomas are one of the commonest causes of focal seizures.

REFUSED FROM MEMORY, AND THE DECLARED GAPS Corpus gap register: 213, 215, 216

The exam line that NCC is the single commonest cause of adult-onset seizures in India is not stated verbatim in a clean corpus source, so the grounded figures above stand in; JE virology and the tuberculous-meningitis syndrome are left as declared gaps.

COLOUR KEY

teal = the grounded clue, neuropsychiatric picture and confirming test for each infection

grey = a source note

coral = safety-critical: lines refused from memory and the declared corpus gaps

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% OF EPILEPSY IN ENDEMIC REGIONS ATTRIBUTABLE TO THE PARASITE	**> 10%** OF THE ENDEMIC POPULATION CARRY SPECIFIC SERUM ANTIBODIES	**10 to 20%** 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.

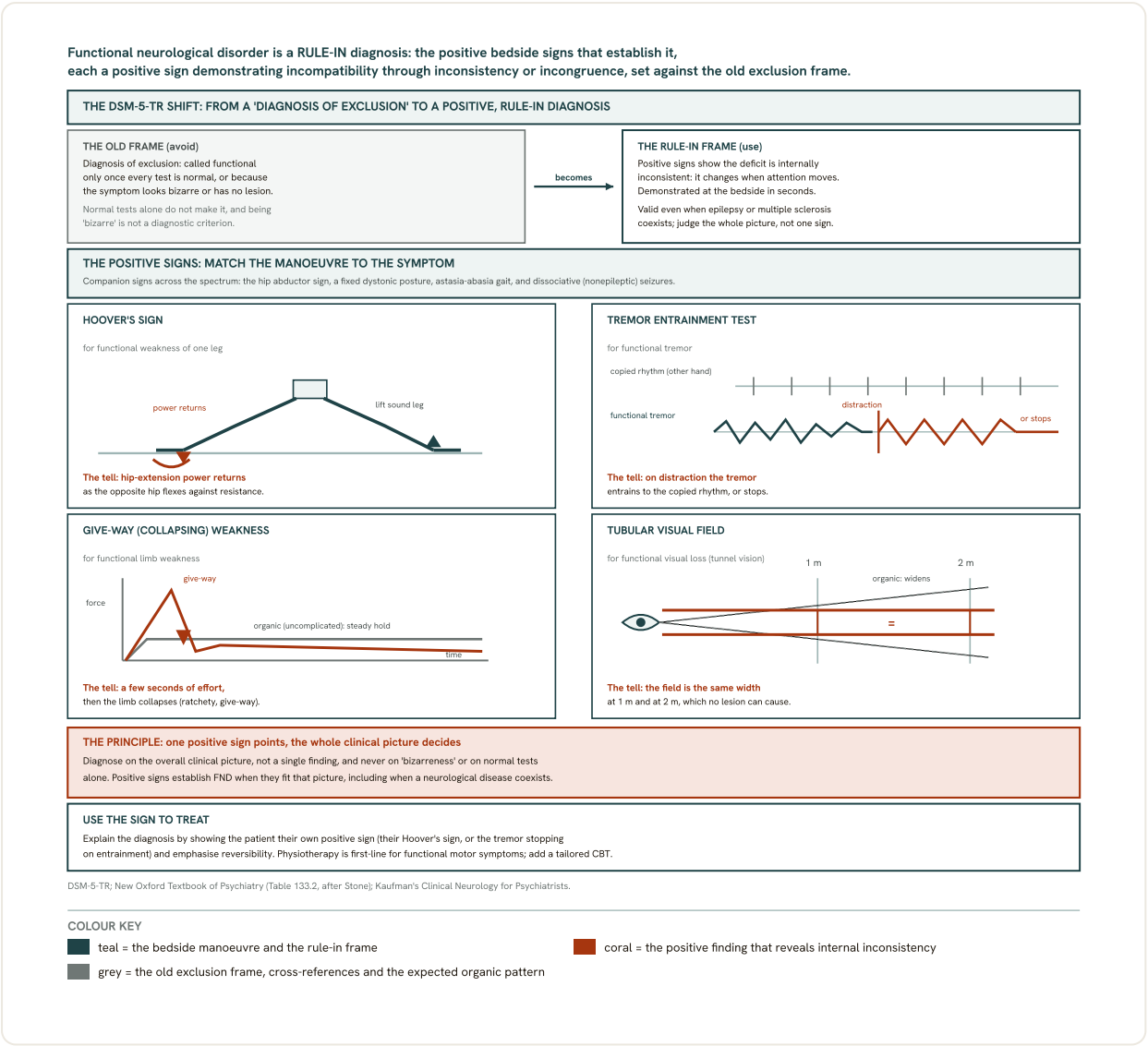

Fig 35.10 Functional neurological disorder: the positive signs that rule it in. DSM-5-TR reframes functional neurological symptom disorder as a rule-in diagnosis demonstrated by internal inconsistency, not a diagnosis of exclusion, and it can be made even when a neurological disease such as epilepsy 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.

Sadock BJ, Sadock VA, Ruiz P.
Kaplan and Sadock's Comprehensive Textbook of Psychiatry. 11th ed. Wolters Kluwer, 2024. The primary reference for HIV neuropsychiatry, the movement-disorder psychiatry and the autoimmune and infective encephalitides.

Arciniegas DB, Yudofsky SC, Hales RE (Kaufman).
Kaufman's Clinical Neurology for Psychiatrists. 8th ed. Elsevier. Parkinson disease, Huntington disease, the neuromuscular disorders and the bedside examination.

Brazis PW, Masdeu JC, Biller J.
Localization in Clinical Neurology. 8th ed. Wolters Kluwer. Localisation of the degenerative and demyelinating disorders.

Tasman A, Kay J, Lieberman JA, et al.
Tasman's Psychiatry. 5th ed. Springer. Psychiatric comorbidity in HIV, multiple sclerosis and the systemic diseases.

Geddes JR, Andreasen NC, Goodwin GM (New Oxford).
New Oxford Textbook of Psychiatry. 3rd ed. Oxford University Press. Psychoneuroimmunology and the immune hypothesis.

Johnstone EC, Owens DGC, Lawrie SM, et al.
Companion to Psychiatric Studies. 8th ed. Elsevier. Neurosyphilis, the CNS infections and the hereditary ataxias.

American Psychiatric Association.
Diagnostic and Statistical Manual of Mental Disorders, 5th ed, Text Revision (DSM-5-TR). APA, 2022; and the World Health Organization ICD-11 Clinical Descriptions and Diagnostic Requirements (CDDR).

Taylor D, Barnes TRE, Young AH.
The Maudsley Prescribing Guidelines in Psychiatry. 14th ed. Wiley-Blackwell; and Stahl SM, Prescriber's Guide, Stahl's Essential Psychopharmacology. Cambridge University Press. Prescribing in Parkinson disease psychosis, HIV and neuromuscular disease.

David AS, Fleminger S, Kopelman MD, et al. (Lishman).
Lishman's Organic Psychiatry: A Textbook of Neuropsychiatry. 4th ed. Wiley-Blackwell. The organic and systemic causes of psychiatric presentation across this chapter.

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