PART IV · PAPER IV

IV

Neuropsychiatry & Advances

Part IV takes on the organic mind, the neurology interface, and the recent advances that mark the moving frontier of the field.

ONE-DAY REVISION · PAPER 4

Delirium & the Acute Organic Syndromes

An acute, fluctuating failure of attention and awareness, driven from outside the brain. The whole topic hangs on three moves: spot the inattention, hunt the cause, and treat the body before the behaviour. Delirium is a medical emergency wearing a psychiatric mask.

● CONCEPT ● RULE ● TRAP ● KEY NUMBER ● MNEMONIC

The colour tells you what kind of fact it is. Inattention is the hallmark; everything else is supporting evidence.

★ HIGH YIELD TOP 5 IF NOTHING ELSE

1. The hallmark is **inattention** with acute onset and a fluctuating course on a background of altered arousal; if attention is intact and arousal clear, it is very unlikely to be delirium.
2. **Hypoactive delirium is the trap**: quiet, drowsy and withdrawn, it is the most commonly missed subtype, carries the worst prognosis, and mimics depression, so screen for delirium before accepting low mood in an elderly inpatient.
3. Delirium vs dementia vs depression is the single most examined table: delirium is acute, fluctuating, inattentive and clouded with **visual** hallucinations and **diffuse EEG slowing**, and is usually reversible if the cause is treated.
4. Management order is fixed: treat the underlying cause first, then environmental measures, drugs last; antipsychotic (haloperidol **0.5 to 1 mg**) only for severe agitation or risk, **except** benzodiazepines are first-line in alcohol or sedative-hypnotic withdrawal delirium.
5. **Avoid antipsychotics in Lewy body and Parkinson's disease dementia**: even a single dose can trigger life-threatening neuroleptic sensitivity (rigidity, autonomic collapse, a neuroleptic-malignant-like picture).

1 Definition & the core

Delirium is an **acute confusional state**: a disturbance of **attention and awareness** that develops over **hours to days**, **fluctuates** over the day, and is the **direct physiological consequence** of a medical condition, substance or its withdrawal. It is, by definition, organic and (usually) reversible.

DSM-5 criteria (A to E)

	Criterion	The point
A	Disturbance of **attention** (reduced ability to direct, focus, sustain, shift) and **awareness** (reduced orientation to environment)	the **hallmark**; inattention is the cardinal sign
B	Develops over a **short period** (hours to days), a **change from baseline**, and **fluctuates** in severity through the day	acute onset + waxing and waning
C	An additional **cognitive** disturbance (memory, disorientation, language, visuospatial, perception)	not explained by attention deficit alone
D	A and C are **not** better explained by a pre-existing, established or evolving **neurocognitive disorder**, and not in a severely reduced arousal such as coma	separates it from dementia and from coma
E	Evidence it is a **direct physiological consequence** of a medical condition, substance intoxication or withdrawal, a toxin, or multiple causes	the organic-cause requirement

◆ **The hallmark** – **inattention**. If attention is intact, it is very unlikely to be delirium. Test it at the bedside before anything else (digit span, months backwards, serial sevens).

● TRAP

Delirium is the modern umbrella term. The older labels (**acute confusional state, acute organic brain syndrome, toxic/metabolic encephalopathy, ICU psychosis, "sundowning"**) all describe the same thing. ICD-11 frames it as "delirium" with the same attention-plus-awareness core. Do not let a fancy synonym hide the diagnosis.

2 Clinical features & motor subtypes

The phenomenology is broad, but it always sits on the same spine: **inattention that fluctuates**, on a background of **altered arousal**.

Core features

- **Inattention & fluctuation** – the cardinal pair. Lucid intervals alternate with confusion; typically **worse at night** (sundowning).
- **Altered level of arousal** – clouded consciousness, ranging from drowsy/stuporous to hypervigilant. This is what most reliably separates it from dementia.
- **Disorganised thinking** – rambling, incoherent, tangential speech; loosened associations; impaired reasoning.
- **Perceptual disturbance** – **illusions** and **visual hallucinations** (often vivid, frightening, sometimes Lilliputian). Visual > auditory, unlike primary psychosis. Poorly systematised, fleeting persecutory delusions are common.
- **Sleep-wake reversal** – fragmented, inverted cycle; drowsy by day, agitated and awake by night.
- **Emotional lability** – rapid swings of fear, anger, perplexity, apathy; affect shifts with the perceptual state.

The three motor subtypes

Subtype	Presentation	Mistaken for	Note
Hyperactive	restless, agitated, hypervigilant, loud; pulling lines, climbing out of bed; florid hallucinations	functional psychosis, mania, agitation	most easily *recognised*; the minority
Hypoactive	quiet, withdrawn, drowsy, slowed, apathetic, reduced responsiveness	depression, fatigue, "a good patient"	most commonly missed; worst prognosis; commoner in the elderly
Mixed	fluctuates between hyper- and hypoactive within the same day	"settling, then relapsing"	the most common pattern overall

HOLD THIS

The dangerous subtype is **hypoactive**: quietest, most missed, worst outcome. If an elderly inpatient goes suddenly "flat" or "depressed," screen for delirium before you accept low mood.

● CLASSIC TRAP

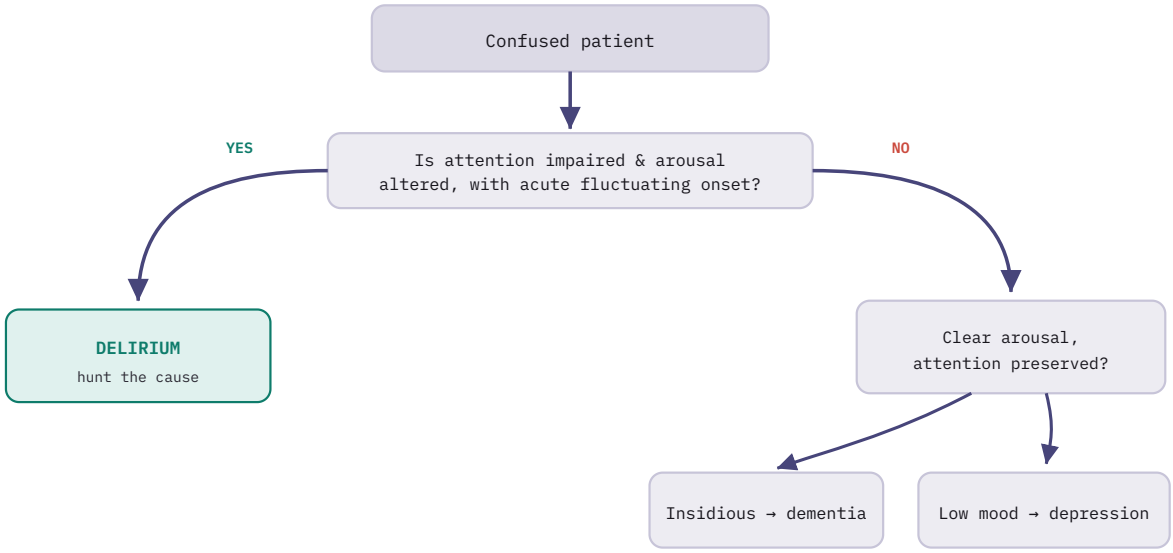
Hypoactive delirium is not depression. The giveaways are acute onset, fluctuation, inattention and clouded arousal – none of which belong to a primary depressive episode. Sedating an apparently "agitated" patient who is actually hypoactive, or antidepressing a delirious one, both delay the search for the real cause.

3 Delirium vs dementia vs depression

The single most examinable table in the topic. Learn it as columns, not rows: pick a patient and read down.

Feature	Delirium	Dementia	Depression
Onset	acute (hours to days)	insidious (months to years)	subacute (weeks)
Course	fluctuating, worse at night	steadily progressive, stable through the day	fairly stable, diurnal mood variation
Duration	days to weeks (often reversible)	months to years (chronic)	weeks to months
Attention	markedly impaired (the hallmark)	relatively preserved until late	may be reduced (poor effort), but testable
Consciousness / arousal	clouded, altered	clear (until end stage)	clear
Hallucinations	common, **visual**	uncommon early (except Lewy body)	rare (mood-congruent if psychotic)
Sleep-wake cycle	grossly disrupted, reversed	fragmented, less acute	early-morning waking
Psychomotor	variable (hyper/hypo, fluctuates)	usually normal early	retardation or agitation
Reversibility	usually reversible if cause treated	largely irreversible	reversible with treatment
EEG	diffuse slowing	usually normal or mild changes	normal

THE ACUTE-CONFUSION TRIAGE LOGIC



Attention plus arousal is the fork. Acute, fluctuating, inattentive, clouded means delirium until proven otherwise: stop and hunt the cause. Preserved attention with clear arousal points to dementia (insidious) or depression (low mood).

● RULE

Delirium and dementia are **not** mutually exclusive. Dementia is the single biggest *risk factor* for delirium; a sudden worsening in a person with dementia ("delirium superimposed on dementia") is delirium until proven otherwise. Always ask the family about *baseline* cognition.

4 Causes

Delirium is a **syndrome, not a diagnosis**. The work is to name the cause, which is frequently multifactorial in a vulnerable (old, demented, sensory-impaired) brain. The exam wants the structured mnemonic.

MNEMONIC

"I WATCH DEATH"

The standard organic-cause checklist for delirium. Eleven groups, each one a place to look.

Letter	Group	Examples
I	Infection	UTI, pneumonia, sepsis, encephalitis, meningitis, COVID
W	Withdrawal	**alcohol** (delirium tremens), benzodiazepines, barbiturates
A	Acute metabolic	electrolytes (Na, Ca), acidosis/alkalosis, hepatic or renal failure, dehydration
T	Trauma	head injury, post-operative state, burns, heat stroke
C	CNS pathology	stroke, haemorrhage, tumour, seizure / post-ictal, abscess
H	Hypoxia	hypoxaemia, anaemia, cardiac failure, pulmonary embolism, carbon monoxide
D	Deficiencies	**thiamine** (B1), B12, folate, niacin
E	Endocrine	thyroid (hyper/hypo), glucose (hypo/hyper), adrenal (Cushing/Addison), parathyroid
A	Acute vascular	hypertensive encephalopathy, shock, vasculitis
T	Toxins / drugs	medications (see below), alcohol, recreational drugs
H	Heavy metals	lead, mercury, manganese, arsenic

The common drug culprits

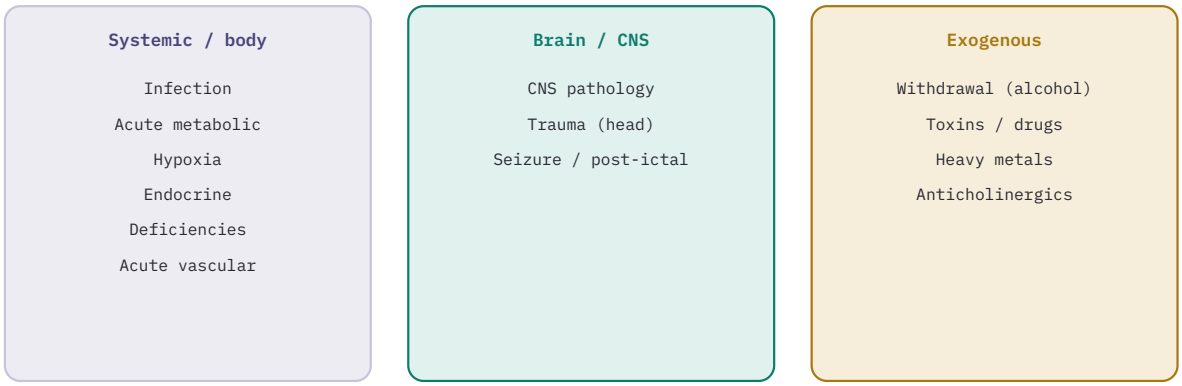
▲ **Anticholinergics** – the single biggest offender. Tricyclics, antihistamines, oxybutynin, low-potency antipsychotics, antiparkinsonian agents. Watch the cumulative **anticholinergic burden** in the elderly.

▲ **Opioids** – especially pethidine (meperidine, via its metabolite normeperidine). Untreated severe pain is also deliriogenic, so balance the two.

▲ **Benzodiazepines & sedative-hypnotics** – both *intoxication* and *withdrawal* cause delirium; a frequent iatrogenic cause in hospital.

▲ **Corticosteroids** – high-dose steroids cause agitation, mood change and frank delirium. Other culprits: dopaminergics, lithium toxicity, digoxin, fluoroquinolones, H2 blockers.

I WATCH DEATH, GROUPED BY WHERE TO LOOK



A way to remember the eleven groups: is the cause in the body (systemic), in the brain itself, or coming from outside (drugs, toxins, withdrawal)? Most inpatient delirium is multifactorial across all three.

5 Assessment

Two jobs run in parallel: **confirm the syndrome** (bedside attention testing plus a tool), then **find the cause** (history, examination, investigations).

Bedside attention testing

● **Formal attention tests** – **digit span** (forward/backward), **months of the year backwards**, **serial sevens**, days of the week backwards, the **vigilance "A" test** (tap on each A in a string of letters). Collateral history establishes the *baseline* and the *acuity* of change.

Screening & diagnostic tools

Tool	What it is	Key feature
CAM	Confusion Assessment Method (Inouye)	the most widely used; algorithm of four features
CAM-ICU	adaptation for ventilated / non-verbal ICU patients	scoreable without speech
4AT	rapid (<2 min) bedside screen, no training needed	Alertness, AMT4, Attention (months backward), Acute change
DRS-R-98	Delirium Rating Scale-Revised	rates *severity*, for monitoring

◆ **The CAM algorithm** – delirium is present when you have **(1) acute onset and fluctuating course AND (2) inattention**, PLUS **either (3) disorganised thinking OR (4) altered level of consciousness**. Features 1 and 2 are *both* mandatory; you then need at least one of 3 or 4.

Confirm the syndrome

Collateral history (baseline + onset). Bedside attention test. A validated tool: **4AT** for a quick screen, **CAM** to diagnose, **CAM-ICU** on the unit. Document fluctuation across the day.

Find the cause

Bloods: FBC, U&E, glucose, calcium, LFT, TFT, CRP, B12/folate. Cultures, urinalysis. ABG/SpO2. ECG. Drug review (the medication chart is a top yield). Then targeted: CT/MRI head, LP, EEG as indicated.

◆ **EEG finding** – **diffuse background slowing** (loss of the posterior alpha rhythm, generalised theta/delta), correlating with the severity of clouding. The exception: **alcohol/sedative withdrawal delirium shows fast (low-voltage fast) activity, not slowing**. EEG is not routine but helps when the diagnosis is unclear or non-convulsive status epilepticus is suspected.

● TRAP

EEG slowing is **sensitive but not specific** – it confirms an organic encephalopathy and helps distinguish delirium from a functional psychosis (where the EEG is normal), but it does not name the cause. Triphasic waves point toward a metabolic / hepatic encephalopathy.

6 Management

The order is fixed and examinable: **cause first, environment second, drugs last and least**.

1. Treat the underlying cause (paramount)

■ **Find and fix the precipitant** – this is the only definitive treatment. Antibiotics for sepsis, correct electrolytes/hypoxia/glucose, stop the offending drug, give thiamine for suspected Wernicke, treat pain and constipation and urinary retention. Everything else is supportive holding.

2. Supportive & environmental measures (first-line, non-drug)

Domain	Do
Reorient	clock, calendar, familiar faces, repeated gentle orientation, well-lit room by day
Sleep-wake	restore the cycle: daylight and activity by day, quiet and dark by night; minimise night-time obs
Sensory aids	give back glasses and hearing aids; correct sensory deprivation
Mobilise & hydrate	early mobilisation, fluids and nutrition, treat constipation, remove unnecessary lines/catheters
Avoid restraints	physical restraints worsen agitation and injury; one-to-one nursing and family presence instead

3. Pharmacology (judicious, last resort)

■ **When to use a drug** – **only** for severe agitation, distressing perceptual disturbance, or behaviour that endangers the patient or others, when non-drug measures have failed. Drugs treat the *symptom*, not the delirium; they may prolong it.

● **Antipsychotic, low and short** – **haloperidol** low-dose (e.g. 0.5–1 mg) is the traditional first choice; atypicals (quetiapine, olanzapine, risperidone) are alternatives. Use the lowest dose for the shortest time, review daily, watch QTc and extrapyramidal effects.

▲ **Benzodiazepines – the exception** – benzodiazepines **worsen** most delirium and are avoided, *except* they are **first-line for alcohol or sedative-hypnotic withdrawal** delirium (delirium tremens), and for seizure-related delirium. Chlordiazepoxide / lorazepam plus parenteral **thiamine** in DTs.

QUICK RULE

Antipsychotic for the agitated delirious patient, **except** in **withdrawal** delirium (benzodiazepines first), **and except** in **Lewy body dementia / Parkinson's disease dementia** – there antipsychotics can cause life-threatening sensitivity reactions. Use lorazepam or very cautious low-dose quetiapine instead.

● CLASSIC TRAP

Avoid antipsychotics in Lewy body and Parkinson's disease dementia. Severe neuroleptic sensitivity (rigidity, irreversible parkinsonism, autonomic collapse, a neuroleptic-malignant-like picture) can follow even a single dose. If a delirious patient has visual hallucinations, parkinsonism and fluctuating cognition at baseline, think DLB and hold the antipsychotic.

7 Prognosis & prevention

Delirium was long dismissed as a benign "temporary confusion." It is not. It is an independent marker of a sick brain and a poor trajectory.

Prognosis: a marker of poor outcome

◆ **Why it matters** – delirium independently predicts **raised mortality**, **longer hospital stay**, increased institutionalisation, and accelerated, sometimes **persistent cognitive decline** (a recognised risk factor for, and accelerant of, dementia). Many cases (especially hypoactive) do not fully resolve by discharge; symptoms can persist for weeks to months.

● TRAP

Do not reassure that delirium is "just temporary confusion that will pass." Persistent delirium and incomplete recovery are common, and an episode flags both a serious acute illness and a vulnerable brain. The honest message to family is guarded, not dismissive.

Prevention: the highest-yield intervention

■ **Multicomponent prevention works** – up to a third of hospital delirium is preventable. The evidence base is the **HELP model** (Hospital Elder Life Program, Inouye), a bundle of non-pharmacological measures targeting the modifiable risk factors.

HELP: the targeted risk factors

Cognitive impairment → orientation, activities.
Sleep deprivation → non-drug sleep protocol.
Immobility → early mobilisation.
Vision impairment → visual aids.
Hearing impairment → amplifiers.
Dehydration → volume repletion.

The vulnerability equation

Delirium = **predisposing** factors (old age, dementia, sensory impairment, frailty, comorbidity) meeting a **precipitant** (infection, surgery, drugs, metabolic insult). The frailer the brain, the smaller the insult needed. Pharmacological prophylaxis is **not** routinely recommended.

HOLD THIS

Prevention beats treatment: a **multicomponent, non-drug bundle (HELP)** targeting cognition, sleep, mobility, vision, hearing and hydration is the single most effective intervention. There is no drug licensed to prevent delirium.

QUICK-RECALL · DRILL THESE ONE-LINERS

★ **Core:** acute, fluctuating disturbance of **attention and awareness** + a cognitive change, over hours to days, from a medical cause. The hallmark is **inattention**.

- **DSM-5:** A attention/awareness · B acute + fluctuating · C added cognitive change · D not better explained by dementia/coma · E direct physiological cause.
- **Subtypes:** hyperactive (recognised, the minority) · **hypoactive (most missed, worst prognosis)** · mixed (commonest). Hypoactive mimics depression.
- **Vs dementia/depression:** delirium = acute, fluctuating, inattentive, clouded arousal, visual hallucinations, EEG slowing, reversible. Dementia = insidious, progressive, clear arousal. Depression = low mood, clear arousal, intact testable attention.
- **Causes: I WATCH DEATH** – Infection, Withdrawal, Acute metabolic, Trauma, CNS, Hypoxia, Deficiencies, Endocrine, Acute vascular, Toxins, Heavy metals. Drug top offenders: anticholinergics, opioids, benzodiazepines, steroids.

- **Assessment:** test attention (months backward, digit span, serial sevens) + **CAM** (acute/fluctuating AND inattention, PLUS disorganised thinking OR altered consciousness) or **4AT**. EEG = **diffuse slowing** (fast activity in alcohol withdrawal).
- **Management order:** treat the cause (paramount) → environment/reorientation/sleep-wake/sensory aids/mobilise/no restraints → drugs last: low-dose antipsychotic only for severe agitation/distress/risk.
- **Drug exceptions:** benzodiazepines first-line in **alcohol/sedative withdrawal**; **avoid antipsychotics in Lewy body and Parkinson's disease dementia** (neuroleptic sensitivity).
- **Prognosis & prevention:** marker of raised mortality, longer stay, persistent cognitive decline. Best intervention is prevention: multicomponent non-drug bundle (**HELP**) targeting cognition, sleep, mobility, vision, hearing, hydration.

ONE-DAY REVISION · PAPER 4

The Dementias

An acquired, progressive decline across cognitive domains, on a clear sensorium. The exam rewards three reflexes: separate dementia from delirium and depression, exclude the reversible mimics, and place each major dementia by its earliest feature. Every comparison table below is a long-answer in waiting.

CONCEPT · RULE · TRAP · KEY NUMBER · MNEMONIC

The colour tells you what kind of fact it is. Cognitive testing scales live in the companion rating-scales pack.

★ HIGH YIELD TOP 5 IF NOTHING ELSE

1. DLB has severe neuroleptic sensitivity: up to half react to antipsychotics with profound parkinsonism and an NMS-like syndrome that can be fatal, so avoid antipsychotics (never a typical) and treat hallucinations with a cholinesterase inhibitor instead. This is the commonest DLB exam question.
2. Place each dementia by its earliest feature: AD = recent (episodic) memory first and gradual; VaD = stepwise with focal signs; DLB = fluctuation + visual hallucinations + parkinsonism + RBD; FTD = young (45-65), behaviour or language first with memory spared early.
3. Split the AD genes: **APP, PSEN1, PSEN2** are autosomal-dominant early-onset familial; APOE ε4 is only a risk allele for common late-onset AD (not deterministic, not predictive) and ε2 is protective; Down syndrome (extra APP) develops AD pathology early.
4. The 1-year rule for Lewy-body disease: dementia appearing more than a year after motor parkinsonism = Parkinson's disease dementia; cognitive decline before or within a year of parkinsonism = DLB.
5. NPH is the treatable triad "wet, wacky, wobbly": gait apraxia (appears first), urinary incontinence, and dementia, with ventriculomegaly out of proportion to atrophy; may improve with a large-volume tap and a ventriculoperitoneal shunt.

1 Definition & approach

DSM-5 renamed dementia **major neurocognitive disorder**: a significant decline from a prior level in one or more cognitive domains, severe enough to interfere with **independence in everyday activities**, not better explained by delirium or another mental disorder. **Mild** neurocognitive disorder is the same decline but *without* loss of independence (compensatory effort still works).

The six cognitive domains (DSM-5)

Domain	What it covers
Complex attention	sustained, divided, selective attention; processing speed
Executive function	planning, decision-making, working memory, flexibility, inhibition
Learning & memory	immediate, recent and long-term recall; recognition
Language	naming, word-finding, fluency, grammar, comprehension
Perceptual-motor	visuospatial ability, praxis, gnosis (construction, recognition)
Social cognition	recognition of emotions, theory of mind, behavioural regulation

Dementia vs delirium vs depression

Feature	Dementia	Delirium	Depression (pseudodementia)
Onset	insidious, months to years	acute, hours to days	fairly discrete, often datable
Course	chronic, slowly progressive	fluctuating, worse at night	stable through the day
Consciousness	clear (until late)	clouded, impaired	clear
Attention	relatively preserved early	grossly impaired	variable, effort-dependent
Memory complaint	conceals, confabulates	poor registration	highlights deficits; "don't know" answers
Reversibility	usually not	reversible (treat the cause)	reversible (treat the mood)

● CLASSIC TRAP

The **pseudodementia of depression**: a depressed older patient who answers "I don't know," gives poor effort, shows *equal* recent and remote memory loss, and is distressed by the deficit. Contrast true dementia, where the patient confabulates, tries hard, loses recent before remote memory, and is often unconcerned. Depression and dementia coexist (and depression can herald dementia), so a therapeutic antidepressant trial is reasonable before settling the diagnosis.

The reversible mimics – always exclude

● MNEMONIC

"DEMENTIA is treatable until proven otherwise"

Drugs · **E**motional (depression) · **M**etabolic / endocrine (thyroid) · **E**yes & ears (sensory) · **N**utritional (B12, folate, thiamine) · **T**umour & trauma (incl. subdural, NPH) · **I**nfection (neurosyphilis, HIV) · **A**lcohol. The point: a treatable cause must be sought in every workup.

■ **Always exclude** – **B12 and folate** deficiency, **hypothyroidism**, **neurosyphilis**, **HIV**, **normal pressure hydrocephalus**, **depression**, and **medication** (anticholinergics, sedatives, opioids). These are the "reversible dementias" the blood panel and a scan are designed to catch.

2 The major dementias at a glance

This is the centrepiece. If you memorise one table for the dementias, memorise this. Hold the **earliest feature** and the **one discriminating sign** for each.

DEMENTIA SUBTYPES AT A GLANCE

	Alzheimer's (AD)	Vascular (VaD)	Lewy body (DLB)	Frontotemporal (FTD)
Typical onset / age	insidious, >65 (commonest)	variable, vascular risk	insidious, >65	younger, 45–65
Earliest feature	episodic memory (recent)	focal deficit / slowed processing, executive	fluctuating attention, visual hallucinations	personality / behaviour or aphasia
Course	steady, gradual	stepwise, deteriorations	fluctuating	gradual, may be rapid
Key pathology	amyloid-β plaques + tau tangles	infarcts / small-vessel ischaemia	α-synuclein **Lewy bodies**	tau or TDP-43; frontotemporal atrophy
Discriminating sign	hippocampal atrophy on MRI	focal neuro signs; stepwise history	neuroleptic sensitivity; RBD; parkinsonism	early disinhibition / apathy; memory spared early

HOLD THIS

AD = memory first, gradual. **VaD** = stepwise, focal signs. **DLB** = fluctuation + visual hallucinations + parkinsonism + neuroleptic sensitivity. **FTD** = young, behaviour/language first, memory spared early.

RULE

A useful screen for "which dementia": what went *first*? Memory → think AD. A step down after a vascular event → VaD. Seeing things, falling, freezing → DLB. A change in *character* in a younger person → FTD. The earliest feature, not the final picture, discriminates.

3 Alzheimer's disease

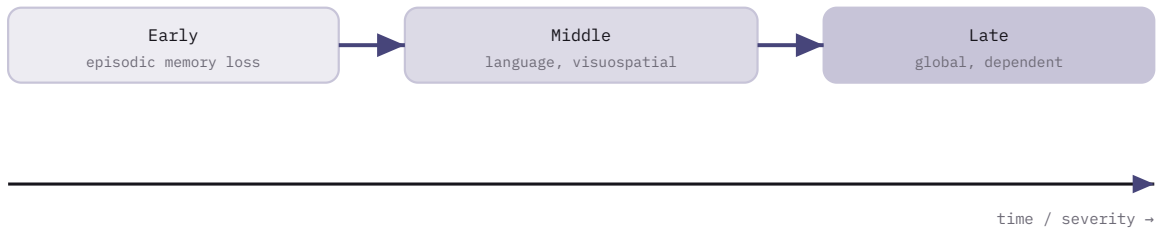
◆ **Epidemiology** – the **commonest** dementia (roughly **60–70%** of cases). Prevalence rises steeply with age, roughly doubling every five years after 65. Female preponderance. Vascular dementia is the second commonest in most series.

Pathology

- **Amyloid-β plaques** – **extracellular** deposits of amyloid-β, cleaved from amyloid precursor protein (APP) by β- and γ-secretase. The "amyloid cascade hypothesis" places this upstream.
- **Neurofibrillary tangles** – **intracellular** aggregates of **hyperphosphorylated tau**. Tangle burden tracks the clinical severity more closely than plaque burden.
- **Neurochemistry & topography** – a **cholinergic deficit** (loss of nucleus basalis of Meynert) underlies the symptomatic rationale for cholinesterase inhibitors. Atrophy begins in the **medial temporal lobe** (entorhinal cortex, hippocampus) and spreads to temporoparietal association cortex.

Clinical course

ALZHEIMER'S: THE SPREAD OF DEFICITS OVER TIME



Early: recent (episodic) memory loss and disorientation. Middle: language (aphasia, word-finding) and visuospatial deficits, apraxia, getting lost. Late: global decline, behavioural symptoms, incontinence, dependence and mutism.

- **Stage sequence** – **early**: insidious *recent* memory loss, repetitive questioning, misplacing items, disorientation to time. **Middle**: language and visuospatial breakdown, apraxia, getting lost in familiar places, BPSD. **Late**: global impairment, loss of recognition, incontinence, immobility, mutism. Mean survival roughly 8–10 years from diagnosis.

Genetics

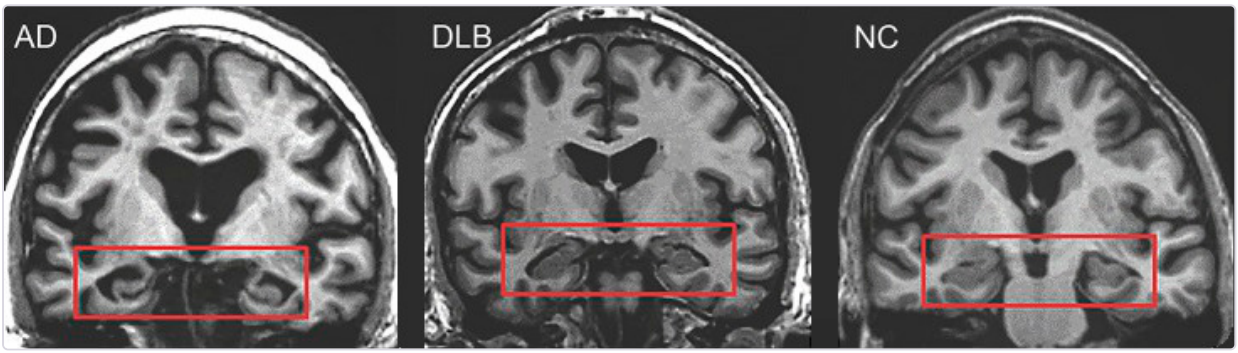
Gene	Chromosome	Role
APP	21	early-onset familial AD (autosomal dominant); also why **Down syndrome** develops AD pathology early

Gene	Chromosome	Role
PSEN1	14	commonest cause of early-onset familial AD
PSEN2	1	rarer early-onset familial AD
APOE ε4	19	risk allele for common late-onset AD (not deterministic); ε2 is protective

TRAP

Separate the two genetic stories. The three **autosomal-dominant** genes (**APP, PSEN1, PSEN2**) cause rare *early-onset familial* AD. **APOE ε4** is a *susceptibility* allele for the common late-onset form: it raises risk and lowers the age of onset but does not by itself cause the disease, so it is not used as a predictive test. Trisomy 21 (Down syndrome) carries an extra APP gene and almost universally develops AD pathology by mid-life.

MEDIAL TEMPORAL ATROPHY IN DEMENTIA



Coronal MRI, hippocampal region boxed: Alzheimer's (AD) shows the most medial-temporal atrophy, dementia with Lewy bodies (DLB) is relatively spared, normal control (NC) is intact. Source: McKeith et al. 2017, DLB Consortium, CC BY 4.0, Wikimedia Commons.

4 Vascular, Lewy body & frontotemporal

Vascular dementia

● **Picture** – cognitive decline attributable to cerebrovascular disease. Classically a **stepwise** deterioration with plateaus, patchy ("islands") of preserved function, early **executive** and processing-speed impairment, and **focal neurological signs** (hemiparesis, brisk reflexes, gait disturbance, pseudobulbar affect).

■ **Risk factors & subtypes** – hypertension, diabetes, atrial fibrillation, smoking, hyperlipidaemia, prior stroke. Subtypes: **multi-infarct**, **small-vessel** (subcortical Binswanger), and strategic **single-infarct**. Management is secondary prevention: control the vascular risk factors. Often coexists with AD (**mixed dementia**).

Dementia with Lewy bodies

Pathology: **α-synuclein** Lewy bodies in cortex and brainstem. The four **core** clinical features:

Core feature	Detail
Fluctuating cognition	marked variation in attention and alertness, hour to hour or day to day
Visual hallucinations	**recurrent, well-formed and detailed** (often people or animals), typically early
Spontaneous parkinsonism	bradykinesia, rigidity, gait instability, falls (not drug-induced)
REM sleep behaviour disorder	acting out dreams; may precede cognitive decline by years

HIGH-YIELD TRAP

Severe neuroleptic sensitivity. Up to half of DLB patients react to antipsychotics with profound parkinsonism, sedation, confusion, and a syndrome resembling neuroleptic malignant syndrome that can be **fatal**. Avoid antipsychotics, and *never* a typical (high-potency) agent. If a drug is unavoidable, a low-dose atypical (e.g. quetiapine) with great caution. This single fact is the commonest DLB exam question.

Frontotemporal dementia

◆ **Onset** – the dementia of the **young** (typically 45–65), a leading cause of dementia under 65. Strong familial component (tau, TDP-43; some overlap with motor neurone disease).

● **Behavioural variant (bvFTD)** – early **personality and behaviour change**: disinhibition, apathy, loss of empathy, stereotyped/compulsive behaviour, hyperorality and dietary change, loss of insight. The picture is frontal, often mistaken early for a primary psychiatric disorder.

● **Primary progressive aphasia** – the language-led variants: **semantic** (loss of word meaning, fluent but empty speech) and **non-fluent / agrammatic** (effortful, halting, agrammatic speech).

■ **The discriminator** – in FTD, **episodic memory and visuospatial skills are relatively preserved early**, while behaviour or language collapse first. That dissociation separates it from AD, where memory goes first.

5 Other causes

● **Parkinson's disease dementia (PDD)** – dementia arising in established Parkinson's disease. Distinguished from DLB by the **1-year rule**: if dementia appears **more than a year after** motor parkinsonism, call it PDD; if cognitive decline precedes or begins within a year of parkinsonism, call it DLB. The two are a spectrum of the same Lewy-body pathology.

● **Huntington's disease** – autosomal-dominant **CAG triplet repeat** (chromosome 4, huntingtin), showing anticipation. A **subcortical** dementia: psychomotor slowing, executive and memory deficits, with **chorea** and prominent psychiatric features (depression, irritability, psychosis, high suicide risk).

▲ **Creutzfeldt-Jakob disease** – prion disease with a **rapidly progressive** dementia (weeks to months), **myoclonus**, and ataxia. EEG: periodic **triphasic sharp-wave complexes** (sporadic CJD). MRI: cortical ribboning and basal-ganglia signal change on DWI. CSF: positive RT-QuIC / 14-3-3 protein. Invariably fatal.

◆ **Normal pressure hydrocephalus** – the **treatable** triad ("wet, wacky, wobbly"): **gait apraxia** (magnetic, shuffling; appears first), **urinary incontinence**, and **dementia**. Ventriculomegaly out of proportion to atrophy. May improve with a large-volume lumbar tap and ventriculoperitoneal **shunt**.

● **Alcohol-related dementia** – chronic alcohol toxicity (plus thiamine deficiency) causing global cognitive decline. Distinguish from **Wernicke-Korsakoff**: Wernicke's encephalopathy (confusion, ophthalmoplegia, ataxia) is a thiamine-deficiency emergency; Korsakoff's is the chronic amnestic syndrome (anterograde amnesia with confabulation). Some stabilisation with abstinence and thiamine.

6 Assessment & investigation

Cognitive testing

- **Bedside cognition** – screen with MMSE, MoCA (more sensitive to executive and early deficits), ACE-III, or the clock-drawing test; profile across all domains. Detailed scale properties and cut-offs are in the companion **rating-scales pack**. Always pair with a collateral history and a functional (ADL) assessment.

Blood panel to exclude reversible causes

First-line bloods (everyone)

FBC, ESR/CRP, U&E, LFT, calcium, glucose/HbA1c, **TFT** (thyroid), **vitamin B12 and folate**. These catch the common reversible mimics.

Second-line (if indicated)

Syphilis serology, **HIV** test, autoimmune / paraneoplastic screen, heavy metals, drug levels. Guided by risk factors, age and tempo.

Structural neuroimaging

- **When and what to scan** – structural imaging is recommended in the workup to exclude reversible/structural causes (tumour, subdural, NPH, infarcts). **MRI** is preferred (better at medial-temporal atrophy and small-vessel/vascular change); **CT** is acceptable when MRI is unavailable or contraindicated, and is enough to exclude a mass or bleed. Scan especially with young onset, rapid progression, focal signs, or atypical features.

CSF & functional biomarkers

- **CSF biomarkers** – in AD, **low amyloid-β42** with **high total and phospho-tau**. Useful in young or atypical cases, not routine. CSF RT-QuIC / 14-3-3 supports CJD.
- **PET** – **FDG-PET** shows the hypometabolism pattern (temporoparietal in AD, frontotemporal in FTD); **amyloid-PET** images plaque load. **DaTscan** (dopamine-transporter SPECT) is abnormal in DLB and supports it against AD. Reserved for diagnostic uncertainty, not first-line.

7 Management

Cognitive enhancers

Drug	Class / action	Indication
Donepezil	cholinesterase inhibitor	mild–moderate (and severe) AD
Rivastigmine	cholinesterase inhibitor (also butyrylcholinesterase)	AD and **PDD**; patch available
Galantamine	cholinesterase inhibitor + nicotinic modulator	mild–moderate AD
Memantine	**NMDA receptor antagonist**	moderate–severe AD; add-on or if ChEI not tolerated

- **How they help** – **cholinesterase inhibitors** raise synaptic acetylcholine; they offer symptomatic, modest benefit and do not halt progression. Main adverse effects are cholinergic: nausea, diarrhoea, bradycardia, syncope (caution in heart block). **Memantine** dampens glutamatergic excitotoxicity and is generally well tolerated.

● DLB-RESPONSIVE CAVEAT

Patients with **DLB** (and PDD) often respond *well* to **cholinesterase inhibitors**, with improvement in cognition and in the visual hallucinations – rivastigmine and donepezil are the agents of choice here. This matters because antipsychotics are contraindicated by neuroleptic sensitivity, so a ChEI is the safer route to treating the hallucinations.

Behavioural & psychological symptoms (BPSD)

■ **Non-pharmacological FIRST** – agitation, aggression, wandering, psychosis and sleep disturbance affect most patients. First-line is always non-drug: identify and treat triggers (pain, infection, constipation, sensory deficit, environment), structured routine, reassurance, carer education and behavioural strategies.

● THE ANTIPSYCHOTIC TRAP

Antipsychotics in dementia carry an FDA **black-box warning**: an increased risk of **stroke / cerebrovascular events and death**. Use only when there is severe distress or risk to self or others, after non-drug measures have failed, at the **lowest dose for the shortest time**, with review and a planned taper. **Absolutely avoid in DLB** (severe neuroleptic sensitivity). Treat any reversible BPSD driver first.

● **Carer support** – central, not optional. Psychoeducation, respite care, attention to **carer burden and depression**, advance care planning, capacity and safeguarding, financial and legal advice, and community/voluntary support. The carer's health predicts whether the patient can stay at home.

QUICK-RECALL · DRILL THESE ONE-LINERS

- **Definition:** DSM-5 major NCD = decline in ≥1 domain that *impairs independence*; mild NCD = decline without losing independence. Six domains: attention, executive, learning/memory, language, perceptual-motor, social cognition.
- **Delirium vs dementia:** delirium = acute, fluctuating, clouded consciousness, impaired attention, reversible. Dementia = insidious, clear sensorium early.
- **Pseudodementia:** depressed, distressed, "don't know", equal recent/remote loss, poor effort – reversible. True dementia conceals and confabulates.
- **Reversible mimics:** B12/folate, thyroid, neurosyphilis, HIV, NPH, depression, medication. Always exclude.
- **The big four:** AD = memory first, gradual, amyloid + tau. VaD = stepwise, focal signs, vascular risk. DLB = fluctuation + visual hallucinations + parkinsonism + RBD. FTD = young, behaviour/language first, memory spared.
- **AD genetics:** APP / PSEN1 / PSEN2 = autosomal-dominant early-onset familial. APOE ε4 = risk allele for late-onset (not deterministic); ε2 protective. Down syndrome (trisomy 21, extra APP) = early AD.
- ★ **DLB:** recurrent well-formed visual hallucinations + fluctuating cognition + spontaneous parkinsonism + RBD. **Severe neuroleptic sensitivity** – can be fatal; avoid antipsychotics.
- **1-year rule:** dementia >1 year after parkinsonism = PDD; cognitive decline before or within a year = DLB.
- **CJD:** rapidly progressive + myoclonus + periodic triphasic sharp waves on EEG + DWI cortical ribboning. NPH triad: gait apraxia, incontinence, dementia (wet, wacky, wobbly) – shunt-responsive.
- **Management:** ChEIs (donepezil, rivastigmine, galantamine) for AD; memantine (NMDA antagonist) moderate–severe. DLB responds to ChEIs. BPSD = non-drug first; antipsychotics carry stroke/mortality risk and are contraindicated in DLB.

ONE-DAY REVISION · PAPER 4

Epilepsy & Psychiatry

Epilepsy and psychiatric disorder sit in a two-way relationship: each raises the risk of the other. Hold the seizure classification, the temporal map of the psychoses, the NEAD-vs-epilepsy table, and the prescribing rules. These are the lines that carry the marks.

● CONCEPT ● RULE ● TRAP ● KEY NUMBER ● MNEMONIC

The colour tells you what kind of fact it is. Seizure first-aid and detailed EEG live in the neurology pack.

★ HIGH YIELD TOP 5 IF NOTHING ELSE

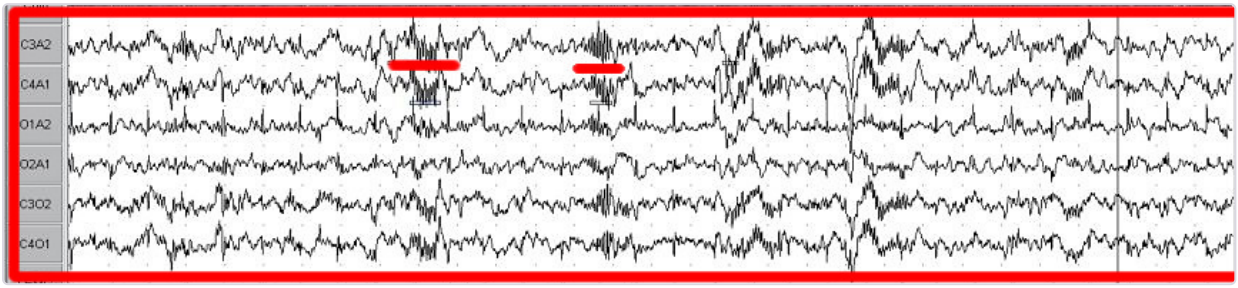
1. The psychoses of epilepsy are classified by **timing to the seizure** (PIPI: pre-ictal, ictal, post-ictal, interictal); **post-ictal is the commonest**, follows a lucid interval of **1-6 days**, is self-limiting, and responds to a short low-dose antipsychotic.
2. **SSRIs are first-line and relatively safe** for depression in epilepsy; **bupropion and clozapine lower the seizure threshold the most** (both dose-dependent), so never under-treat depression for fear of seizures.
3. NEAD vs epileptic seizure: NEAD shows gradual fluctuating asynchronous movements, eyes **closed** and resisting opening, no post-ictal confusion, and a **normal post-ictal prolactin**; **video-EEG telemetry is the gold standard**.
4. **Forced normalisation (Landolt)** is the trap: psychosis emerges as the EEG normalises and seizures stop, so tighter seizure control can paradoxically unmask psychosis (alternative psychosis, Tellenbach).
5. Epilepsy definition = **≥2** unprovoked seizures >24 h apart (or one with ≥60% recurrence risk, or a syndrome); status epilepticus = a seizure **≥5 min** or no recovery between seizures; valproate, carbamazepine and lamotrigine double as mood stabilisers.

1 Seizures and epilepsy: definitions & classification

A **seizure** is a transient event; **epilepsy** is the enduring tendency to have them. Get the two definitions and the ILAE axis (focal vs generalised onset) right and the rest is detail.

- **Seizure** – a transient occurrence of signs or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain (ILAE).
- **Epilepsy (operational)** – at least **two** unprovoked seizures >24 h apart; *or* one unprovoked seizure with a high (≥60%) recurrence risk; *or* a diagnosed epilepsy syndrome.
- **Aura** – the subjective onset of a focal seizure (a focal aware seizure in its own right): rising epigastric sensation, deja vu, fear, an odd smell. The patient's window into where the seizure begins.

EPILEPTIFORM EEG



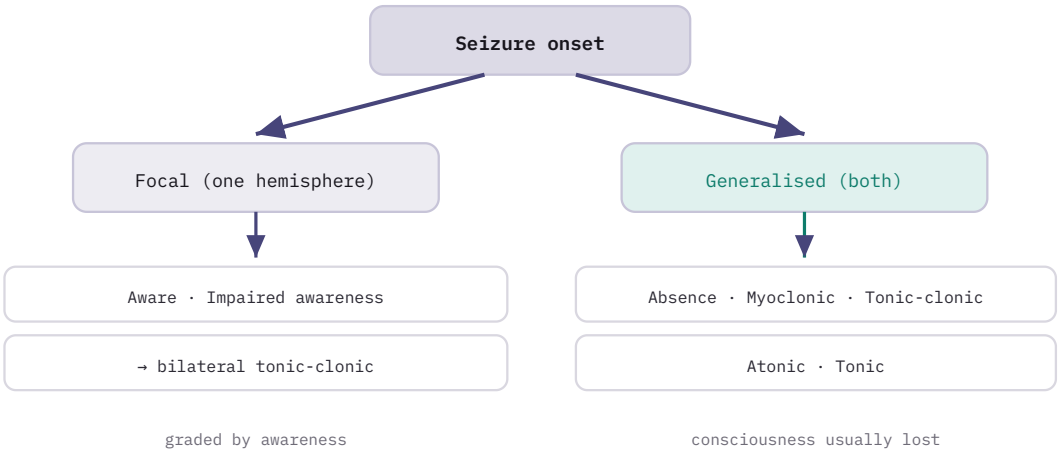
Scalp EEG showing an epileptiform discharge. An interictal epileptiform discharge supports, but is not required for, the clinical diagnosis of epilepsy. Source: Der Lange, CC BY-SA 3.0, Wikimedia Commons.

ILAE classification of seizure types (2017)

The first split is **where the seizure starts**: one part of one hemisphere (focal) or both hemispheres at once (generalised). Focal seizures are then graded by **awareness**.

Onset	Seizure type	One-line feature
Focal (one hemisphere)	Focal **aware** (old: simple partial)	awareness fully retained; e.g. an aura, a focal motor jerk; no loss of consciousness
	Focal **impaired awareness** (old: complex partial)	awareness reduced; often automatisms (lip-smacking, fumbling); typically temporal lobe
	Focal to **bilateral tonic-clonic** (old: secondary generalised)	begins focal, then spreads to a bilateral convulsion
Generalised (both hemispheres)	**Absence**	brief blank stare, abrupt onset/offset, no aura, no post-ictal phase; 3 Hz spike-and-wave
	Myoclonic	sudden, brief, shock-like muscle jerks; consciousness usually preserved
	Tonic-clonic (old: grand mal)	stiffening (tonic) then rhythmic jerking (clonic); tongue-bite, incontinence, post-ictal confusion
	Atonic	sudden loss of tone, a “drop attack”; injury risk
	Tonic	sustained stiffening of muscles, often in sleep

THE FIRST BRANCH POINT: WHERE THE SEIZURE STARTS



ILAE 2017 splits seizures first by onset: focal (one hemisphere, then graded by awareness) versus generalised (both hemispheres at once). Awareness, not the old "simple/complex" pair, is now the key qualifier.

TRAP

The old terms are out: **simple partial → focal aware**, **complex partial → focal impaired awareness**, **secondarily generalised → focal to bilateral tonic-clonic**. Examiners still use the old names interchangeably; know both maps.

◆ **Status epilepticus** – a seizure lasting **≥5 min**, or repeated seizures without recovery of consciousness between them. A medical emergency (the older "30 min" definition is the threshold for long-term neuronal injury). Convulsive status carries significant mortality; **non-convulsive status** can present as a fluctuating confusional or psychiatric state and is easily missed.

2 Why epilepsy matters to psychiatry

The relationship is **bidirectional**, not one-way. Epilepsy raises the risk of psychiatric disorder, and a prior psychiatric disorder raises the risk of later epilepsy. They share substrate, not just consequence.

● **Bidirectional relationship** – people with epilepsy have higher rates of depression, anxiety and psychosis; conversely, a history of depression or psychosis precedes a first seizure more often than chance. Suggests shared neurobiology (limbic circuitry, neurotransmitter and inflammatory pathways), not merely the burden of a chronic illness.

◆ **Comorbidity burden** – roughly **one in three** people with epilepsy meet criteria for a psychiatric disorder over their lifetime, far above the general population. Depression and anxiety lead; psychosis is rarer but disproportionately associated with epilepsy.

Epilepsy → psychiatry

Seizures, the limbic focus, antiseizure drug effects, stigma and the burden of a chronic, unpredictable illness all raise psychiatric risk. **Temporal lobe** epilepsy is the most psychiatrically loaded.

Psychiatry → epilepsy

A history of **depression or psychosis raises the risk of later unprovoked seizures** (population cohorts). The arrow runs both ways, pointing to common mechanisms rather than simple cause and effect.

HOLD THIS

The link is **bidirectional** and the comorbidity burden is high (~1 in 3). Depression is the commonest and most under-treated comorbidity, and it predicts quality of life more than seizure frequency does.

3 Psychiatric comorbidity in epilepsy

Depression & anxiety

▲ **Depression** – the **commonest** psychiatric comorbidity and the **most under-recognised and under-treated**. Often atypical and intermittent (the *interictal dysphoric disorder* pattern: labile mood, irritability, somatic pain, brief euthymic spells). Drives quality of life more than seizure count.

▲ **Suicide risk** – markedly raised in epilepsy (several-fold over the general population; higher still in temporal lobe epilepsy and after epilepsy surgery). Screen for it actively; it is the reason depression here is never benign.

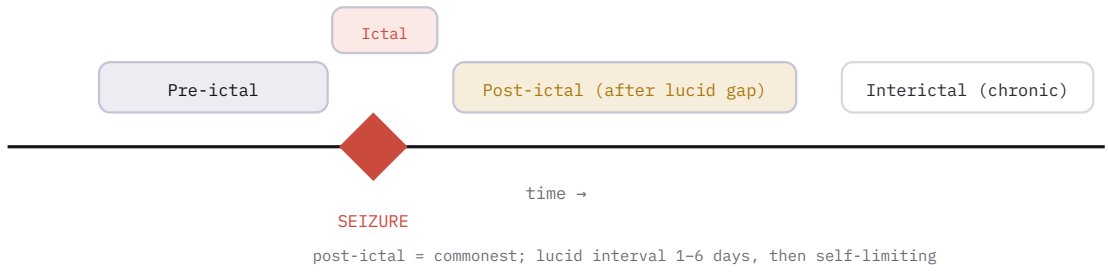
● **Anxiety** – common and frequently entwined with depression. Includes anticipatory fear of seizures ("seizure phobia"), agoraphobic avoidance, panic, and ictal fear (a temporal lobe seizure presenting *as* sudden terror).

The psychoses of epilepsy – classified by timing

The single most examinable idea here: psychosis in epilepsy is classified by its **temporal relationship to the seizure**. Learn the four windows.

Type	Timing relative to seizure	Clinical picture
Pre-ictal	builds in the hours/days **before** a seizure	rising dysphoria, irritability or psychotic symptoms; relieved by the seizure
Ictal	psychosis **is** the seizure	non-convulsive status (esp. focal/limbic): fluctuating confusion, hallucinations, automatisms; an EEG diagnosis
Post-ictal	after a **lucid interval** (typically 1–6 days) following a seizure cluster	most common; affect-laden, often grandiose/religious; self-limiting (days to weeks); responds to short-course antipsychotic
Interictal	**between** seizures, unrelated to any single one	chronic, schizophrenia-like psychosis of epilepsy; relatively preserved affect/personality; less negative symptoms than schizophrenia

TEMPORAL MAP OF THE PSYCHOSES OF EPILEPSY



Psychosis is mapped by its distance from the seizure: pre-ictal (builds before), ictal (the seizure itself, on EEG), post-ictal (after a lucid gap; the commonest), and interictal (chronic, schizophrenia-like, unrelated to any one seizure).

▲ **Forced normalisation (Landolt)** – psychiatric symptoms (often psychosis) *emerge as the EEG normalises and seizures stop*, frequently after a new antiseizure drug. Described on EEG by **Landolt**; the clinical counterpart is **alternative psychosis** (Tellenbach): seizures and psychosis

seesaw, one improving as the other worsens. A trap because better seizure control can *unmask* psychosis.

MNEMONIC

"PIPI" → Pre, Ictal, Post, Inter

The four windows of psychosis in epilepsy, in time order: **P**re-ictal, **I**ctal, **P**ost-ictal (the commonest), **I**nterictal (the chronic schizophrenia-like one). Forced normalisation = psychosis appears *when the EEG goes quiet*.

4 Temporal lobe epilepsy & behaviour

The temporal lobe is the psychiatrically loaded one: its seizures look behavioural, and its interictal personality is the classic (and contested) exam topic.

Ictal semiology

- **Aura** – commonly a **rising epigastric sensation**, fear, deja vu or jamais vu, an odd taste or smell (uncinate). A focal aware seizure that warns of what follows.
- **Automatisms** – involuntary, semi-purposeful movements during a focal impaired-awareness seizure: **oro-alimentary** (lip-smacking, chewing, swallowing) and **manual** (fumbling, picking). The patient is not aware and does not recall them.
- **Post-ictal** – confusion, dysphasia (if dominant temporal lobe), and amnesia for the event. Recovery over minutes to an hour.

The interictal personality (Geschwind syndrome)

A contested cluster of **interictal** behavioural traits described in some temporal lobe epilepsy. Real as an association, over-stated as a syndrome; examinable as a named tetrad.

Feature	What it looks like
Hyperreligiosity	intense religious or philosophical preoccupation, sometimes conversion experiences
Hypergraphia	compulsive, copious, detailed writing or drawing
Viscosity	"stickiness" in thought and conversation: circumstantiality, over-inclusiveness, difficulty terminating an interaction
Altered sexuality	most often hyposexuality (reduced libido); occasionally altered interests

TRAP

Geschwind syndrome (also Gastaut-Geschwind) is an **interictal** personality change, not an ictal phenomenon and not a formal diagnosis. The association is real but inconsistent and likely over-reported; do not present it as inevitable in temporal lobe epilepsy. The other classic ictal-to-behaviour link is **Kuver-Bucy syndrome** with bilateral temporal (amygdala) damage: hyperorality, hypersexuality, placidity, visual agnosia.

The differentials that matter to psychiatry

TLE vs panic disorder

Ictal fear from a temporal seizure can mimic panic. Pointers to seizure: very brief, stereotyped, with deja vu / epigastric aura / automatisms, impaired awareness, and post-ictal confusion. Panic: longer, situational, with prominent cognitive catastrophising and no post-ictal phase.

TLE vs dissociation

Temporal seizures can cause depersonalisation, derealisation, deja vu and automatisms that resemble **dissociative** states. Stereotypy, brevity, impaired awareness and an EEG correlate favour epilepsy. Also consider transient epileptic amnesia in the differential of amnestic episodes.

5 Non-epileptic attack disorder (NEAD)

NEAD (also psychogenic non-epileptic seizures, PNES, or dissociative seizures) are paroxysmal episodes resembling seizures but *without* the EEG correlate of epilepsy. A dissociative/conversion phenomenon, not feigning. The distinguishing features are a guaranteed exam table.

Feature	Epileptic seizure	NEAD (dissociative)
Onset	abrupt, stereotyped	**gradual**, may wax and wane
Motor pattern	synchronous, rhythmic	**fluctuating, asynchronous**, out-of-phase limb movements
Head movement	turning to one side (versive)	**side-to-side** head shaking
Pelvis	uncommon	**pelvic thrusting** (suggestive, not pathognomonic)
Eyes	usually **open** during the event	**closed**, often resisting opening
Awareness in bilateral motor activity	lost	**may be preserved** (recall of the event)
Duration	typically <2–3 min	**prolonged**, can last many minutes
Post-ictal state	confusion, drowsiness common	**no significant post-ictal confusion**; rapid reorientation
Emotional features	uncommon	**weeping**, distress during/after
Tongue bite	lateral border	tip, or absent
Serum prolactin (10–20 min post)	**rises** (esp. after tonic-clonic)	**normal** (no rise)

NEAD VS EPILEPTIC SEIZURE – THE DISCRIMINATING SIGNS

The columns line up the discriminators. None is fully pathognomonic in isolation; the diagnosis rests on the whole pattern and, decisively, on **video-EEG telemetry** capturing a typical event with no ictal EEG change.

◆ **Serum prolactin** – a **normal post-ictal prolactin** supports NEAD; a rise (roughly >2× baseline, sampled 10–20 min after the event) supports a generalised or complex partial seizure. A supportive test, *not* definitive: a normal level does not exclude epilepsy (it does not rise reliably after frontal or simple partial seizures), so it never replaces video-EEG.

■ **Video-EEG telemetry** – the **gold standard**: simultaneous video and EEG that captures a habitual attack and shows no ictal correlate. Resolves the diagnosis where history and prolactin leave doubt.

● MANAGEMENT

Delivery of the diagnosis is the intervention. Be **sensitive and non-confrontational**: the attacks are real and involuntary, not faked or "in the mind." Name it positively (a dissociative response to stress the brain has learned), avoid implying deception, validate the distress, and explain that this is treatable and that withdrawing unnecessary antiseizure drugs is part of recovery. Treatment is **psychological** (CBT-informed), with management of comorbid depression/anxiety/trauma and close liaison with neurology. Co-occurrence with genuine epilepsy is possible, which is why the diagnosis must be secure.

6 Antiseizure medications & the mind

Two directions to hold: how antiseizure drugs affect mood and cognition, and how psychotropics affect the seizure threshold. Both are heavily examined and clinically load-bearing.

Psychiatric & behavioural effects of antiseizure drugs

Drug	Psychiatric / cognitive effect
Levetiracetam	irritability, agitation, depression, anxiety ("levetiracetam rage"); pyridoxine may help; a frequent reason to switch
Valproate	mood-stabilising (anti-manic); also a migraine prophylactic. Teratogenic: avoid in women of child-bearing potential
Carbamazepine	mood-stabilising (esp. in mania/aggression); a strong enzyme inducer
Lamotrigine	mood-stabilising, with antidepressant/bipolar-depression efficacy; generally cognitively favourable; watch for rash/SJS
Topiramate	cognitive blunting, word-finding difficulty, psychomotor slowing, paraesthesiae; can also lower mood
Phenobarbital / vigabatrin	phenobarbital: sedation, depression, paradoxical hyperactivity in children; vigabatrin: depression/psychosis (and visual field loss)

● MNEMONIC

"Keppra makes you crabby; Topamax = Dopamax"

Levetiracetam (Keppra) → irritability/depression. **Topiramate (Topamax)** → cognitive slowing and word-finding difficulty ("Dopamax"). **Valproate, carbamazepine and lamotrigine** double as mood stabilisers.

Enzyme induction & interactions

▲ Enzyme inducers – **carbamazepine, phenytoin, phenobarbital** induce hepatic CYP450 and **lower plasma levels** of many psychotropics (antipsychotics, antidepressants, some benzodiazepines) and of oral contraceptives. Watch for therapeutic failure and contraceptive breakthrough.

▲ Valproate as an inhibitor – valproate *inhibits* metabolism and roughly **doubles lamotrigine levels** (raising rash/SJS risk): halve the lamotrigine dose and titrate slowly when co-prescribed. The opposite direction to the inducers.

Prescribing psychotropics in epilepsy: the seizure threshold

Direction	Agents	Note
Lower the threshold (use with caution)	bupropion (dose-dependent, highest risk), clozapine (dose-dependent), **high-dose TCAs**, chlorpromazine, maprotiline	avoid or use cautiously with EEG/level monitoring; clozapine may need valproate cover at higher doses
Relatively safe	SSRIs (and SNRIs), most newer antidepressants at therapeutic doses; haloperidol and most second-generation antipsychotics (except clozapine) at standard doses	SSRIs are first-line for depression in epilepsy

● CLASSIC TRAP

Bupropion and **clozapine** are the two psychotropics flagged hardest for lowering the seizure threshold (both dose-dependent); high-dose tricyclics follow. Conversely, **SSRIs are relatively safe** and may even raise the threshold – so the worry that "antidepressants cause seizures" does not justify leaving depression in epilepsy untreated. Untreated depression is the larger risk.

7 Management principles

The liaison brief: treat the psychiatric comorbidity properly, manage the suicide risk, optimise seizure control, and work alongside neurology rather than around it.

- **Treat the comorbidity** – **SSRIs are generally safe and first-line** for depression and anxiety in epilepsy (sertraline, citalopram/escitalopram favoured). Do not withhold antidepressants for fear of seizures; start low, go slow, monitor. CBT has good evidence and avoids drug interactions.
- **Address the suicide risk** – screen routinely (depression is under-treated and suicide risk is several-fold raised). Pay particular attention after epilepsy surgery and in temporal lobe epilepsy. Risk assessment is part of every review, not an afterthought.
- **Optimise seizure control** – review the antiseizure regimen as a possible driver of mood/behaviour (consider switching levetiracetam or topiramate where these are implicated). But beware **forced normalisation**: aggressive control can occasionally unmask psychosis, so monitor as seizures settle.
- **Liaison with neurology** – shared care is the model. Coordinate drug changes (interactions, enzyme induction, lamotrigine-valproate dosing), secure the diagnosis in NEAD via video-EEG before withdrawing antiseizure drugs, and manage the psychosocial burden (driving, employment, stigma) together.
- **Acute psychosis of epilepsy** – post-ictal psychosis is usually self-limiting and responds to a **short course of a low-dose antipsychotic** (and benzodiazepine cover); interictal (chronic) psychosis is managed like schizophrenia with a seizure-sparing agent (avoid clozapine where possible; haloperidol or a standard-dose atypical preferred). Treat ictal psychosis (non-convulsive status) as a seizure, not as primary psychosis.

HOLD THIS

SSRIs first-line for depression in epilepsy and they are safe. **Never under-treat** the depression or its suicide risk for fear of seizures. **Bupropion and clozapine** lower the threshold most. **Valproate / carbamazepine / lamotrigine** double as mood stabilisers. Manage in liaison with neurology.

QUICK-RECALL · DRILL THESE ONE-LINERS

- **Definitions:** seizure = a transient event; epilepsy = ≥2 unprovoked seizures >24 h apart (or 1 + high recurrence risk, or a syndrome). Status epilepticus = ≥5 min or no recovery between seizures.
- **ILAE 2017:** first split = onset (focal vs generalised). Focal graded by awareness: aware (simple partial), impaired awareness (complex partial), focal to bilateral tonic-clonic (secondary generalised). Generalised: absence, myoclonic, tonic-clonic, atonic, tonic.
- **Bidirectional:** epilepsy raises psychiatric risk *and* depression/psychosis precede epilepsy. ~1 in 3 have a psychiatric comorbidity.
- **Depression:** commonest and most under-treated comorbidity; predicts quality of life; suicide risk several-fold raised – screen actively.

★ **Psychoses (PIPI):** pre-ictal, ictal (= non-convulsive status, on EEG), post-ictal (commonest; lucid interval 1–6 days, self-limiting), interictal (chronic, schizophrenia-like). Forced normalisation (Landolt) / alternative psychosis = psychosis appears as the EEG normalises.

- **TLE:** epigastric/deja-vu aura, oro-alimentary & manual automatisms, post-ictal confusion. Geschwind (interictal): hyperreligiosity, hypergraphia, viscosity, altered (hypo)sexuality. Differentials: panic disorder, dissociation.
- **NEAD:** gradual onset, asynchronous/fluctuating movements, side-to-side head, pelvic thrust, eyes closed, awareness may be preserved, prolonged, no post-ictal confusion, weeping, **normal prolactin**. Gold standard = video-EEG. Manage sensitively, non-confrontationally; CBT.
- **Antiseizure drugs:** levetiracetam → irritability/depression; topiramate → cognitive blunting / word-finding difficulty; valproate, carbamazepine, lamotrigine = mood stabilisers. Carbamazepine/phenytoin/phenobarbital induce CYP450 (lower psychotropic & OCP levels); valproate doubles lamotrigine.
- **Threshold:** bupropion and clozapine lower it most (dose-dependent), then high-dose TCAs; SSRIs relatively safe and first-line.
- **Management:** treat the comorbidity (SSRIs/CBT), address suicide risk, optimise seizure control (watch forced normalisation), liaise with neurology. Post-ictal psychosis = short low-dose antipsychotic.

ONE-DAY REVISION · PAPER 4

Neuropsychiatry of Brain Disorders

When a brain lesion writes a psychiatric syndrome, the lesion's address predicts the phenotype. Learn the three frontal-subcortical circuits, then read each disorder as a variation on them. The recurring exam move: spot the red flag that says this depression, this psychosis, this personality change is organic.

CONCEPT · RULE · TRAP · KEY NUMBER · MNEMONIC

The colour tells you what kind of fact it is. Real scans are flagged where a labelled image would help; none are drawn here.

★ HIGH YIELD — TOP 5 IF NOTHING ELSE

1. Three frontal-subcortical circuits (DOA): Dorsolateral → dysexecutive, Orbitofrontal → disinhibited (Phineas Gage), Anterior cingulate → apathetic/abulic (akinetic mutism at the extreme); a lesion anywhere on the loop reproduces the frontal syndrome, so subcortical disease looks frontal.
2. Visual hallucinations, disorientation and clouding of consciousness are organic until proven otherwise; primary psychotic disorders give auditory hallucinations in clear consciousness, so a fluctuating disoriented patient has delirium, not schizophrenia.
3. Huntington's: chorea + cognitive decline + psychiatric disturbance with early high suicide risk that often precedes chorea; autosomal-dominant CAG repeat in *HTT* on chromosome 4, ≥40 fully penetrant, anticipation worse with paternal transmission, caudate atrophy.
4. Parkinson's psychosis is usually treatment-related (visual hallucinations) and impulse-control disorders track dopamine agonists, not levodopa; use quetiapine, clozapine or pimavanserin and never typicals or risperidone.
5. Post-stroke depression is the commonest sequel (~one-third of survivors): know Robinson's left-anterior-lesion hypothesis versus Carson's null meta-analysis showing no reliable lesion-location link; SSRIs are first line.

1 The principle and the circuits

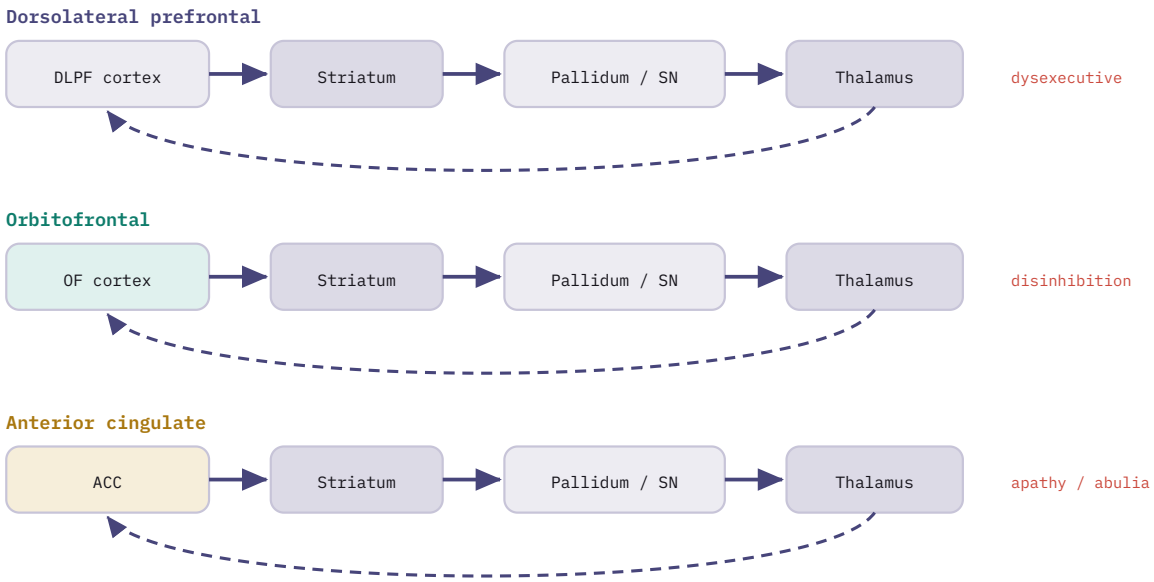
Two facts anchor the whole topic. First, focal brain lesions can produce **specific** psychiatric syndromes, not just generic "organicity." Second, the frontal lobe does not act alone: it runs through **parallel frontal-subcortical circuits** (Alexander, Cummings) that loop frontal cortex → striatum → globus pallidus / substantia nigra → thalamus → back to cortex. A lesion *anywhere* on a circuit can reproduce the "frontal" syndrome, which is why subcortical disease (Parkinson's, Huntington's, vascular, HIV) looks frontal.

The three behavioural frontal-subcortical circuits

Circuit	Syndrome when lesioned	Picture
Dorsolateral prefrontal (DLPFC)	Dysexecutive syndrome	poor planning, set-shifting, working memory, fluency; perseveration; concrete thinking. The "cognitive" frontal lobe.
Orbitofrontal (OFC)	Disinhibition (pseudopsychopathic)	impulsivity, tactlessness, facetiousness (*Witzelsucht*), socially inappropriate behaviour, emotional lability, poor judgment. Personality change with preserved intellect.

Circuit	Syndrome when lesioned	Picture
Anterior cingulate (ACC)	Apathy / abulia	reduced drive, flat motivation, poverty of speech and movement; at the extreme, **akinetic mutism** (awake, eyes open, but no spontaneous movement or speech).

THE THREE BEHAVIOURAL FRONTAL-SUBCORTICAL CIRCUITS



Each circuit runs cortex → striatum → pallidum/substantia nigra → thalamus → back to cortex (dashed return). DLPFC lesion = dysexecutive; orbitofrontal = disinhibited/pseudopsychopathic; anterior cingulate = apathetic/abulic, akinetic mutism at the extreme. A lesion anywhere on a loop mimics the frontal syndrome.

● MNEMONIC

"DOA" → Dorsolateral = Dysexecutive, Orbitofrontal = Disinhibited, Anterior cingulate = Apathetic

Three circuits, three D/A syndromes. The orbitofrontal picture is the classic **Phineas Gage** change: intelligence intact, the man "no longer Gage."

● CLASSIC TRAP

A "frontal" syndrome does **not** require a frontal-cortex lesion. Because the circuits pass through caudate, pallidum and thalamus, **subcortical disease mimics frontal pathology** (subcortical dementia: psychomotor slowing, apathy, dysexecutive deficits, with relatively spared cortical functions like language and praxis). This is why Parkinson's, Huntington's, HIV and vascular disease all present "frontally."

QUICK RULE

Localise the behaviour: **cognition flat → dorsolateral**; **conduct off → orbitofrontal**; **drive gone → cingulate**. Memory failure points temporal/limbic; the medial frontal/cingulate extreme is akinetic mutism.

2 Traumatic brain injury

TBI is the commonest cause of acquired neuropsychiatric disability in the young. Severity is graded on the acute injury; the psychiatric sequelae then unfold over months to years. The orbitofrontal and anterior temporal poles are most vulnerable to contusion (bony floor of the skull), so disinhibition and amnesia dominate.

Grading severity

Severity	GCS (initial)	Loss of consciousness	Post-traumatic amnesia (PTA)
Mild (concussion)	13–15	< 30 min	< 24 hours
Moderate	9–12	30 min – 24 h	1 – 7 days
Severe	3–8	> 24 h	> 7 days

◆ **PTA is the best single predictor** – the duration of post-traumatic amnesia (time from injury until continuous day-to-day memory returns) predicts outcome **better than the duration of unconsciousness**. Longer PTA, worse cognitive and psychiatric prognosis.

The neuropsychiatric sequelae

● **Cognitive impairment** – slowed processing, attention and memory deficits, dysexecutive problems. Most recovery occurs in the first 6–12 months.

● **Personality change** – the orbitofrontal pattern: disinhibition, irritability, impaired judgment, apathy or emotional lability. Often the most disabling for families.

▲ **Irritability and aggression** – common and distressing; episodic dyscontrol. Treat with environmental measures first; pharmacologically **SSRIs, beta-blockers (propranolol), anticonvulsants/mood stabilisers** and atypical antipsychotics are used. Avoid sedatives that worsen cognition.

● **Depression and anxiety** – depression follows TBI in roughly **a quarter to a half** over the first year; raises suicide risk. PTSD can coexist even when the event itself is amnesic. SSRIs are first line.

● **Psychosis** – less common; delusions and hallucinations can emerge, sometimes after a delay; post-traumatic epilepsy raises the risk.

■ **Post-concussion syndrome** – after mild TBI: **headache, dizziness, fatigue, poor concentration, irritability, insomnia, noise/light sensitivity**. Usually resolves in weeks to months; persistence is shaped by psychological and litigation factors. Reassurance and graded return are the core management.

Chronic traumatic encephalopathy (CTE)

◆ **CTE** – a progressive **tauopathy** from *repetitive* head impacts (boxers "dementia pugilistica," contact-sport athletes, military blast). Features: mood and behavioural change (depression, impulsivity, aggression, suicidality) preceding later cognitive decline and parkinsonism. **Diagnosis is currently only confirmed at post-mortem** (perivascular phosphorylated-tau at the depths of sulci).

● TRAP

A single severe TBI and repetitive mild TBI are different exposures. **CTE is a disease of repetitive impact**, not of one big bleed. And a clinical CTE label cannot yet be made in a living patient: the in-vivo construct ("traumatic encephalopathy syndrome") remains research-level. Do not diagnose CTE on history alone in an exam stem.

3 Stroke and cerebrovascular disease

Post-stroke depression (PSD)

◆ **Frequency** – the commonest psychiatric sequel of stroke: roughly **a third** of survivors (pooled prevalence about 30–33%), peaking in the first months to a year. It worsens rehabilitation, function and mortality, and is under-recognised.

- **The left-anterior-lesion hypothesis (Robinson)** – the classic claim that **left frontal / left basal ganglia** lesions, especially those *near the frontal pole*, carry the highest risk and severity of early depression.

▲ **The critique** – later meta-analyses (Carson, 2000, in *Lancet*) found **no reliable association between lesion location and depression**. Modern view: PSD is multifactorial (disability, social, psychological and biological factors), and the strict left-anterior rule is not robust. Know both the hypothesis and its rebuttal: that contrast is the marks.

- **Treatment** – SSRIs are first line and effective; they may also aid motor recovery. Nortriptyline has trial support. Routine prophylactic antidepressants are not standard.

Other post-stroke psychiatric syndromes

- **Post-stroke mania** – rare; classically linked to **right-hemisphere** lesions (right orbitofrontal, basotemporal, thalamus, caudate). Presents as secondary mania; treat with mood stabilisers/antipsychotics.
- **Post-stroke anxiety** – common, often comorbid with depression (generalised anxiety and post-stroke worry); under-treated.
- **Vascular cognitive impairment** – spans from mild vascular cognitive impairment to **vascular dementia**. Clues: stepwise decline, focal signs, gait disturbance early, executive and processing-speed deficits out of proportion to memory, plus vascular risk factors and white-matter change on imaging.

Pathological laughing and crying (pseudobulbar affect)

◆ **Pseudobulbar affect (PBA)** – **brief, stereotyped, involuntary outbursts of laughing or crying that are out of proportion to, or incongruent with, the mood**, and which the patient cannot control. Caused by disruption of corticobulbar / cortico-pontine-cerebellar pathways that normally inhibit the brainstem affect-motor centres. Seen in stroke, MS, ALS/motor neurone disease, TBI and dementia.

▲ **Not the same as depression** – the affect is dissociated from the underlying mood (a patient cries without feeling sad). This is the key discriminator from a true depressive episode, though the two can coexist.

■ **Treatment** – responds, often rapidly and at low dose, to **SSRIs or tricyclics**. In the US, **dextromethorphan-quinidine** is licensed specifically for PBA.

Pseudobulbar affect

Outburst is **brief, stereotyped, involuntary**; mood between episodes is normal or incongruent; patient distressed by the lack of control; responds to low-dose antidepressant.

Depressive episode

Sustained low mood with anhedonia, biological symptoms, cognitions of worthlessness; crying is **congruent** with felt sadness; needs a full antidepressant course.

4 Parkinson's disease and movement disorders

Parkinson's disease (PD): the psychiatric features

Non-motor symptoms drive much of PD disability, and several are **treatment-related**, which makes the management a balancing act between motor benefit and psychiatric cost.

Feature	Note
Depression	very common (around 35–40%); may **predate** the motor signs. SSRIs/SNRIs; pramipexole (D3 agonist) has antidepressant signal.
Anxiety	frequent, often with motor fluctuations ("off"-period anxiety/panic).

Feature	Note
Apathy	distinct from depression; loss of drive without sadness. Maps to the dopaminergic-cingulate circuit.
Psychosis	usually treatment-related: visual hallucinations (often well-formed, of people/animals) and delusions from dopaminergic drugs; also disease-intrinsic in advanced PD.
Impulse-control disorders	dopamine-agonist-driven: pathological gambling, hypersexuality, compulsive shopping, binge eating; also punding and dopamine dysregulation syndrome.
Dementia	up to ~80% over the long course (Parkinson's disease dementia); a dysexecutive, attentional, visuospatial profile with fluctuations.

■ **Managing PD psychosis** – first **reduce/withdraw the offending drug** (in reverse order: anticholinergics → amantadine → dopamine agonists → MAO-B/COMT → reduce levodopa last). If antipsychotic is needed, use **quetiapine or clozapine** (least motor worsening); **pimavanserin** (5-HT2A inverse agonist) is licensed where available. **Avoid typical antipsychotics and risperidone** (worsen parkinsonism). Cholinesterase inhibitors (rivastigmine) help PD dementia and its hallucinations.

● CLASSIC TRAP

Impulse-control disorders in PD are **iatrogenic**: they track **dopamine agonists** (pramipexole, ropinirole) far more than levodopa. The history of new-onset gambling or hypersexuality in a treated parkinsonian patient should prompt an agonist review, not a primary psychiatric label. Conversely, **visual hallucinations** are the cardinal "too much dopamine" sign and an organic red flag elsewhere.

Huntington's disease (HD)

◆ **The triad** – **chorea + cognitive decline + psychiatric disturbance**. Autosomal dominant; degeneration of the **caudate and putamen** (striatum), giving the subcortical/dysexecutive picture. Psychiatric features (depression, irritability, apathy, obsessionality, psychosis) and a **high suicide risk** often **precede** the chorea.

◆ **Genetics** – expanded **CAG trinucleotide repeat** in the *HTT* gene on **chromosome 4** (codes a polyglutamine tract in huntingtin). Normal < 27 repeats; **≥ 40** fully penetrant; 36–39 reduced penetrance. **Anticipation**: the repeat expands across generations (especially paternal transmission), so onset is earlier and disease more severe in successive generations.

● **Management** – symptomatic: chorea treated with **tetrabenazine / deutetrabenazine** (VMAT2 inhibitors; watch for depression) or antipsychotics; treat depression and psychosis directly; genetic counselling is central.

● MNEMONIC

"Hunting 4 a CAG"

Huntington's = chromosome **4**, **CAG** repeat, **anticipation** (worse each generation), caudate atrophy. Triad: chorea, cognition, psychiatric (with early suicide risk).

Wilson's disease (pointer)

● **Wilson's disease** – autosomal recessive copper accumulation (*ATP7B*, chromosome 13); a young patient with movement disorder plus personality change, mood or psychotic symptoms, Kayser-Fleischer rings and deranged liver function. It is the must-not-miss treatable cause. **Full work-up in the Metabolic and inherited disorders pack.**

5 Multiple sclerosis

MS is a demyelinating disease of young adults whose disseminated white-matter lesions readily produce neuropsychiatric symptoms; some are primary, some are reactive, and some are drug-induced.

◆ **Depression and suicide** – the commonest psychiatric feature: lifetime depression around **50%**, far above the general population, with an elevated **suicide risk**. Multifactorial (lesion load, inflammation, disability, and disease-modifying drugs). Screen actively; SSRIs are first line.

● **Pathological affect** – pseudobulbar affect (laughing/crying) occurs, as in other white-matter diseases.

▲ **Euphoria (*euphoria sclerotica*)** – the "classic" MS mood: an incongruous cheerfulness/optimism in the face of significant disability. It is actually **uncommon** and marks **advanced disease with heavy frontal white-matter and cognitive involvement**. Distinguish from mania and from PBA.

● **Cognitive impairment** – in up to half: a subcortical pattern with slowed processing, attention, working memory and word-finding; cortical functions relatively spared early.

■ **Iatrogenic effects** – **corticosteroids** (for relapses) can cause mood elevation, irritability, insomnia, even steroid psychosis or, on withdrawal, depression. Among disease-modifying therapies, **interferon-beta** carries a depression/flu-like-symptom warning (consider screening before and during); always ask whether a new mood change is drug-related.

● TRAP

The exam loves the contrast: depression is the *common* MS mood disturbance; **euphoria is the famous-but-rare** one, tied to advanced frontal disease. And before attributing a new depressive or manic picture to the MS itself, ask about **steroids and interferon-beta**.

6 Brain tumours and other lesions

Psychiatric symptoms can be the first or only manifestation of an intracranial mass. Location predicts the syndrome more than histology does; rate of growth matters too (a slow-growing tumour may produce isolated personality change with few hard signs).

Site	Psychiatric / behavioural picture
Frontal lobe	personality change (apathy or disinhibition by sub-region), poor judgment, executive failure; often few localising signs (the "silent" lobe) so a frontal tumour masquerades as "depression" or "late-onset psychosis."
Temporal lobe	complex partial seizures, deja vu / jamais vu, olfactory and gustatory hallucinations, fear/derealisation auras, psychosis, mood and memory change; medial-temporal lesions resemble a schizophrenia-like or affective picture.
Diencephalic / limbic (third ventricle, hypothalamus, thalamus)	amnesia, hypersomnia, endocrine and appetite change, apathy, sometimes a Korsakoff-like confabulatory amnesia.
Parietal / occipital	less "psychiatric": neglect, apraxia, visual field and perceptual deficits, complex visual hallucinations (occipital).

◆ **Clinical clues a tumour underlies the presentation** – new **headache (worse on waking, with vomiting), seizures, focal neurological signs, papilloedema, progressive cognitive decline, a markedly atypical or treatment-resistant psychiatric picture, and onset at an unusual age**. Any of these mandates neuroimaging.

- **Other lesions to keep in mind** – subdural haematoma (fluctuating confusion in the elderly/alcoholic after a minor fall), normal-pressure hydrocephalus (the triad: gait apraxia, urinary incontinence, dementia – "wet, wobbly, wacky"), and limbic/autoimmune (anti-NMDA-receptor) encephalitis presenting as acute psychosis with seizures and dyskinesias.

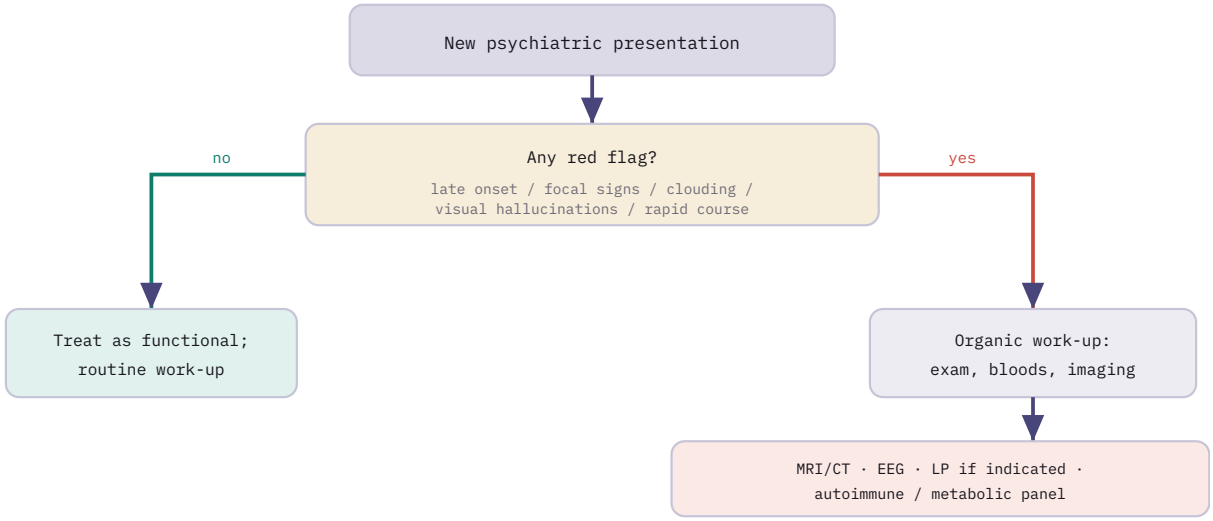
7 Red flags for an organic cause

The single most examinable skill: recognising when a "psychiatric" presentation is really a brain disorder. The flags below shift the prior toward organic and trigger investigation. None is individually specific; clustered, they are decisive.

THE RED FLAGS

Late or atypical age of onset (first psychosis after 40, first mania after 50) · **focal neurological signs** · **rapid or fluctuating progression** · **disorientation or clouding of consciousness** (think delirium, not functional) · **visual (rather than auditory) hallucinations** · **cognitive decline, headache, seizures, incontinence** · **no personal or family psychiatric history** · **poor response to standard treatment.**

TRIAGE LOGIC: IS THIS PRESENTATION ORGANIC?



Screen every new presentation for red flags. None present and history typical → treat as functional. Any flag → examine, take bloods, image, and escalate to EEG, lumbar puncture and autoimmune panels as indicated.

The investigations

Step	What and why
Bedside	full neurological exam, cognitive screen (MMSE/MoCA/ACE), fundoscopy for papilloedema, vitals, drug/alcohol history.
Bloods	FBC, U&E, LFT, calcium, glucose, **TFTs**, **B12/folate**, **HIV/syphilis serology**, ESR/CRP, autoantibodies; copper/caeruloplasmin if young (Wilson's); toxicology.
Imaging	**MRI** (preferred; better for tumour, demyelination, vascular and limbic change) or CT if MRI unavailable/urgent bleed.
Neurophysiology / CSF	**EEG** (epilepsy, encephalopathy, delirium slowing); **lumbar puncture** for infective, inflammatory and **autoimmune (anti-NMDA-R) encephalitis** when suspected.

● RULE

Visual hallucinations, disorientation and clouding of consciousness are organic until proven otherwise. Primary psychotic disorders give *auditory* hallucinations in clear consciousness; prominent *visual* hallucinations point to delirium, occipital/temporal lesions, Lewy body dementia, drug effects or withdrawal. Always test orientation: a fluctuating, disoriented patient has delirium, not schizophrenia.

QUICK-RECALL · DRILL THESE ONE-LINERS

★ **Circuits (DOA):** Dorsolateral = dysexecutive · Orbitofrontal = disinhibited/pseudopsychopathic (Phineas Gage) · Anterior cingulate = apathetic/abulic, akinetic mutism at the extreme. A lesion anywhere on the loop mimics a frontal syndrome (subcortical dementia).

- **TBI:** PTA duration is the best outcome predictor. Sequelae: cognitive, personality (orbitofrontal), irritability/aggression, depression (a quarter to half), PCS after mild TBI. CTE = repetitive-impact tauopathy, post-mortem diagnosis only.
- **Stroke:** post-stroke depression ~one-third; Robinson's left-anterior hypothesis vs Carson's null meta-analysis (know both); SSRIs first line. Post-stroke mania = right hemisphere. Vascular dementia = stepwise, dysexecutive, focal signs.
- **Pseudobulbar affect:** brief, involuntary, stereotyped laughing/crying, incongruent with mood; corticobulbar disruption; responds to low-dose SSRI/TCA or dextromethorphan-quinidine. Not depression.
- **Parkinson's:** depression (may predate motor signs), apathy, anxiety; psychosis is usually treatment-related (visual hallucinations); ICDs track **dopamine agonists**; PD dementia up to ~80%. Use quetiapine/clozapine/pimavanserin, never typicals/risperidone.
- **Huntington (Hunting-4-a-CAG):** chorea + cognition + psychiatric (early suicide risk); chromosome 4, CAG repeat ≥40 fully penetrant; anticipation, worse with paternal transmission; caudate atrophy. Wilson's = treatable copper differential (Metabolic pack).
- **MS:** depression common (~50%, raised suicide risk); euphoria famous-but-rare (advanced frontal disease); subcortical cognitive impairment; watch **steroids and interferon-beta** for drug-induced mood change.
- **Tumours:** frontal = personality change with few signs; temporal = seizures, hallucinations, psychosis; diencephalic = amnesia, endocrine. Clues: headache (worse on waking), seizures, focal signs, papilloedema, atypical/treatment-resistant picture → image.
- **Red flags (organic until proven otherwise):** late/atypical onset, focal signs, rapid/fluctuating course, disorientation/clouding, **visual** hallucinations, no psychiatric history, treatment resistance. Work-up: exam + cognitive screen, bloods (TFT, B12, HIV/syphilis, autoantibodies), MRI, then EEG and LP.

ONE-DAY REVISION · PAPER 4

CNS Infections & Psychiatry

A treatable organic cause must never be missed. Infections of the brain wear a psychiatric mask: psychosis, mania, cognitive decline, a personality that has quietly changed. The exam rewards the one who screens, images and taps the fluid before settling on a functional label. Hold the microbe, the syndrome it imitates, and the single test that confirms it.

CONCEPT · RULE · TRAP · KEY NUMBER · MNEMONIC

The colour tells you what kind of fact it is. Red flags, CSF profiles and the "great imitators" carry the marks.

★ HIGH YIELD TOP 5 IF NOTHING ELSE

1. New or atypical psychiatric symptoms with any neurological sign, fever, seizure, focal deficit, rapid cognitive change or fluctuating consciousness are organic until the screen is negative; diagnose the brain before the mind.
2. Anti-NMDA-receptor encephalitis: a young woman with a psychiatric prodrome who then develops seizures, orofacial dyskinesia, autonomic instability and reduced consciousness; antibodies target the NR1 subunit, hunt the ovarian teratoma, and catatonia plus antipsychotic intolerance should trigger the workup.
3. HSV encephalitis is the commonest sporadic fatal viral encephalitis (HSV-1, temporal-lobe predilection); start IV aciclovir on suspicion before confirmation and confirm by CSF HSV PCR.
4. Neurosyphilis: GPI = progressive dementia with grandiosity and psychosis, the Argyll Robertson pupil accommodates but does not react to light; a non-reactive serum VDRL does not exclude late neurosyphilis, TPHA/FTA-ABS stays positive for life, treat with penicillin.
5. In HIV with a focal mass: toxoplasmosis = multiple ring-enhancing lesions that respond to empirical therapy, primary CNS lymphoma = a single EBV-PCR-positive lesion that does not, and PML = white-matter lesions with no enhancement and no mass effect.

1 The principle: organic causes hide as psychiatry

A first psychotic episode, a late-onset mood change, a delirium with fever or seizures: each can be the surface of a CNS infection. The liaison rule is simple. Treat the brain as an organ before treating the mind as a story. Miss neurosyphilis, HSV encephalitis or autoimmune encephalitis and the damage becomes permanent or the patient dies.

Red flags that demand an organic screen

Red flag	Why it points organic
Acute or subacute onset	functional psychosis usually builds over weeks to months; days suggest a lesion or infection
Fever, headache, neck stiffness	meningoencephalitis until proven otherwise
Seizures, focal signs, movement disorder	cortical or limbic involvement; not a primary psychiatric feature

Red flag	Why it points organic
Fluctuating consciousness / delirium	the hallmark of an organic, not functional, state
Cognitive decline, rapid	infective or prion dementia outpaces neurodegenerative dementia
Atypical age or no family history	new psychosis after 40, or mania de novo in the elderly
Autonomic instability	limbic / brainstem involvement (classic in anti-NMDA encephalitis)
Poor response to standard treatment	antipsychotic-refractory psychosis should reopen the organic question

HOLD THIS

The organic screen is the safety net. **History → examination (including neurological) → bloods → imaging → CSF**. The cost of one missed lumbar puncture is a treatable encephalitis turned into a lifelong deficit.

● RULE

New-onset psychiatric symptoms with **any** neurological sign, fever, seizure or rapid cognitive change are organic until the screen is negative. “Diagnose the brain before you diagnose the mind.”

2 HIV and the nervous system (neuroAIDS)

HIV enters the CNS early, carried in by infected monocytes, and is itself neurotoxic. The result is a spectrum of cognitive disorder, direct mood and psychotic syndromes, drug effects, and the opportunistic infections that arrive once CD4 counts fall.

HIV-associated neurocognitive disorder (HAND)

A subcortical pattern: slowed processing, poor attention and memory, apathy and motor slowing, rather than the cortical aphasia/agnosia of Alzheimer disease. Graded by severity.

Stage	Cognition	Function
ANI (asymptomatic neurocognitive impairment)	impaired on testing (≥1 SD in ≥2 domains)	everyday function preserved
MND (mild neurocognitive disorder)	impaired on testing	mild interference with daily activities
HAD (HIV-associated dementia)	marked impairment (≥2 SD)	marked functional disability; the old “AIDS dementia complex”

- **Pattern** – HAND is a **subcortical dementia**: psychomotor slowing, executive and memory difficulty, apathy. Combination antiretroviral therapy (cART) has made severe HAD rare, but milder ANI/MND persist.
- **Frascati criteria** – the standard staging of HAND into ANI, MND and HAD by the degree of cognitive deficit (SD on testing) and the degree of functional impairment.

HIV mania and depression

- **HIV mania** – mania emerging late in HIV, with low CD4 and cognitive impairment, often with irritability and psychomotor slowing rather than the classic elation. Distinguish from earlier-stage mania (which behaves more like primary bipolar disorder).
- **Depression** – the commonest psychiatric disorder in HIV; multifactorial (the diagnosis, the neuropathology, social stress). Raises non-adherence and worsens outcomes; screen and treat actively.

Neuropsychiatric effects of antiretrovirals

▲ **Efavirenz** – the standout offender. Vivid dreams, insomnia, dizziness, dysphoria, and rarely psychosis or suicidal ideation; typically early and often settling, but a recognised reason to switch agents. Crosses the radar of every exam answer on ART side effects.

The major opportunistic infections (low CD4)

Infection	CD4 / clue	Imaging signature	Confirm
Cerebral toxoplasmosis	CD4 <100; commonest focal mass lesion	multiple ring-enhancing lesions, basal ganglia	serology + response to empirical anti-toxoplasma therapy
Cryptococcal meningitis	CD4 <100; subacute headache, raised ICP	often non-specific	CSF India ink, cryptococcal antigen (CrAg)
PML (progressive multifocal leukoencephalopathy)	JC virus; CD4 <200	multifocal white-matter lesions, no enhancement, no mass effect	CSF JC virus PCR
Primary CNS lymphoma	EBV-driven; CD4 <50	usually single enhancing periventricular lesion	biopsy; EBV PCR + thallium SPECT support

● CLASSIC TRAP

Toxoplasmosis vs CNS lymphoma in an HIV patient with a mass lesion: toxoplasmosis is typically *multiple* ring-enhancing lesions and improves on empirical anti-toxoplasma therapy; lymphoma is typically a *single* lesion that does not respond and is EBV-PCR positive. The trial of treatment is part of the diagnostic algorithm. PML is the one that is **not** enhancing and has **no** mass effect.

● MNEMONIC

"Toxo Two, Lymphoma Lone"

Toxoplasmosis = multiple ring lesions; primary CNS lymphoma = a single lesion. PML = white matter, no ring, no mass.

3 Neurosyphilis: the great imitator

Tertiary *Treponema pallidum* infection of the CNS, appearing years to decades after primary infection. Historically it filled the asylums and gave psychiatry one of its first proofs that a mental disorder could have a microbial cause. It mimics almost any psychiatric or neurological picture, hence "the great imitator."

General paresis of the insane (GPI)

◆ **GPI** – a parenchymatous neurosyphilis presenting as a **progressive dementia** with **psychosis, grandiosity** (classic grandiose delusions) and personality change, plus dysarthria, tremor and (late) seizures. A textbook organic cause of dementia and of grandiose presentations.

● **Tabes dorsalis** – degeneration of the **dorsal columns** and dorsal roots: sensory ataxia, lightning pains, loss of proprioception and reflexes, a positive Romberg sign, and Charcot joints.

● **Argyll Robertson pupil** – the small, irregular pupil that **accommodates but does not react to light** (light-near dissociation). The "prostitute's pupil" mnemonic: accommodates but does not react.

● MNEMONIC

"PARESIS"

Personality, **A**ffect, **R**eflexes (hyperactive), **E**ye (Argyll Robertson), **S**ensorium (illusions, delusions, hallucinations), **I**ntellect (decline in memory, judgement), **S**peech (slurred). The classic features of general paresis.

Diagnosis

Test	Type	Role
VDRL / RPR	non-treponemal (serum)	screening; titre tracks activity and falls with treatment; can give false positives
TPHA / FTA-ABS	treponemal (serum)	confirmatory; stays positive for life
CSF examination	cerebrospinal fluid	raised lymphocytes and protein; CSF VDRL is specific (but insensitive) for neurosyphilis

■ **Treatment** – **penicillin** (intravenous benzylpenicillin / aqueous crystalline penicillin G for neurosyphilis). Watch for the **Jarisch-Herxheimer reaction** (fever, worsening symptoms hours after the first dose, from treponeme lysis).

● TRAP

A **non-reactive serum VDRL does not exclude neurosyphilis** in late disease (it can be negative). The treponemal test (TPHA/FTA-ABS) stays positive lifelong and so cannot tell active from treated infection. For activity and treatment response, follow the non-treponemal titre. Note the historical weight: **Noguchi and Moore** demonstrated the spirochaete in the brain of GPI patients, anchoring the "organic cause of insanity" principle.

4 Autoimmune & limbic encephalitis

Antibody-mediated encephalitis is the modern reason every "first-episode psychosis" deserves a second look. The antibodies target neuronal surface receptors; the picture starts psychiatric and then declares itself neurologically. Immunotherapy and tumour removal can reverse it, which is why it is high-yield.

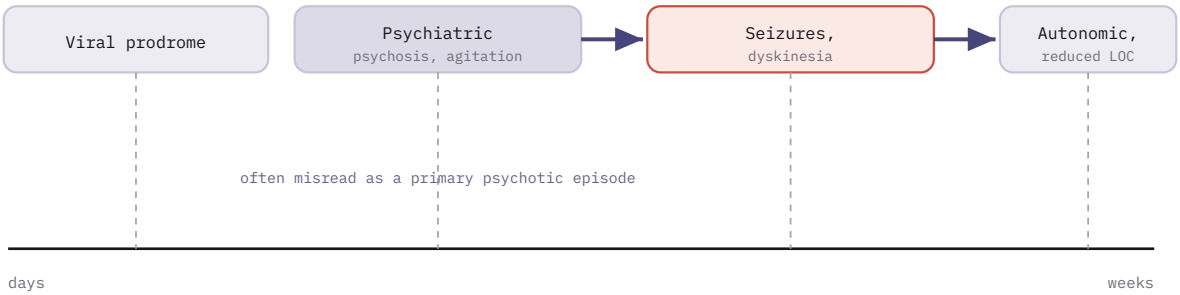
Anti-NMDA-receptor encephalitis

● **The classic story** – a **young woman** with a **psychiatric prodrome** (anxiety, psychosis, agitation, bizarre behaviour), then **seizures**, **orofacial / limb dyskinesia**, **autonomic instability**, and a **reduced level of consciousness**. Antibodies are against the **NR1 subunit of the NMDA receptor**.

◆ **Ovarian teratoma** – the classic tumour association. In a young woman, search for it; removal plus immunotherapy drives recovery. (Many cases, especially in men and children, are non-paraneoplastic.)

● **Other antibody encephalitides** – **anti-LGI1** (faciobrachial dystonic seizures, hyponatraemia, amnesia, older patients), **anti-CASPR2** (Morvan syndrome, neuromyotonia), **anti-GABA-B** (seizures, small-cell lung cancer), and the older **paraneoplastic** antibodies against intracellular antigens (anti-Hu, anti-Ma2) that respond less well.

ANTI-NMDA-RECEPTOR ENCEPHALITIS: THE TYPICAL EVOLUTION



A viral-like prodrome gives way to a psychiatric phase (often mistaken for first-episode psychosis), then seizures and orofacial dyskinesia, then autonomic instability and a falling level of consciousness. Recognising the trajectory is the diagnosis.

CENTREPIECE: when to suspect autoimmune encephalitis behind a psychiatric presentation

Red flag	What it looks like	Weight
Rapid progression	psychosis evolving over days to a few weeks, not months	strong
Seizures	new seizures with a psychiatric presentation, especially faciobrachial dystonic (LGI1)	strong
Movement disorder	orofacial / limb dyskinesia, catatonia, dystonia	strong
Autonomic instability	labile BP/HR, hyperthermia, hypoventilation	strong
Reduced / fluctuating consciousness	not a feature of primary psychosis	strong
Decreased speech / mutism	progressive language breakdown, echolalia	moderate
Autonomic or focal neuro signs	any focal deficit alongside the psychiatric picture	moderate
Headache / hyponatraemia	hyponatraemia is a clue to LGI1	moderate
Antipsychotic intolerance	severe or unexpected reaction (neuroleptic sensitivity)	moderate

INVESTIGATE WHEN FLAGGED

MRI brain (medial temporal T2/FLAIR hyperintensity in limbic encephalitis), **EEG** (slowing, the "extreme delta brush" in anti-NMDA), **CSF** (lymphocytic pleocytosis, oligoclonal bands), and **serum + CSF autoantibody panel**. Screen for the associated tumour.

● CLASSIC TRAP

A young woman admitted as "acute psychosis" who then develops seizures, orofacial dyskinesia and autonomic storms is anti-NMDA-receptor encephalitis until disproved. Do not anchor on the psychiatric label. **Catatonia** in this setting should trigger the autoimmune workup, and these patients are often intolerant of antipsychotics.

5 Other infections relevant in India

Herpes simplex encephalitis (HSE)

▲ HSV encephalitis – the commonest sporadic fatal viral encephalitis; HSV-1 with a predilection for the **temporal lobes** and orbitofrontal cortex. Fever, headache, confusion, seizures, behavioural change and aphasia. A **neurological emergency**: start **intravenous aciclovir** on suspicion, before

confirmation, because delay costs brain.

- **Sequelae** – survivors often have **amnesia** (medial temporal damage), personality and behavioural change, and may show a **Kluver-Bucy-like** picture (placidity, hyperorality, hypersexuality). Confirm by CSF **HSV PCR**; MRI shows temporal-lobe change. *(Real MRI/EEG images would belong here.)*

Tuberculous and bacterial meningitis

- **Tuberculous meningitis (TBM)** – subacute; in India a leading cause. Basal meningitis with cranial-nerve palsies, hydrocephalus and stroke; can present as a confusional state or apathy. CSF: high protein, low glucose, lymphocytic, raised pressure; **may form a fibrin web** on standing.
- **Acute bacterial meningitis** – rapid fever, headache, neck stiffness, photophobia and altered sensorium; a true emergency. CSF: **neutrophilic**, high protein, low glucose, high pressure. Delirium is the usual psychiatric face.

Neurocysticercosis (NCC)

- **Neurocysticercosis** – larval *Taenia solium* cysts in the brain; a **very common cause of seizures in India** and the developing world. New-onset seizures, headache, and at times psychiatric symptoms or a focal deficit. Imaging: cysts at various stages, often a **calcified nodule with a scolex**. A core differential for adult-onset seizures and for ring-enhancing lesions.

TRAP

A single ring-enhancing lesion in an Indian patient with new seizures is more often **neurocysticercosis** (or tuberculoma) than tumour. In an HIV patient the same picture shifts toward **toxoplasmosis** or lymphoma. Context (HIV status, geography) reorders the differential.

Japanese encephalitis (JE)

- **Japanese encephalitis** – a mosquito-borne **flavivirus** endemic to rural Asia including parts of India; the leading cause of epidemic viral encephalitis in the region. Fever, reduced consciousness, seizures and a **parkinsonian / movement-disorder** picture from **thalamic** and basal-ganglia involvement. Survivors carry cognitive, behavioural and motor sequelae. Vaccine-preventable.

6 Prion disease: Creutzfeldt-Jakob disease

A transmissible misfolded protein (PrP). The psychiatric relevance is a **rapidly progressive dementia** that can open with mood, behavioural or psychotic change before the neurology becomes unmistakable. Always invariably fatal.

Form	Onset	Opening features	Marker
Sporadic CJD (commonest)	older adults (~60s)	rapid dementia + myoclonus; ataxia, visual signs	EEG periodic complexes
Variant CJD (bovine link)	younger adults	prominent psychiatric onset (depression, anxiety, withdrawal), then ataxia, dementia	MRI pulvinar sign

- **Characteristic findings** – **EEG**: periodic sharp-wave / triphasic complexes (sporadic CJD). **MRI**: cortical ribboning and basal-ganglia DWI hyperintensity; the **pulvinar sign** (posterior thalamus) in variant CJD. CSF: **14-3-3 protein** and RT-QuIC support the diagnosis. *(Cross-reference the Dementias pack for the rapidly progressive dementia workup.)*

Real image placeholder · CJD: EEG periodic complexes and MRI cortical ribboning / pulvinar sign. Not drawn (no real EEG/radiology in schematic SVG).

MNEMONIC

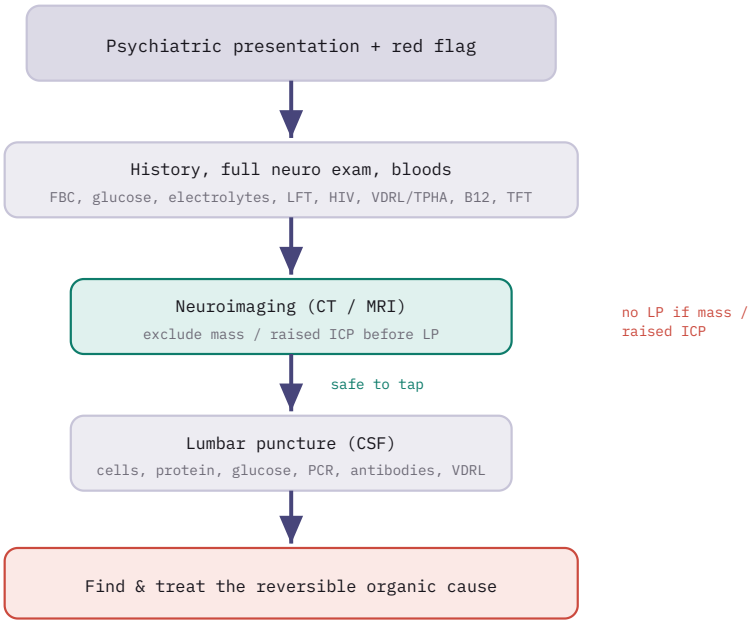
“Rapid Dementia + Myoclonus = think CJD”

A dementia advancing over weeks to months with myoclonus and a startle response, periodic EEG complexes, and 14-3-3 in CSF. Variant CJD opens psychiatrically in a younger patient.

7 The approach: image, tap, find the reversible cause

When the red flags fire, the workup follows an order. Imaging first (to exclude a mass and make the tap safe), then the lumbar puncture, then the targeted tests the picture demands.

THE ORGANIC-SCREEN DECISION FLOW



Red flags trigger the screen. Bloods and imaging come before the lumbar puncture; imaging also excludes a mass lesion or raised pressure that would make the tap dangerous. The CSF then carries the targeted infective and autoimmune tests.

When to image and when to tap

- **Neuroimaging** – for any focal sign, seizure, papilloedema, immunocompromise, reduced consciousness, or before LP when raised intracranial pressure or a mass lesion is possible. CT excludes bleed/mass quickly; MRI is more sensitive for encephalitis, limbic change and demyelination.
- **Lumbar puncture** – the central test for meningitis, encephalitis, neurosyphilis and autoimmune encephalitis. **Image first** if there is any sign of a mass or raised ICP, to avoid coning. Send the antibody and PCR tests on CSF, not just serum.

CSF profile basics

Cause	Cells (predominant)	Protein	Glucose
Bacterial	neutrophils (high)	high	low
Viral / encephalitis	lymphocytes	normal or mildly high	normal
Tuberculous	lymphocytes	high	low
Fungal (cryptococcal)	lymphocytes	high	low

Cause	Cells (predominant)	Protein	Glucose
Autoimmune	lymphocytes (mild) or normal	normal or mildly high	normal

HOLD THIS

Low CSF glucose narrows it to **bacterial, tuberculous or fungal**. Neutrophils = bacterial; lymphocytes with low glucose = TB or fungal; lymphocytes with normal glucose = viral or autoimmune. The reversible cause is the prize: **find it, treat it, and the psychiatry often lifts with it.**

● OVERRIDING RULE

The single principle behind this whole topic: in any atypical psychiatric presentation, the question is not "which functional diagnosis" but "have I excluded a treatable organic one." HSV encephalitis, neurosyphilis and autoimmune encephalitis are the ones you cannot afford to miss, because each is reversible if caught.

QUICK-RECALL · DRILL THESE ONE-LINERS

★ **Principle:** new/atypical psychiatric symptoms + fever, seizure, focal sign, rapid cognitive change or fluctuating consciousness = organic until the screen is negative. Diagnose the brain before the mind.

- **HIV / HAND:** subcortical dementia, staged by Frascati into ANI → MND → HAD. HIV mania = late, low CD4. **Efavirenz** = vivid dreams, dysphoria, rarely psychosis.
- **HIV opportunistic:** toxoplasmosis = multiple ring lesions (responds to empirical therapy); CNS lymphoma = single lesion, EBV PCR; PML = JC virus, white matter, no enhancement; cryptococcus = India ink / CrAg.
- **Neurosyphilis:** the great imitator. **GPI** = dementia + grandiosity + psychosis. Tabes dorsalis = dorsal columns. **Argyll Robertson** pupil = accommodates, not reacts. VDRL/RPR (activity) + TPHA (lifelong). Treat with **penicillin**.
- **Anti-NMDA-receptor encephalitis:** young woman → psychiatric prodrome → seizures, orofacial dyskinesia, autonomic instability, reduced consciousness. Hunt the **ovarian teratoma**. EEG = extreme delta brush. Catatonia + antipsychotic intolerance = workup.
- **Limbic encephalitis others:** LGI1 (faciobrachial dystonic seizures, hyponatraemia), CASPR2 (Morvan), GABA-B (SCLC).
- **HSV encephalitis:** temporal lobe, amnesia, behavioural change; an emergency – **IV aciclovir on suspicion**; confirm by CSF HSV PCR.
- **India:** TBM (basal, low glucose, lymphocytic, fibrin web), neurocysticercosis (commonest cause of adult-onset seizures; calcified cyst + scolex), Japanese encephalitis (flavivirus, thalamic, parkinsonism).
- **Prion / CJD:** rapidly progressive dementia + **myoclonus**. Sporadic = EEG periodic complexes; variant = psychiatric onset, MRI pulvinar sign; CSF 14-3-3 / RT-QuIC.
- **Approach:** red flag → bloods → image (before LP if mass/raised ICP) → LP with PCR + antibodies + VDRL. Low glucose = bacterial/TB/fungal; neutrophils = bacterial; lymphocytes + normal glucose = viral/autoimmune.

ONE-DAY REVISION · PAPER 4

Metabolic, Endocrine & Nutritional Neuropsychiatry

The psychiatric presentations that are not psychiatric. Every endocrine gland, every vitamin, every deranged electrolyte can wear the mask of depression, mania, anxiety or psychosis. The exam reward is the same as the ward reward: screen for the body before you settle on the mind. Learn the disturbance-to-syndrome map, the single confirming test for each, and the one emergency rule (thiamine before glucose) that saves a brain.

● CONCEPT ● RULE ● TRAP ● KEY NUMBER ● MNEMONIC

The colour tells you what kind of fact it is. The master table in section 1 is the 10-mark spine; every later section fills one of its rows.

★ HIGH YIELD TOP 5 IF NOTHING ELSE

1. In any malnourished or alcohol-dependent patient, give parenteral thiamine BEFORE (or with) glucose; a glucose load first can precipitate Wernicke encephalopathy, and treat on suspicion without waiting for the full triad.
2. Wernicke triad = confusion, ophthalmoplegia and ataxia (full triad in only a minority); Korsakoff is the irreversible sequel of anterograde amnesia with confabulation from mammillary body and dorsomedial thalamic lesions.
3. Wilson's disease (autosomal recessive, ATP7B) is the treatable young-person mimic; diagnostic triad = low caeruloplasmin, raised 24-hour urinary copper, Kayser-Fleischer ring, treated with chelation (penicillamine or trientine) plus zinc.
4. Trap: endogenous cortisol excess (Cushing's) most often causes depression, whereas exogenous steroids most often cause early euphoria or hypomania swinging to depression on longer courses; TSH is the single best screen for thyroid disease, and apathetic hyperthyroidism in the elderly looks depressed yet is biochemically overactive.
5. Acute intermittent porphyria = abdominal pain, autonomic instability, neuropathy and psychosis with urine that darkens on standing and raised urinary PBG; barbiturates are the contraindicated precipitant, and in hyponatraemia correct sodium slowly to avoid central pontine myelinolysis.

1 The principle & the organic work-up

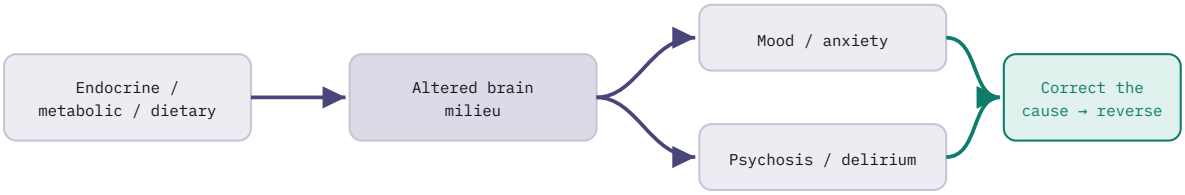
A new psychiatric syndrome is not automatically a primary psychiatric illness. Endocrine, metabolic and nutritional derangements **cause** mood, anxiety and psychotic syndromes, and most are reversible if caught. Red flags that should push you to screen the body: **late or atypical onset**, no family history, **cognitive changes** out of proportion, fluctuating course, prominent physical symptoms, poor response to standard treatment, and any **delirium**.

The baseline organic screen

■ **First-line bloods** – FBC, electrolytes, urea & creatinine, glucose, calcium, liver function, and **TSH**. These pick up most common reversible mimics cheaply.

■ **Second-line / targeted** – B12 and folate, HbA1c, magnesium and phosphate, **serum caeruloplasmin** (Wilson's in the young), morning cortisol or dexamethasone suppression (Cushing's), and **urinary porphobilinogen** in suspected acute porphyria. Add neuroimaging and EEG where indicated.

HOW A BODILY DISTURBANCE BECOMES A PSYCHIATRIC SYNDROME



hormones, glucose, electrolytes, toxins, vitamins all shift neuronal function

The same disturbance can surface as mood, anxiety, psychosis or delirium. Because the lesion is bodily, correcting the cause can reverse the syndrome. This is why the screen comes first.

Master table: disturbance → classic psychiatric picture

Disturbance	Classic psychiatric picture	Confirming test
Hypothyroidism	depression, cognitive slowing, "myxoedema madness" psychosis	↑ TSH, low free T4
Hyperthyroidism	anxiety, agitation, mania; *apathetic* in the elderly	↓ TSH, ↑ free T4
Hyperparathyroidism	depression, "psychic moans", fatigue, cognitive impairment	↑ calcium, ↑ PTH
Cushing's syndrome	**depression** (most common), also mania, psychosis	↑ cortisol; failed dexamethasone suppression
Addison's disease	apathy, fatigue, depression, irritability	↓ cortisol; short Synacthen test
Phaeochromocytoma	**paroxysmal** panic-like episodes with headache, palpitations, sweating	↑ plasma / urinary metanephrines
Wilson's disease	behaviour / personality change, psychosis, mood lability in the **young**	↓ caeruloplasmin, ↑ urinary copper, KF ring
Acute intermittent porphyria	anxiety, psychosis, delirium with abdominal pain & neuropathy	↑ urinary **PBG** / ALA; urine darkens on standing
Thiamine (B1) deficiency	Wernicke (confusion, ophthalmoplegia, ataxia); Korsakoff amnesia	clinical; response to parenteral thiamine
B12 / folate deficiency	dementia, depression, psychosis, neuropathy (SACD)	↓ B12 / folate, ↑ MCV, ↑ homocysteine
Niacin (B3) deficiency	pellagra: dementia (the third D)	clinical; response to niacin
Hepatic encephalopathy	fluctuating consciousness, delirium, asterixis	↑ ammonia; clinical (West Haven grade)
Hyponatraemia	confusion, lethargy; seizures if severe	↓ sodium; urine & serum osmolality

HOLD THIS

Screen **TSH, calcium, glucose, B12, sodium, LFTs** in any atypical, late-onset or treatment-resistant presentation. The cheapest blood test can undo the most disabling "psychiatric" diagnosis.

2 Thyroid & parathyroid

Thyroid

State	Psychiatric picture	The trap
Hypothyroidism	depression, psychomotor & cognitive slowing, low energy; in severe cases **"myxoedema madness"** – a psychosis with paranoia, hallucinations or agitation	mimics a primary depression or dementia; reversible with thyroxine
Hyperthyroidism	anxiety, restlessness, irritability, insomnia, agitation; can reach **mania** or a toxic psychosis	in the elderly it can present as **apathetic hyperthyroidism**: withdrawn, flat, depressed-looking, not anxious

■ **Screen with TSH** – **TSH is the single best screening test**. A raised TSH points to hypothyroidism, a suppressed TSH to hyperthyroidism; confirm with free T4. Thyroid disease is among the most common reversible causes of a mood disorder, so a TSH belongs in every affective work-up.

● CLASSIC TRAP

Apathetic hyperthyroidism reverses the expected picture: an older patient who looks depressed, slowed and withdrawn, yet is biochemically *over*active. If you anchor on "hyperthyroid = anxious and agitated", you will miss it. Always check the TSH, not the bedside impression.

Parathyroid & calcium

● **Hyperparathyroidism (hypercalcaemia)** – the classic teaching line is **"bones, stones, abdominal groans and psychic moans"**. The psychiatric component (the *psychic moans*) is depression, lassitude, anxiety, irritability, cognitive impairment and, at high calcium, delirium or psychosis. Check the **serum calcium**.

● **Hypocalcaemia** – the mirror image: anxiety, irritability and depression, with neuromuscular irritability (perioral and digital paraesthesia, carpopedal spasm; Chvostek and Trousseau signs). Severe acute drops can precipitate seizures or a confusional state.

● MNEMONIC

"Bones, Stones, abdominal Groans & psychic Moans"

The four organ systems of hypercalcaemia. The last, *psychic moans*, is the examinable psychiatric clue: depression and cognitive change in a patient with a high calcium. High calcium slows; low calcium irritates.

3 Adrenal & pituitary

Disorder	Hormone state	Psychiatric picture
Cushing's syndrome	cortisol **excess**	**depression most common** (in the majority); also mania, anxiety, irritability, cognitive impairment, psychosis
Addison's disease	cortisol **deficiency**	apathy, fatigue, depression, irritability, social withdrawal; rarely psychosis or delirium in crisis
Phaeochromocytoma	**paroxysmal** catecholamine surges	discrete **panic-like attacks**: anxiety, headache, palpitations, sweating, tremor, pallor – with raised blood pressure

● **Cushing's** – chronic cortisol excess. **Depression is the commonest psychiatric feature** and can precede the physical signs (central obesity, striae, hypertension, proximal myopathy). Mood usually improves as cortisol normalises after treatment. Confirm with elevated cortisol and a failed dexamethasone suppression test.

● **Addison's** – chronic cortisol (and aldosterone) deficiency. The psychiatric face is hypoactive: apathy, fatigue and depression, easily mistaken for a primary depression. Look for the physical clues (hyperpigmentation, postural hypotension, hyponatraemia, weight loss). An **Addisonian crisis** can present as acute confusion.

▲ **Phaeochromocytoma** – the great mimic of **panic disorder**. The attacks are *paroxysmal* and stereotyped, often with marked hypertension, headache and pallor between which the patient is well. Suspect it when "panic attacks" come with severe hypertension or a headache; confirm with plasma or urinary metanephrines.

Exogenous corticosteroids

■ **Steroid-induced mood change** – prescribed glucocorticoids commonly cause mood disturbance. Effects are **dose-related**: higher doses carry higher risk. Most often **euphoria or hypomania early**, and **depression with longer or higher-dose courses**; insomnia, irritability and anxiety are frequent.

▲ **Steroid psychosis** – at high doses a frank psychosis or severe mood episode (the older umbrella term "steroid psychosis") can emerge, usually in the first weeks. It typically resolves on lowering or stopping the steroid; antipsychotics are used short-term. Beware: **abrupt withdrawal** of steroids can also precipitate depression and fatigue.

● TRAP

Endogenous cortisol **excess** (Cushing's) most often causes **depression**, but exogenous steroids given as a drug most often cause an early **euphoria / hypomania**, swinging to depression with longer courses. Same hormone, different commonest presentation. Both are dose-related and both can reach psychosis.

4 Wilson's disease: the great young mimic

Wilson's disease (hepatolenticular degeneration) is an **autosomal recessive** defect of copper transport (the **ATP7B** gene) causing copper to accumulate in the liver, brain and cornea. It is the must-not-miss organic cause of new psychiatric or behavioural symptoms in a **young person**, because it is treatable and otherwise progressive.

Psychiatric onset (a substantial minority)

A meaningful proportion present **first to psychiatry**: personality and behaviour change, irritability, impulsivity, disinhibition, mood disorder (depression or, less often, mania), or frank psychosis. Cognitive decline and falling school or work performance are common. Psychiatric symptoms can **precede** the neurological and hepatic signs.

Neurological & hepatic signs

Tremor (classically a coarse "wing-beating" tremor), **dystonia, dysarthria, drooling, parkinsonism**, clumsiness and gait disturbance; the "risus sardonicus" fixed smile. Hepatic: chronic hepatitis, cirrhosis or acute liver failure. Onset usually in the teens to thirties.

The Kayser-Fleischer ring

◆ **Kayser-Fleischer ring** – a **golden-brown to greenish ring** of copper deposited in **Descemet's membrane at the corneal margin (limbus)**. It is best seen on slit-lamp examination, appearing first at the upper and lower poles of the cornea. It is almost always present when there are neurological signs, and it fades with treatment. (Described in words only here; do not picture it.)

The diagnostic triad

Test	Result in Wilson's	Why
Serum caeruloplasmin	low	the main copper-carrying protein is reduced
24-hour urinary copper	raised	free copper spills into the urine

Test	Result in Wilson's	Why
Kayser-Fleischer ring	present	corneal copper deposition (slit-lamp)

Supporting findings: low serum total copper (but raised *free* copper), raised hepatic copper on biopsy, and ATP7B mutation testing. MRI may show the **"face of the giant panda"** sign in the midbrain.

■ **Treatment** – lifelong removal of copper. **Copper chelation** with **penicillamine** or **trientine**, and/or **zinc** (which blocks intestinal copper absorption), plus a low-copper diet. Started early it can reverse or arrest the disease; untreated it is fatal.

● CLASSIC TRAP

Any young person with new psychosis, personality change or a movement disorder – especially with deranged liver function – needs a **serum caeruloplasmin** and a slit-lamp exam. Wilson's is one of the few treatable, reversible causes of psychosis, and missing it is a known examiner favourite. A normal caeruloplasmin does not fully exclude it, so pursue urinary copper if suspicion is high.

5 Porphyria

Acute intermittent porphyria (AIP) is the classic porphyria that mimics psychiatric and neurological disease. It is an **autosomal dominant** defect in haem synthesis (porphobilinogen deaminase deficiency) producing acute, episodic attacks; it is commoner in women and presents in early adulthood.

The attack

● **Abdominal & autonomic** – severe, poorly localised **abdominal pain** with no surgical findings, vomiting and constipation; autonomic instability with **tachycardia and hypertension**. Hyponatraemia is common.

● **Neurological** – a **peripheral (motor) neuropathy**, sometimes progressing to weakness; seizures can occur.

● **Psychiatric** – anxiety, restlessness, insomnia, depression, and in attacks an acute **psychosis or delirium** with confusion and hallucinations. The psychiatric features come and go with the attacks.

◆ **The urine sign** – the urine may be normal when passed but **darkens to a port-wine / reddish-brown colour on standing** in light, as porphobilinogen oxidises. Diagnosis: raised urinary **porphobilinogen (PBG)** and ALA during an attack.

● CLASSIC TRAP

Barbiturates are the textbook precipitant and are contraindicated. Other triggers: many anticonvulsants (phenytoin, carbamazepine), sulphonamides, alcohol, the oral contraceptive and other sex steroids, fasting, infection and stress. The trap is giving an enzyme-inducing drug to a "psychiatric" patient and worsening the attack. Manage with **haem arginate / haematin** and high carbohydrate intake, and remove the trigger.

● MNEMONIC

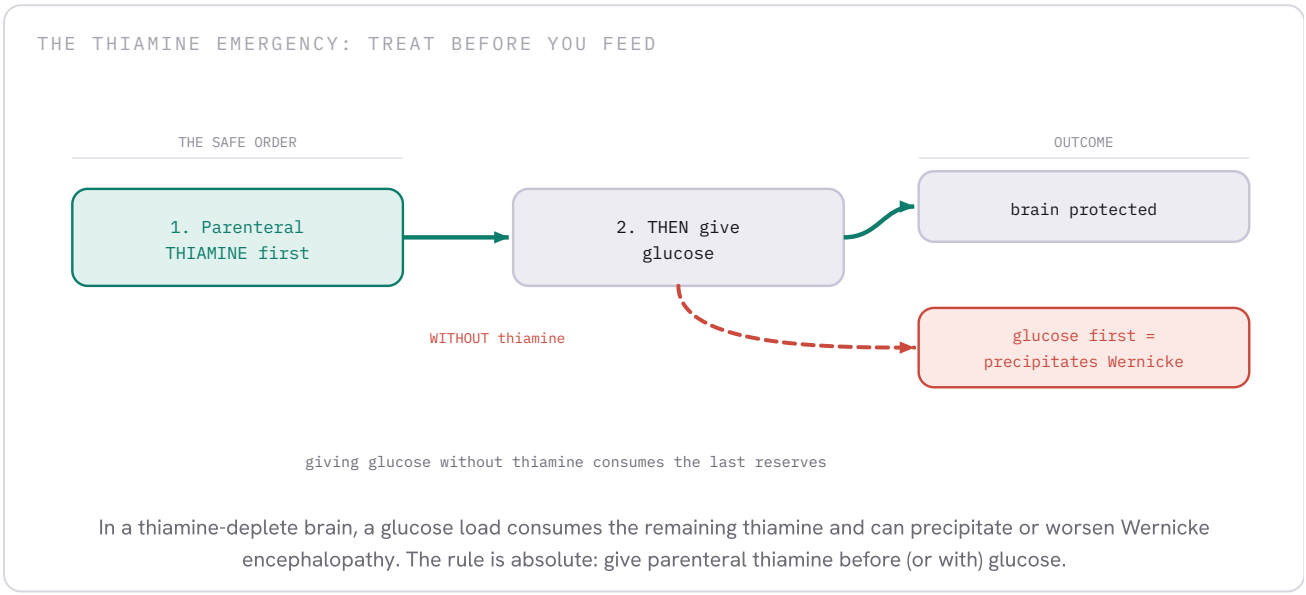
"Painful belly, Purple pee, Psychosis, Polyneuropathy"

The four P's of an acute intermittent porphyria attack: abdominal Pain, urine turning Purple on standing, Psychiatric disturbance, and peripheral Polyneuropathy. Barbiturates are the precipitant to avoid.

6 Nutritional deficiencies

Thiamine (vitamin B1): Wernicke and Korsakoff

- **Wernicke encephalopathy** – an acute, reversible thiamine-deficiency state, most often in alcohol dependence (also hyperemesis, starvation, bariatric surgery). The classic **triad: confusion, ophthalmoplegia (nystagmus, lateral rectus / VI palsy) and ataxia**. The full triad is present in only a minority, so a low threshold to treat is essential.
- **Korsakoff syndrome** – the chronic, often **irreversible** sequel: a profound **anterograde (and some retrograde) amnesia** with **confabulation**, relatively preserved other cognition and intact consciousness. Lesions in the **mammillary bodies** and dorsomedial thalamus.



In a thiamine-deplete brain, a glucose load consumes the remaining thiamine and can precipitate or worsen Wernicke encephalopathy. The rule is absolute: give parenteral thiamine before (or with) glucose.

EMERGENCY RULE

In any malnourished or alcohol-dependent patient, give **parenteral thiamine BEFORE glucose**. A glucose load given first can precipitate Wernicke encephalopathy. Wernicke is a clinical emergency: treat on suspicion, do not wait for the full triad.

Vitamin B12 and folate

- **Psychiatric picture** – **depression, fatigue, irritability, psychosis** ("megaloblastic madness") and a reversible **dementia / cognitive impairment**. Both B12 and folate deficiency can cause these; folate deficiency is particularly linked to depression.
- **Neurological picture (B12)** – a **peripheral neuropathy** and **subacute combined degeneration of the cord (SACD)**: degeneration of the dorsal columns (loss of proprioception and vibration sense) and lateral corticospinal tracts (weakness, upgoing plantars). Neurological damage from B12 deficiency can become irreversible if untreated.

▲ **The folate trap** – treating B12 deficiency with **folate alone** can correct the anaemia while the **neurological damage progresses**. Always check and replace B12 before, or alongside, folate. Macrocytosis (↑ MCV) and raised homocysteine point to either deficiency.

Niacin (vitamin B3): pellagra

◆ **The three Ds** – pellagra (niacin deficiency) gives **Dermatitis** (a photosensitive rash, e.g. Casal's necklace), **Diarrhoea**, and **Dementia** (the psychiatric D: cognitive impairment, depression, apathy, psychosis, even delirium). A fourth D, **Death**, if untreated. Seen in poverty, alcoholism, malabsorption and carcinoid.

MNEMONIC

Pellagra = the three (four) D's

Dermatitis, Diarrhoea, Dementia, (Death). Niacin (B3) deficiency. The dementia is the examinable neuropsychiatric feature; the rash is photosensitive.

Refeeding syndrome

Refeeding syndrome – the dangerous metabolic shift when nutrition is reintroduced too quickly to a starved patient (severe anorexia nervosa, chronic alcoholism, prolonged fasting). Carbohydrate triggers an insulin surge that drives **phosphate, potassium and magnesium** into cells. The hallmark is **hypophosphataemia**, with cardiac arrhythmia, heart failure, delirium and seizures. Prevent it: refeed slowly, monitor and replace electrolytes, and give **thiamine** before refeeding.

TRAP

Refeeding syndrome links eating-disorder psychiatry to acute medicine. The killer is **low phosphate**; thiamine must be given before refeeding because the same glucose load that drives refeeding can also precipitate Wernicke in a depleted patient. Two reasons to give thiamine first.

7 Systemic & electrolyte disturbance

Hepatic encephalopathy

Picture – a fluctuating, reversible neuropsychiatric syndrome of liver failure: from subtle cognitive and personality change, sleep reversal and irritability, through confusion and disorientation, to stupor and coma. **Asterixis** (a coarse "flapping" tremor of the outstretched hands) is the classic sign. **Ammonia** is typically raised, though it correlates poorly with grade.

West Haven grade	Clinical state
Grade I	mild: short attention span, altered sleep, mild confusion, irritability
Grade II	lethargy, disorientation to time, personality change; **asterixis** present
Grade III	somnolent but rousable, marked confusion, disorientation to place
Grade IV	coma, unresponsive to stimuli

Treatment targets ammonia: **lactulose** and **rifaximin**, plus treating the precipitant (infection, GI bleed, constipation, sedatives, electrolyte upset).

Uraemic encephalopathy

Uraemic encephalopathy – the neuropsychiatric syndrome of renal failure with accumulated toxins: fatigue and apathy, poor concentration and memory, irritability, then a fluctuating delirium with **asterixis, myoclonus** and, in severe cases, seizures. It improves with dialysis. (Note the separate *dialysis disequilibrium* syndrome from over-rapid correction.)

Glucose

Hypoglycaemia

An **adrenergic / autonomic** phase (anxiety, tremor, sweating, palpitations, hunger) mimicking a panic attack, then a **neuroglycopenic** phase (confusion, behaviour change, drowsiness, seizures, coma). Acute, dramatic, rapidly reversible with glucose.

Hyperglycaemia

More **insidious**: lethargy, poor concentration, low mood, and in DKA or a hyperosmolar state, **delirium** progressing to coma. Both extremes of glucose impair cognition.

Sodium

● **Hyponatraemia** – low sodium causes lethargy, headache, nausea, irritability and confusion, with seizures and coma when severe or rapid. It is an under-recognised cause of delirium and falls in older psychiatric patients.

◆ **The SIADH / drug link** – **SSRIs and carbamazepine** are common psychotropic causes of **SIADH** and hyponatraemia, especially in the elderly. Suspect it when an older patient becomes confused or drowsy after starting one. The mechanism is excess ADH and water retention.

▲ **The correction trap** – correcting chronic hyponatraemia **too rapidly** risks **osmotic demyelination (central pontine myelinolysis)**: a delayed, often catastrophic syndrome of dysarthria, dysphagia, quadriparesis and the "locked-in" state. The rule is to raise sodium **slowly**.

● CLASSIC TRAP

A new confusion in an elderly patient recently started on an **SSRI or carbamazepine** is hyponatraemic SIADH until proven otherwise: check the sodium. And once you find it, the danger flips – correcting it **too fast** causes osmotic demyelination. Slow and steady on the way up.

QUICK-RECALL · DRILL THESE ONE-LINERS

- **Principle:** any atypical, late-onset or treatment-resistant case → screen the body. Baseline: TSH, calcium, glucose, B12, sodium, LFTs.
- **Thyroid:** hypo = depression / slowing / myxoedema madness (psychosis); hyper = anxiety / mania, but **apathetic** in the elderly. **TSH** screens both.
- **Calcium:** hyperparathyroid = "bones, stones, abdominal groans & psychic moans". High calcium slows; low calcium irritates (tetany, anxiety).
- **Adrenal:** Cushing's (cortisol excess) = **depression** most common; Addison's (deficiency) = apathy / fatigue / depression; phaeochromocytoma = **paroxysmal panic-like** attacks (metanephrines).
- **Steroids (exogenous):** dose-related; early euphoria / hypomania, later depression; high dose → steroid psychosis. Withdrawal can also depress.
- **Wilson's:** young + new psychiatric / movement / liver problem. Triad = **low caeruloplasmin, high urinary copper, KF ring**. Treat with chelation (penicillamine / trientine) + zinc.
- **AIP:** abdominal pain + autonomic + neuropathy + anxiety / psychosis; urine darkens on standing; raised urinary PBG. **Barbiturates** precipitate.
- ★ **Thiamine:** Wernicke triad = confusion + ophthalmoplegia + ataxia; Korsakoff = amnesia + confabulation (mammillary bodies). **Thiamine before glucose**, always.
- **B12 / folate:** dementia / depression / psychosis / neuropathy / SACD (dorsal columns + corticospinal). Never give folate alone in B12 deficiency.
- **Niacin:** pellagra = the 3 D's, Dermatitis, Diarrhoea, Dementia (+Death). **Refeeding:** low phosphate is the killer; thiamine first.
- **Systemic:** hepatic encephalopathy = asterixis + raised ammonia, West Haven I–IV (lactulose / rifaximin); uraemic = asterixis + myoclonus.
- **Sodium:** SSRIs & carbamazepine → SIADH / hyponatraemia in the elderly; correct **slowly** or risk osmotic demyelination (central pontine myelinolysis).

ONE-DAY REVISION · PAPER 4

Neurology for Psychiatrists

The neurology a psychiatrist actually uses: a clean examination sequence, the upper- versus lower-motor-neuron split that localises any weakness, the pupils and movements that betray disease, and the positive signs that name a functional disorder rather than just excluding everything else. Most psychiatric drugs act on this same motor system, and many "psychiatric" presentations are neurological. Competence here is what separates a safe assessment from a missed lesion.

● CONCEPT ● RULE ● TRAP ● KEY NUMBER ● MNEMONIC

The colour tells you what kind of fact it is. Drug-induced movement disorders are cross-referenced to the Psychopharmacology pack.

★ HIGH YIELD TOP 5 IF NOTHING ELSE

1. UMN = tone up, reflexes up, plantar up-going, no wasting, no fasciculation; LMN = tone down, reflexes down, marked early wasting and fasciculations. Acute trap: a fresh UMN lesion is flaccid with absent reflexes first (spinal shock), so the up-going plantar (Babinski) is the earliest reliable UMN sign.
2. Argyll Robertson pupils are small, irregular, bilateral, and accommodate but do not react to light (light-near dissociation) → neurosyphilis; Holmes-Adie shares the dissociation but is large, unilateral, and benign, the exact opposite in size and danger.
3. A pupil-involving third-nerve palsy (down-and-out eye, ptosis, fixed dilated pupil) is a neurosurgical emergency (posterior communicating aneurysm, uncal herniation) until proven otherwise; pupil-sparing CN III is ischaemic (diabetes).
4. The four antipsychotic movement disorders separate by time course: acute dystonia in hours to days (anticholinergic IM), akathisia in days to weeks (propranolol), parkinsonism in weeks to months, tardive dyskinesia in months to years (may be irreversible). Akathisia is felt, not just seen, is misread as anxiety, and links to suicidality.
5. A positive Romberg (much worse eyes closed) is a sensory ataxia sign localising to the dorsal columns or peripheral nerve, NOT a cerebellar test; FND is a rule-in diagnosis on positive signs (Hoover sign, tremor entrainment), not a diagnosis of exclusion.

1 The neurological examination for psychiatrists

A psychiatrist examines the nervous system to catch the organic mimic, to baseline before prescribing, and to track drug-induced signs. The sequence is always the same; running it in order is what stops you forgetting a step under pressure.

The structured sequence

Step	What you test	Why it matters in psychiatry
Higher mental function	consciousness, orientation, attention, memory, language, praxis, frontal/executive	separates delirium and dementia from primary psychiatric illness; the MMSE/MoCA sit here
Cranial nerves	I–XII, especially pupils, fundi, eye movements, face, swallow	pupils and fundi flag neurosyphilis, raised pressure, brainstem disease

Step	What you test	Why it matters in psychiatry
Motor	bulk, tone, power, abnormal movements	tone and abnormal movements track antipsychotic effects and catatonia
Sensory	light touch, pin-prick, vibration, proprioception, cortical sensation	a glove-and-stocking or non-anatomical pattern reframes the complaint
Coordination	finger-nose, heel-shin, dysdiadochokinesia, rebound	cerebellar signs appear with lithium toxicity and alcohol
Gait	stance, stride, arm swing, turning, tandem, Romberg	often the single most informative test; do it early, watch them walk in
Reflexes	deep tendon jerks, plantar response, primitive/frontal release signs	brisk reflexes with an up-going toe localise to the upper motor neuron

ORDER TO HOLD

Higher function → cranial nerves → motor → sensory → coordination → gait → reflexes. Inspect before you touch; tone before power; always watch the gait.

Why competence matters – a large minority of patients on a psychiatric ward have an undiagnosed or contributory neurological problem. The examination baselines extrapyramidal signs before an antipsychotic starts, detects emerging tardive dyskinesia, distinguishes catatonia from a neurological mute state, and gives the confidence to call a presentation functional on positive grounds.

TRAP

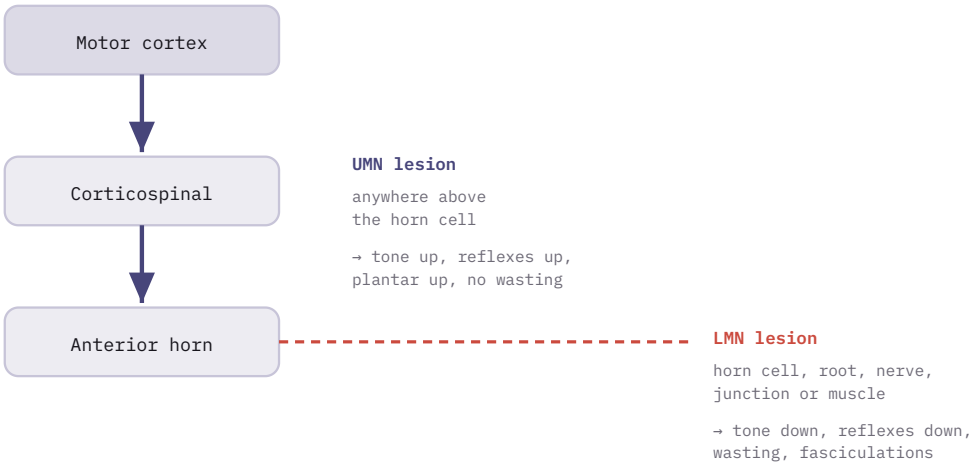
Frontal release signs (grasp, pout, palmomental, glabellar tap that does not fatigue) are normal in infancy and re-emerge with diffuse frontal disease. A few in isolation are non-specific in the elderly; a cluster in a younger patient with personality change points to a frontal process, not a primary psychiatric one.

2 Localising the lesion

The first fork in any weak limb: is this an **upper** motor neuron lesion (the pathway from cortex down to the anterior horn cell) or a **lower** motor neuron lesion (anterior horn cell and everything distal to it)? Get this split right and the localisation follows.

Sign	Upper motor neuron (UMN)	Lower motor neuron (LMN)
Tone	increased (spasticity, clasp-knife)	decreased (flaccid, hypotonia)
Power / pattern	weak in a **pyramidal** pattern (arm extensors, leg flexors)	weak in the **territory** of the affected root, nerve or muscle
Deep tendon reflexes	exaggerated (brisk)	reduced or absent
Plantar response	extensor (up-going, Babinski positive)	flexor (down-going) or absent
Wasting	none, or only mild disuse atrophy late	marked, early
Fasciculations	absent	present (a denervation sign)
Clonus	present (sustained ankle clonus)	absent

UMN VERSUS LMN: WHERE THE LESION SITS



The anterior horn cell is the watershed. Lesions above it (cortex, internal capsule, brainstem, cord tract) give UMN signs; the cell body and everything distal give LMN signs. A mixed picture (UMN and LMN together) is the hallmark of motor neuron disease.

ACUTE TRAP

In the first hours to days of an acute UMN lesion (a fresh stroke or cord transection) the limb is **flaccid with absent reflexes**, not spastic – this is "spinal shock" or cerebral diaschisis. Tone and brisk reflexes develop later. The up-going plantar is the earliest reliable UMN sign.

A one-line map of the patterns

- **Cortical** – weakness plus cortical signs: aphasia, neglect, apraxia, cortical sensory loss, focal seizures. Face, arm and leg affected unequally (the homunculus is spread out).
- **Subcortical (internal capsule)** – a **dense, equal** hemiplegia of face, arm and leg with no cortical signs (fibres are packed tight); the classic lacunar pure motor stroke.
- **Brainstem** – **crossed** signs: an ipsilateral cranial nerve palsy with contralateral limb weakness. Often with diplopia, vertigo, dysarthria.
- **Cord (myelopathy)** – a sensory **level**, bilateral UMN signs below it, sphincter involvement. Brown-Sequard if hemisection.
- **Peripheral** – LMN pattern: glove-and-stocking sensory loss in polyneuropathy, or a single nerve/root territory in mononeuropathy and radiculopathy.

3 Cranial nerves and the eye in psychiatry

The eye is the one window onto the brain you can inspect at the bedside. A handful of pupil and fundus findings carry most of the marks and most of the clinical danger.

The pupils worth knowing

Finding	What you see	Lesion / association
Argyll Robertson	small, irregular pupils; **accommodate but do not react to light** (light-near dissociation); bilateral	neurosyphilis (tabes); also diabetes. "Prostitute's pupil" – accommodates but does not react
Horner syndrome	**miosis, partial ptosis, anhidrosis** (and apparent enophthalmos)	interrupted sympathetic chain: lateral medulla, apical lung (Pancoast), carotid dissection

Finding	What you see	Lesion / association
Third-nerve (CN III) palsy	**down-and-out** eye, ptosis; pupil dilated and fixed if "surgical"	pupil-involving → compressive (posterior communicating aneurysm, uncal herniation); pupil-sparing → ischaemic (diabetes)
Holmes-Adie	large, tonic pupil, slow to react; often with absent reflexes	benign; young women. The opposite size to Argyll Robertson
RAPD (Marcus Gunn)	swinging-light test: affected pupil dilates when the light swings to it	optic nerve / retina disease (optic neuritis)

CLASSIC TRAP

Both Argyll Robertson and Holmes-Adie show light-near dissociation (poor light reaction, preserved near response), but they are opposites in size and danger: Argyll Robertson is **small, bilateral, and signals neurosyphilis**; Holmes-Adie is **large, usually unilateral, and benign**. A pupil-involving third-nerve palsy is a neurosurgical emergency (think aneurysm) until proven otherwise.

Nystagmus, the disc, and the fields

- **Nystagmus** – involuntary rhythmic eye oscillation. Named by the fast phase. **Horizontal/gaze-evoked** with vertigo: peripheral vestibular or cerebellar. **Vertical** nystagmus is central until proven otherwise. Drug causes: alcohol, lithium, phenytoin, benzodiazepines, barbiturates.
- **Papilloedema** – bilateral optic disc swelling from **raised intracranial pressure**: blurred margins, loss of venous pulsation, enlarged blind spot, preserved acuity early. A red flag demanding imaging. Distinguish from unilateral disc swelling in optic neuritis (which loses acuity early and is painful on eye movement). `[real fundus photograph belongs here]`
- **Visual fields, lesion by lesion** – **optic nerve**: monocular loss. **Optic chiasm**: bitemporal hemianopia (pituitary tumour, craniopharyngioma). **Optic tract / radiation**: homonymous hemianopia. **Occipital cortex**: homonymous hemianopia with macular sparing. The field defect tells you exactly how far back the lesion sits.

MNEMONIC

"Argyll Robertson Accommodates"

Both names start with A: the pupil **A**ccommodates but does not react to light. Small, irregular, bilateral, and it points to neurosyphilis.

4 Movement disorders for the psychiatrist

Psychiatrists generate movement disorders (with antipsychotics) and must recognise them. Start by naming the phenomenology, then ask what state it occurs in: rest, posture, or action.

Tremor: the three states

Tremor	Appears at…	Typical cause
Rest	at rest, settles on movement	**Parkinsonism** (4–6 Hz, pill-rolling); also drug-induced parkinsonism
Postural	holding a posture against gravity	**Essential** tremor, physiological, lithium, valproate, anxiety, thyrotoxicosis
Intention (kinetic)	worsens as the hand nears a target	**Cerebellar** disease; lithium toxicity

The drug-induced movement disorders

Four antipsychotic-related disorders, separated by their time course. Cross-reference the Psychopharmacology pack for management detail.

Disorder	Onset after starting/raising	Picture & first move
Acute dystonia	hours to days	sustained spasm: oculogyric crisis, torticollis, laryngospasm. Young men. Anticholinergic (procyclidine) IM
Akathisia	days to weeks	inner restlessness, cannot keep still; mistaken for agitation or anxiety. Reduce dose; propranolol
Parkinsonism	weeks to months	bradykinesia, rigidity, rest tremor. Reduce dose; anticholinergic; switch agent
Tardive dyskinesia	months to years	choreoathetoid orofacial/lingual movements; may be irreversible. Stop offending drug if able; VMAT2 inhibitor

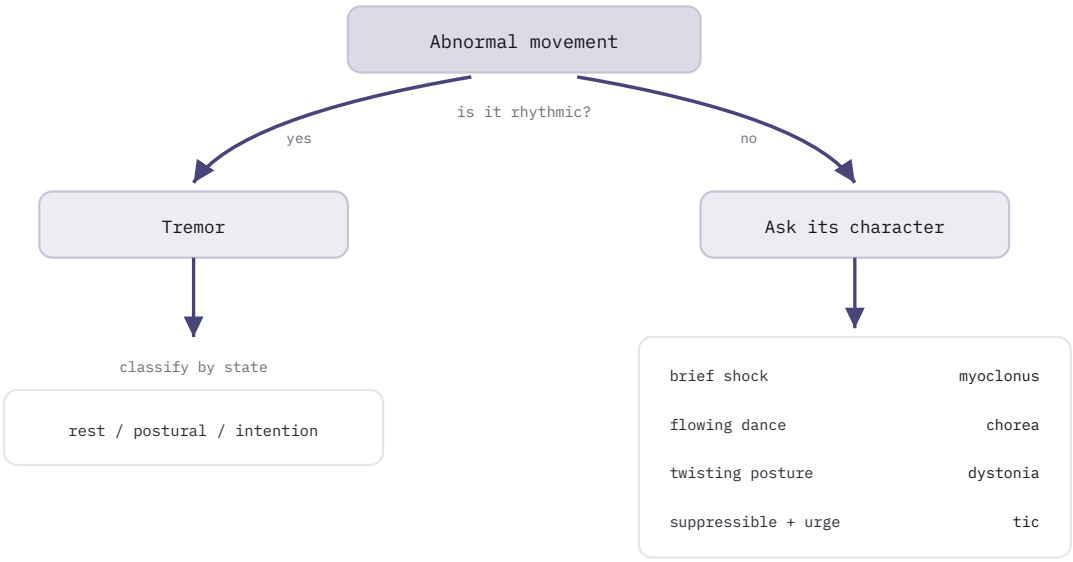
● CLASSIC TRAP

Akathisia is felt, not just seen: the core is a subjective, distressing restlessness. It is repeatedly misread as worsening anxiety or psychotic agitation, prompting a dose increase that makes it worse. It carries a real link to suicidality. Always ask if the movement is driven by an irresistible urge from within.

The hyperkinetic phenomenologies

Phenomenology	Rhythm / character	Examples
Tremor	**rhythmic**, oscillatory, regular	parkinsonian, essential, cerebellar
Chorea	irregular, flowing, **dance-like**; flits between body parts	Huntington, Sydenham (rheumatic), SLE, pregnancy
Athetosis	slow, writhing, sinuous (distal)	cerebral palsy; merges with chorea as choreoathetosis
Dystonia	sustained or repetitive, **twisting**, abnormal posture	acute drug-induced, writer's cramp, torticollis
Myoclonus	**brief, shock-like**, lightning jerk	juvenile myoclonic epilepsy, CJD, metabolic; hypnic jerks (normal)
Tics	stereotyped, **suppressible**, preceded by an urge, relieved by release	Tourette syndrome; simple (blink) vs complex
Ballismus	violent, large-amplitude flinging (proximal)	hemiballismus: subthalamic nucleus lesion

MAPPING A MOVEMENT: A QUICK DECISION LOGIC



First ask whether the movement is rhythmic. If yes, it is a tremor, then classify by state (rest, postural, intention). If not, the character names it: shock-like (myoclonus), flowing (chorea), twisting (dystonia), or suppressible with a premonitory urge (tic).

The motor signs of catatonia

- **Catatonia** – a motor syndrome, not a subtype of schizophrenia, seen across mood, psychotic, and medical illness. Screen with the **Bush-Francis** scale.
- **Core motor signs** – **stupor**, **mutism**, **negativism** (resisting), **posturing** and **catalepsy** (holding a posture), **waxy flexibility** (cerea flexibilitas), **echopraxia/echolalia**, **stereotypy**, **mannerisms**, and **automatic obedience**.
- **The lorazepam challenge** – a positive response to IV lorazepam both confirms catatonia and is first-line treatment; ECT for malignant or refractory cases. Antipsychotics can worsen it and risk neuroleptic malignant syndrome.

OVERLAP TRAP

Malignant catatonia and neuroleptic malignant syndrome (NMS) overlap heavily: rigidity, fever, autonomic instability, raised creatine kinase. NMS is the drug-induced form. Both are treated by stopping antipsychotics, supportive care, benzodiazepines, and ECT – not by adding more antipsychotic.

5 Gait and coordination

Watching a patient walk is the highest-yield neurological test there is. Each diagnostic gait has a signature you can name on sight.

Gait	What you see	Localises to
Hemiplegic	stiff leg **circumducts**; arm flexed and adducted	UMN lesion, one side (old stroke)
Spastic / scissoring	stiff, narrow-based, legs cross; toe-walking	bilateral UMN (spastic diplegia, cord)
Parkinsonian	stooped, **shuffling, festinant**, reduced arm swing, turns en bloc	basal ganglia (Parkinson, drug-induced)
Ataxic / cerebellar	**broad-based**, staggering, lurches to the lesion side; Romberg negative	cerebellum (alcohol, lithium toxicity)

Gait	What you see	Localises to
Sensory ataxic	broad-based, high-stepping, **stamping**, watches the feet; Romberg positive	dorsal columns (B12, tabes), peripheral neuropathy
Apraxic	feet "stuck to the floor", hesitant, magnetic; normal power on the couch	frontal lobe, normal-pressure hydrocephalus
High-stepping (foot drop)	lifts the foot high to clear a dropped toe; slaps down	LMN: common peroneal palsy, L5 root
Functional (non-organic)	inconsistent, effortful, often elaborate; improves when distracted	functional neurological disorder (see section 7)

● ROMBERG TRAP

A positive **Romberg** (much worse with eyes closed) is a **sensory ataxia** sign: vision was compensating for lost proprioception. It is **not** a cerebellar test – a cerebellar patient sways with eyes open and closed alike. Romberg localises to the dorsal columns or peripheral nerve, not the cerebellum.

Cerebellar signs: DANISH

● MNEMONIC

"DANISH"

Dysdiadochokinesia · **A**taxia (broad-based gait, limb) · **N**ystagmus · **I**ntention tremor · **S**canning (staccato) speech · **H**ypotonia (and heel-shin incoordination). Add dysmetria and rebound. Signs are **ipsilateral** to the cerebellar lesion.

- **Testing coordination** – finger-nose (dysmetria, intention tremor), rapid alternating movements (dysdiadochokinesia), heel-shin, and rebound (overshoot when resistance is removed). A midline (vermis) lesion gives truncal and gait ataxia; a hemisphere lesion gives ipsilateral limb ataxia.

6 Headache and the psychiatric interface

Headache is one of the commonest complaints carried into a psychiatric clinic, both as a primary disorder and as somatic distress. Know the three primary headaches, the overuse trap, and the red flags.

Headache	Pattern	Hallmarks
Migraine without aura	4–72 h, **unilateral, throbbing**, moderate-severe	nausea, photophobia, phonophobia; worse with activity; women > men
Migraine with aura	reversible aura over 5–60 min, then headache	visual (zigzag, scotoma) or sensory aura; raises stroke risk with combined pill + smoking
Tension-type	bilateral, **band-like, pressing**, mild-moderate	no nausea, not aggravated by activity; the commonest headache
Cluster	strictly **unilateral, orbital, excruciating**; 15–180 min, in bouts	autonomic: lacrimation, red eye, ptosis, rhinorrhoea; **restless**; men > women
Medication-overuse	≥15 days/month, on a background of regular analgesic/triptan use	the treatment becomes the cause; withdraw the overused drug

● TRAP

Cluster patients are agitated and pace (unlike migraine, where they lie still in a dark room). The autonomic features and the strictly unilateral orbital pain are the giveaway. Do not mislabel the restlessness as anxiety or drug-seeking.

Red flags for a secondary cause: SNOOP

MNEMONIC

"SNOOP"

Systemic symptoms/signs (fever, weight loss) or Secondary risk (cancer, HIV) · **N**eurological signs or symptoms · **O**nset sudden (thunderclap → subarachnoid haemorrhage) · **O**lder (new headache after 50 → giant cell arteritis, tumour) · **P**attern change, Positional, Papilloedema, or Precipitated by Valsalva. Any flag → image and investigate.

◆ **The migraine–mood comorbidity** – migraine is robustly and **bidirectionally** linked with depression and anxiety: each roughly doubles the risk of the other. The shared substrate involves serotonergic dysregulation. This matters in prescribing: avoid triptan plus serotonergic drug overload, watch for medication overuse in distressed patients, and choose agents (amitriptyline, venlafaxine, topiramate) that treat both.

PRESCRIBING RULE

Several drugs treat both migraine and a psychiatric comorbidity: **amitriptyline** and **venlafaxine** (prophylaxis + depression), **topiramate** and **valproate** (prophylaxis + mood stabilisation). Beta-blockers (propranolol) help migraine and performance anxiety but can lower mood. Match the agent to both problems.

7 Functional neurological disorder

Functional neurological disorder (FND, conversion disorder) is diagnosed on **positive** signs of internal inconsistency, not by excluding everything else. The symptoms are real and involuntary; the problem is in the functioning of the nervous system, not its structure.

The positive signs

Sign	How to elicit	What a positive means
Hoover sign	hand under the "weak" heel; ask the patient to flex the *good* hip against resistance	the weak leg **presses down automatically**; weakness disappears with distraction
Tremor entrainment	ask the patient to tap a rhythm with the good hand	the functional tremor **adopts that rhythm** or stops; an organic tremor does not
Give-way / collapsing weakness	test power; resistance gives way in **ratchety, intermittent** jerks	inconsistent effort, not a fixed pyramidal weakness
Drift without pronation	arm drift test in suspected functional arm weakness	the arm drifts **down without pronating** (organic UMN drift pronates)
Dissociative (functional) seizure clues	observe the event; check timing and responsiveness	long duration, fluctuating course, eyes **closed** and resisting opening, side-to-side head movements, preserved awareness, normal post-ictal state

HOLD THIS

FND is a **rule-in** diagnosis. **Hoover sign** (leg weakness that vanishes on contralateral hip flexion) and **tremor entrainment** are the two positive signs to know. Internal inconsistency, not normal scans, makes the diagnosis.

Feigning, and the modern model

● **FND versus feigning** – FND symptoms are **genuinely involuntary**; the inconsistency is in the nervous system's functioning, not in conscious deception. **Factitious disorder** (deception for the sick role) and **malingering** (deception for external gain) are conscious and are *not* FND. The positive

signs detect inconsistency, not motive; do not equate a positive Hoover sign with faking.

■ **Software, not hardware** – the modern frame: the brain's **hardware is intact** but the **software (how attention, prediction, and self-agency run) is misfiring**. Aberrant predictions and abnormally directed attention generate real, involuntary symptoms. This replaces the old purely psychogenic, "all in the mind" view.

Sensitive, validating management

● **Explain positively** – name it as FND, show the patient their own Hoover sign or entrainment, and frame it as a **common, recognised, potentially reversible** problem with the nervous system's functioning. The diagnosis is the start of treatment, not a dismissal.

● **Avoid the two errors** – do not over-investigate (it entrenches illness belief) and do not say "there is nothing wrong" (it is wrong and it alienates). Validate that the symptoms are real and not the patient's fault.

■ **Treatment** – multidisciplinary: **physiotherapy** for functional motor and gait symptoms, **FND-informed CBT**, and treatment of comorbid depression and anxiety. Engagement hinges on the patient accepting the diagnosis.

● FINAL TRAP

FND and organic disease **co-occur** often: a patient with epilepsy can also have dissociative seizures, and a positive Hoover sign does not exclude a coexisting structural lesion. Diagnose FND on its own positive signs, but stay alert to a second, organic diagnosis sitting alongside it.

QUICK-RECALL · DRILL THESE ONE-LINERS

- **Exam sequence:** higher function → cranial nerves → motor → sensory → coordination → gait → reflexes. Inspect before touching; tone before power; always watch the gait.
- ★ **UMN vs LMN:** UMN = tone up, reflexes up, plantar up, no wasting, no fasciculation. LMN = tone down, reflexes down, wasting, fasciculations. Acute UMN is flaccid first (spinal shock); the up-going toe is the earliest sign.
- **Localisation:** cortical = unequal + cortical signs; capsular = dense equal hemiplegia; brainstem = crossed signs; cord = a sensory level; peripheral = glove-and-stocking or single territory.
- **Pupils:** Argyll Robertson = small, irregular, accommodates not reacts, neurosyphilis. Horner = miosis + ptosis + anhidrosis. Pupil-involving CN III = aneurysm/herniation (emergency); pupil-sparing = ischaemic.
- **Fields:** chiasm = bitemporal hemianopia (pituitary); tract/radiation = homonymous; occiput = homonymous with macular sparing. Papilloedema = bilateral, raised ICP, image it.
- **Tremor:** rest = parkinsonism; postural = essential / lithium; intention = cerebellar. Akathisia is felt not just seen and links to suicidality.
- **Drug-induced (by time):** acute dystonia (hours, anticholinergic IM) · akathisia (days, propranolol) · parkinsonism (weeks) · tardive dyskinesia (months-years, may be irreversible).
- **Hyperkinetic:** chorea = flowing dance (Huntington, Sydenham); myoclonus = brief shock; dystonia = sustained twist; tics = suppressible with premonitory urge (Tourette); hemiballismus = subthalamic nucleus.
- **Catatonia:** motor syndrome across diagnoses; Bush-Francis screen; lorazepam challenge confirms and treats; ECT if malignant; avoid antipsychotics (NMS risk).
- **Gait:** hemiplegic circumducts; parkinsonian shuffles/festinates; cerebellar broad-based (Romberg negative); sensory ataxic stamps (Romberg positive); apraxic magnetic (NPH). Romberg = dorsal columns, not cerebellum.
- **Cerebellar = DANISH:** Dysdiadochokinesia, Ataxia, Nystagmus, Intention tremor, Scanning speech, Hypotonia. Signs ipsilateral to the lesion.
- **Headache:** migraine = unilateral throbbing + nausea/photophobia; tension = band-like; cluster = unilateral orbital, autonomic, restless. Overuse if ≥15 days/month. Red flags = SNOOP. Migraine and depression/anxiety are bidirectional.

- **FND:** rule-in on positive signs. Hoover sign and tremor entrainment are the two to know. Software not hardware; symptoms real and involuntary (not feigning). Validate, physiotherapy + FND-CBT; can co-occur with organic disease.

ONE-DAY REVISION · PAPER 4

Recent Advances: Psychopharmacology

The field is moving off the monoamine axis. Glutamate, GABA-A neurosteroids, muscarinic receptors, orexin, the gut-incretin and immune systems, and the genome itself are now drug targets. Hold the mechanism, the lead agent, the indication, and one cardinal caution for each. Know clearly what is approved versus investigational.

● CONCEPT ● RULE ● TRAP ● KEY NUMBER ● MNEMONIC

The colour tells you what kind of fact it is. "Approved" means a major regulator (US FDA / EMA) has licensed it; psychedelics remain investigational.

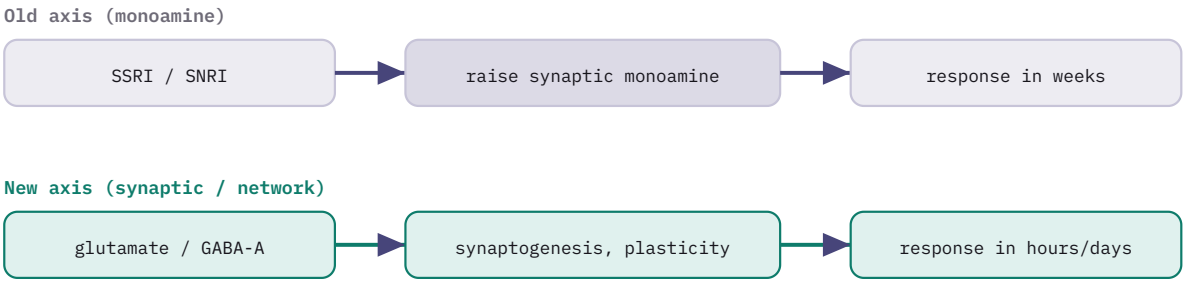
★ HIGH YIELD TOP 5 IF NOTHING ELSE

1. Ketamine/esketamine work by NMDA antagonism on GABAergic interneurons → glutamate surge → AMPA/BDNF/mTOR → synaptogenesis, giving response within hours and a distinct rapid drop in suicidal ideation; intranasal esketamine FDA-approved 2019, but the effect is not durable after a single dose.
2. Screen for HLA-B*1502 before starting carbamazepine in South or East Asian ancestry (a positive result contraindicates it for SJS/TEN risk); HLA-A*3101 covers a broader carbamazepine reaction spectrum across European/Japanese ancestry. This is the strongest actionable pharmacogenetic rule in psychiatry.
3. KarXT (xanomeline-trospium) is the first non-D2 antipsychotic: an M1/M4 muscarinic agonist (M4 lowers striatal dopamine) plus peripheral antimuscarinic trospium, so it has no EPS, no hyperprolactinaemia and low metabolic burden (FDA 2024).
4. Brexanolone (IV, 60 h inpatient infusion) and zuranolone (oral, 14 days) are allopregnanolone-analogue GABA-A positive allosteric modulators for postpartum depression; zuranolone was NOT approved for major depressive disorder, only PPD.
5. CYP2D6 and CYP2C19 phenotypes run poor → intermediate → normal → ultrarapid: poor metaboliser = high drug level = more toxicity at standard dose, ultrarapid = low level = under-treatment; combinatorial pharmacogenetic panels remain promising but not yet routine.

1 The frame: beyond the monoamine hypothesis

The monoamine hypothesis (depression as a serotonin/noradrenaline/dopamine deficit) explained the SSRIs but left gaps: the **delayed** onset, the third of patients who are treatment-resistant, and the weak link between acute monoamine rise and clinical response. The new agents target **different systems** and, in several cases, act within hours rather than weeks.

THE SHIFT IN ANTIDEPRESSANT TARGETS



The old monoamine drugs raise synaptic serotonin or noradrenaline and act over weeks. The newer rapid-acting agents work through glutamate and GABA-A signalling, driving synaptogenesis and producing response within hours to days.

Master table: the novel agents

Agent	Mechanism	Indication	Status
Ketamine	NMDA-receptor antagonist	treatment-resistant depression (off-label IV); anaesthesia (licensed)	Approved (anaesthetic); off-label in TRD
Esketamine (intranasal)	NMDA-receptor antagonist (S-enantiomer)	treatment-resistant depression; MDD with acute suicidal ideation	Approved (FDA 2019, EMA 2019)
Brexanolone (IV)	GABA-A receptor positive allosteric modulator (neurosteroid)	postpartum depression	Approved (FDA 2019)
Zuranolone (oral)	GABA-A receptor positive allosteric modulator (neurosteroid)	postpartum depression	Approved (FDA 2023, PPD only)
Xanomeline-trospium (KarXT)	M1/M4 muscarinic agonist + peripheral antimuscarinic	schizophrenia	Approved (FDA 2024)
Lumateperone	serotonin-dopamine-glutamate modulator	schizophrenia; bipolar depression	Approved (FDA)
Cariprazine	D3-preferring D2/D3 partial agonist	schizophrenia; bipolar mania, depression; MDD adjunct	Approved
Suvorexant (DORA)	dual orexin receptor antagonist	insomnia	Approved (FDA 2014)
Lecanemab / Donanemab	anti-amyloid-β monoclonal antibody	early Alzheimer's disease	Approved (FDA 2023 / 2024)
Psilocybin	5-HT2A receptor agonist (serotonergic psychedelic)	treatment-resistant / major depression	Investigational (Phase II/III)
MDMA	monoamine releaser; oxytocin / fear-extinction modulator	PTSD (assisted psychotherapy)	Investigational (FDA declined 2024)

QUICK RULE

Rapid-acting antidepressants act on **glutamate** (ketamine/esketamine) or **GABA-A** (brexanolone/zuranolone). Novel antipsychotic mechanism = **muscarinic** (KarXT), the first non-D2 antipsychotic. Psychedelics are **investigational, not standard care**.

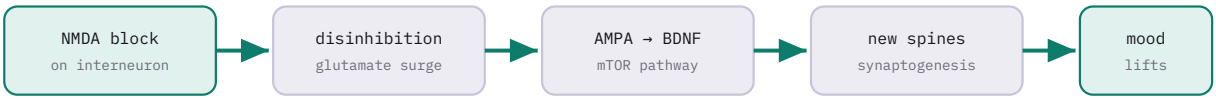
2 Rapid-acting antidepressants: ketamine & esketamine

The landmark advance: a single dose lifts depression within **hours**, where SSRIs take weeks. The discovery reframed depression around **glutamate and synaptic plasticity** rather than monoamines.

Mechanism

- **NMDA antagonism** – ketamine blocks the NMDA glutamate receptor, preferentially on inhibitory GABAergic interneurons. This *disinhibits* pyramidal neurons, causing a **glutamate surge** that activates AMPA receptors.
- **Synaptogenesis hypothesis** – AMPA activation triggers **BDNF release → mTOR pathway → rapid formation of new dendritic spines** in the prefrontal cortex. The antidepressant effect tracks this synaptic regrowth, not the acute receptor block.
- **Metabolite debate** – one hypothesis holds that the (2R,6R)-hydroxynorketamine metabolite drives the effect via AMPA, independent of NMDA block. Still contested; cited as evidence the mechanism is not purely NMDA.

HOW KETAMINE ACTS WITHIN HOURS



NMDA block on inhibitory interneurons disinhibits pyramidal cells, producing a glutamate surge. AMPA activation drives BDNF and mTOR signalling, which builds new synapses in the prefrontal cortex. The synaptic regrowth, not the acute receptor block, underlies the sustained mood effect.

Clinical effect

- **Rapid & anti-suicidal** – response within **hours to 24 h** in treatment-resistant depression; a distinct, rapid reduction in **suicidal ideation** independent of overall mood change. Intranasal esketamine is licensed alongside an oral antidepressant.
- **Route & dosing** – racemic ketamine is given IV (off-label, ~0.5 mg/kg over 40 min); esketamine is an intranasal spray (licensed), dosed twice weekly in induction then tapering. Both given under monitored, in-clinic supervision.

● CAUTIONS

Dissociation (peri-dose, transient) and a transient **rise in blood pressure** require a post-dose monitoring window (esketamine: at least 2 h, REMS programme). Ketamine has **abuse liability** (a controlled substance / Schedule III) and a history of recreational misuse. Cystitis and cognitive effects follow chronic high-dose use.

● DURABILITY

The effect is real but **not durable** after a single dose – relapse follows within days to weeks, so repeated dosing is needed and the long-term safety of maintenance is still under study. Durability remains the open question and a common viva point.

3 Neuroactive steroids: brexanolone & zuranolone

The first agents developed specifically for **postpartum depression**, built on a falling-allopregnanolone model: a sharp post-delivery drop in this neurosteroid is implicated in PPD. The drugs replace its action at GABA-A.

● **Mechanism** – both are synthetic analogues of **allopregnanolone**, acting as **positive allosteric modulators of the GABA-A receptor** (at synaptic and extrasynaptic sites). They enhance inhibitory GABAergic tone, correcting the post-delivery neurosteroid drop.

Agent	Route	Schedule	Access note
Brexanolone	IV infusion	continuous over **60 h** (inpatient)	REMS: monitored for sedation and sudden loss of consciousness
Zuranolone	oral	once daily for **14 days**	oral course removes the infusion barrier; PPD indication only

◆ **Rapid course, short duration** – both act fast (days, not weeks) and are given as a **brief course**, not maintenance. Zuranolone's 14-day oral regimen is the practical advance over the 60-h inpatient infusion.

● ACCESS & CAUTION

Brexanolone's cost and 60-h supervised IV limit real-world use; it is restricted to certified sites under a REMS for excessive sedation/syncope. Zuranolone causes **somnolence and dizziness** (driving caution) and was approved **only for PPD** – the FDA did *not* approve it for major depressive disorder. CNS-depressant additivity with alcohol/opioids.

● MNEMONIC

"Brex is the Bag, Zura is the Zip"

Brexanolone = the IV bag, 60-h infusion, inpatient. Zuranolone = oral, fast (zip), 14-day course. Both are GABA-A neurosteroid PAMs for postpartum depression.

4 Psychedelic-assisted therapy (under investigation)

The most discussed and most overstated advance. State it carefully: these are **investigational**, given as **drug plus structured psychotherapy**, and **not approved for routine care**. Promising early trials; major regulatory caution remains.

Agent	Target indication	Proposed mechanism	Status
Psilocybin	treatment-resistant & major depression	**5-HT2A agonist**; increased neuroplasticity, relaxed priors, default-mode network modulation	Phase II/III; Breakthrough Therapy designation
MDMA	PTSD	serotonin/dopamine/noradrenaline release; **oxytocin** rise; reduced amygdala fear response, aids **fear extinction** and the therapeutic alliance	FDA declined 2024; further trials required

● **Mechanism, broadly** – classic psychedelics (psilocybin) act at **5-HT2A**, acutely increasing cortical plasticity and loosening rigid predictive patterns; the psychotherapy is thought to channel this "window". MDMA is an empathogen that lowers fear and raises trust, used to enable trauma processing.

● REGULATORY CAUTION

MDMA-assisted therapy for PTSD was **not approved** – the FDA issued a complete response letter in 2024 and requested an additional trial, citing concerns over **functional unblinding**, trial conduct and durability. Psilocybin holds Breakthrough Therapy designation but is **not yet licensed**. Risks: cardiovascular strain, transient psychological distress ("bad trips"), abuse potential, and the special risk of **boundary violations** in the psychotherapy. Do not present as available treatment.

5 Newer antipsychotic mechanisms

For 70 years every antipsychotic worked through **D2 blockade**. The headline advance is the first that does not: a **muscarinic** agonist.

The muscarinic approach (KarXT)

◆ **Xanomeline-trospium (KarXT)** – the first **non-D2** antipsychotic. **Xanomeline** is an **M1/M4 muscarinic receptor agonist** (M4 mediates the antipsychotic effect by indirectly lowering striatal dopamine). **Trospium** is a peripherally restricted antimuscarinic added to block the peripheral cholinergic side effects (nausea, GI upset) without crossing into the brain.

■ **Why it matters** – no D2 blockade means **no extrapyramidal symptoms, no hyperprolactinaemia, and a low metabolic burden** from the antipsychotic action itself. A genuinely new pharmacological class for schizophrenia (FDA-approved 2024).

Other recent antipsychotic advances

Agent / class	Distinguishing mechanism	Note
Lumateperone	simultaneous serotonin (5-HT2A antagonist), dopamine (presynaptic partial agonist / postsynaptic modulation) and glutamate action	schizophrenia & bipolar depression; favourable metabolic/EPS profile
Cariprazine	**D3-preferring** D2/D3 partial agonist	D3 affinity may aid negative symptoms, anhedonia; bipolar depression
Brexpiprazole	D2 partial agonist (lower intrinsic activity than aripiprazole)	also licensed for agitation in Alzheimer's dementia
Aripiprazole family	D2 **partial agonist** ("dopamine stabiliser")	the established partial-agonist template

Long-acting injectable (LAI) advances

● **Longer intervals** – the trend is toward **fewer injections**: aripiprazole and paliperidone formulations now allow **2-monthly, 3-monthly and 6-monthly** dosing (e.g. paliperidone 3-monthly and 6-monthly; aripiprazole 2-monthly). Longer intervals support adherence in schizophrenia.

● **Subcutaneous options** – newer LAIs (e.g. subcutaneous risperidone and a subcutaneous aripiprazole monohydrate) shift from deep IM to **subcutaneous** depots, easing administration.

● RULE

Partial agonists (aripiprazole, brexpiprazole, cariprazine) act as functional **dopamine stabilisers**: agonist where dopamine is low, antagonist where it is high. This underlies their lower EPS and prolactin burden versus full D2 antagonists. KarXT goes further – it bypasses the D2 receptor entirely.

6 Pharmacogenomics

Genotype shapes both how a drug is metabolised (pharmacokinetic) and the risk of severe reactions (HLA associations). Two CYP enzymes and two HLA alleles carry most of the exam marks.

CYP450 metaboliser status

- **CYP2D6** – metabolises many antidepressants, antipsychotics (risperidone, aripiprazole) and atomoxetine. Phenotypes: **poor, intermediate, normal (extensive), ultrarapid**. Poor metabolisers accumulate the parent drug (more side effects); ultrarapid metabolisers under-respond at standard doses.
- **CYP2C19** – metabolises many SSRIs (citalopram, escitalopram, sertraline) and diazepam. Poor metabolisers have higher exposure (guidelines advise dose reduction, e.g. lower escitalopram); ultrarapid metabolisers may need higher doses.

◆ **Phenotype scale** – **poor → intermediate → normal → ultrarapid**. **Poor metaboliser = high drug level = more toxicity** at a standard dose. **Ultrarapid = low level = under-treatment.** CPIC publishes dosing guidance keyed to these phenotypes.

HLA associations (severe cutaneous reactions)

Allele	Drug	Reaction	Population
HLA-B*1502	carbamazepine (also oxcarbazepine, phenytoin)	Stevens-Johnson syndrome / toxic epidermal necrolysis	**South & East Asian** (Han Chinese, Thai, Indian subcontinent)
HLA-A*3101	carbamazepine	spectrum: SJS/TEN, DRESS, maculopapular rash	European, Japanese, broader ancestry
HLA-B*5701	abacavir (non-psychiatric, classic example)	hypersensitivity reaction	the prototype HLA pharmacogenetic test

■ **Pre-prescription testing** – guidelines recommend **screening for HLA-B*1502 before starting carbamazepine in patients of South or East Asian ancestry**; a positive result is a contraindication. This is the strongest, most actionable pharmacogenetic rule in psychiatry.

● PROMISE VS EVIDENCE

CYP genotyping and combinatorial pharmacogenetic panels are **promising but not yet routine**: evidence for improved outcomes is mixed, panels test many genes with uneven clinical validity, and guidelines support targeted use (single well-validated gene-drug pairs, or after multiple treatment failures) rather than universal screening. The clearest, evidence-backed application is the **HLA-B*1502 / carbamazepine** rule, not whole-panel testing.

7 The horizon & other agents

Orexin antagonists for insomnia

- **Dual orexin receptor antagonists (DORAs)** – orexin (hypocretin) is the wake-promoting peptide; its *loss* causes narcolepsy. **Suvorexant** (and lemborexant, daridorexant) block orexin OX1/OX2 receptors to *reduce wakefulness*, a mechanism distinct from the GABAergic Z-drugs/benzodiazepines.

■ **Why preferred** – DORAs promote sleep without GABAergic sedation, carry **lower dependence/abuse potential** and less next-day cognitive impairment than benzodiazepines, with little rebound insomnia. A genuinely new insomnia class.

Anti-amyloid monoclonal antibodies (Alzheimer's)

◆ **Lecanemab & donanemab** – monoclonal antibodies against amyloid-β that **clear amyloid plaques** and modestly slow cognitive decline in **early** Alzheimer's disease. The first **disease-modifying** (not merely symptomatic) Alzheimer's drugs, validating the amyloid hypothesis in part. Approved for early-stage disease with confirmed amyloid.

● ARIA CAUTION

Their hallmark risk is **ARIA** (amyloid-related imaging abnormalities): **ARIA-E** (oedema) and **ARIA-H** (microhaemorrhages), detected on MRI, often asymptomatic but occasionally serious. Risk is higher in **APOE ε4 homozygotes**. Mandates baseline and surveillance MRI monitoring. Benefit is modest and the agents are costly and infusion-based.

Metabolic & immune research lines

GLP-1 receptor agonists

Incretin drugs (semaglutide, tirzepatide) developed for diabetes/obesity are under study for **antipsychotic-induced metabolic syndrome**, addiction/craving, and possible neuroprotective and mood effects. Research-stage in psychiatry; not a psychiatric indication yet.

Anti-inflammatory agents

The **inflammatory hypothesis** of depression has driven trials of adjunctive anti-inflammatories (celecoxib, minocycline, cytokine inhibitors), with signal in patients showing raised inflammatory markers (e.g. CRP). Promising in a subgroup; not established practice.

● **Other horizon targets** – sigma-1 / rapid agents (e.g. dextromethorphan-bupropion for MDD, approved), kappa-opioid antagonists, and trace-amine (TAAR1) agonists for schizophrenia under trial. The common thread: **moving the target off the classic monoamine and D2 receptors**.

QUICK-RECALL · DRILL THESE ONE-LINERS

- **The frame:** the move is off monoamines onto glutamate, GABA-A, muscarinic, orexin, incretin and immune targets. Rapid-acting = glutamate or GABA-A. Many novel agents now approved; psychedelics still investigational.
- **Ketamine/esketamine:** NMDA antagonist → glutamate surge → AMPA/BDNF/mTOR → synaptogenesis. Rapid (hours) and anti-suicidal in TRD. Esketamine intranasal, FDA 2019. Cautions: dissociation, raised BP, abuse liability; effect not durable.
- **Neurosteroids:** brexanolone (IV, 60 h, inpatient) and zuranolone (oral, 14 days) = GABA-A positive allosteric modulators (allopregnanolone analogues) for postpartum depression. Zuranolone NOT approved for MDD.
- **Psychedelics (investigational):** psilocybin = 5-HT2A agonist for depression (Breakthrough designation); MDMA = empathogen for PTSD (FDA declined 2024, more trials needed). Drug plus psychotherapy; not standard care.
- **Antipsychotics:** KarXT (xanomeline-trospium) = first non-D2, M1/M4 muscarinic agonist + peripheral antimuscarinic, no EPS/prolactin. Lumateperone, cariprazine (D3-preferring). LAIs now 2-, 3- and 6-monthly.
- ★ **Pharmacogenomics:** CYP2D6 & CYP2C19 phenotypes (poor → ultrarapid); poor = high level = toxicity. HLA-B*1502 + carbamazepine = SJS/TEN in South/East Asians (screen before prescribing). HLA-A*3101 = broader carbamazepine reactions. Panels promising, not yet routine.
- **Horizon:** orexin antagonists (suvorexant, DORAs) for insomnia, low dependence. Lecanemab/donanemab = anti-amyloid mAbs, first disease-modifying Alzheimer's drugs; watch for ARIA on MRI (worse in APOE ε4). GLP-1 agonists and anti-inflammatories are research lines.

ONE-DAY REVISION · PAPER 4

Recent Advances: Neurostimulation & Novel Therapeutics

Neurostimulation has moved well past conventional ECT and standard rTMS toward focal, accelerated, closed-loop and connectome-guided approaches. Hold the master table cold: each modality by invasiveness, mechanism, indication and approval status. Know what is regulator-approved versus still investigational, and say so plainly. The targeting revolution (individualised, network-based targets) is the thread running through all of it.

● CONCEPT ● RULE ● TRAP ● KEY NUMBER ● MNEMONIC

The colour tells you what kind of fact it is. "Approved" below means cleared by a major regulator (chiefly US FDA) for a stated psychiatric indication; everything else is investigational unless said otherwise.

★ HIGH YIELD TOP 5 IF NOTHING ELSE

1. iTBS is bursts of 3 pulses at 50 Hz repeated at 5 Hz; intermittent iTBS to the left DLPFC is non-inferior to standard 10 Hz rTMS (THREE-D, 2018) in a ~3-minute session.
2. SAINT / SNT is accelerated iTBS, 10 sessions/day for 5 days, targeted by resting-state fMRI to the DLPFC site most anticorrelated with the sgACC; FDA-cleared 2022, with controlled remission ~50% (quote the RCT, not the ~90% open-label figure).
3. Approved in psychiatry: ECT, rTMS, iTBS, deep TMS, SAINT/SNT, VNS, and DBS for OCD (humanitarian device exemption); still investigational: tDCS, tACS, LIFU, MST, FEAST, and DBS for depression.
4. DBS for depression looked striking open-label (subcallosal cingulate / Area 25, Mayberg) but the blinded BROADEN and VC/VS RCTs failed their primary endpoints; the field reframes this as a targeting failure and moves to connectomic, closed-loop stimulation.
5. VNS stimulates the left vagus nerve (right avoided for cardiac efferents), approved only as a slow long-term adjunct for treatment-resistant depression; tDCS polarity rule: anode facilitatory, cathode inhibitory, sub-threshold and not FDA-cleared.

1 The frame: a map of the modalities

Sort every device along two axes: **how invasive** (non-invasive → convulsive → implanted) and **how it acts** (modulates excitability, induces a seizure, or delivers chronic/closed-loop stimulation). This master table is the high-yield centrepiece: it answers most one-line and short-note questions on its own.

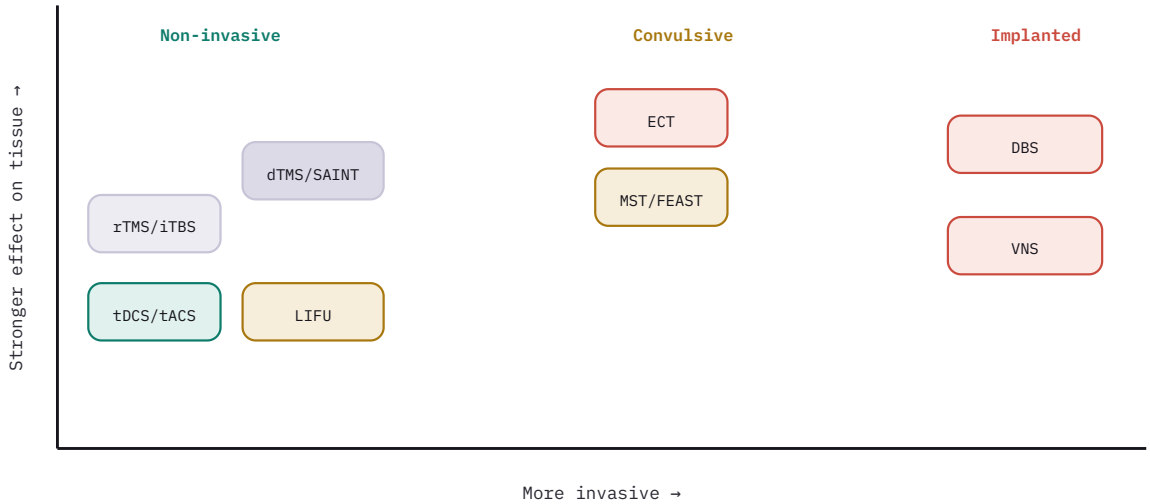
NEUROSTIMULATION DEVICES

	DEVICE PROFILE			
Modality	**Invasiveness**	**Mechanism (in brief)**	**Main psychiatric use**	**Status**
ECT	convulsive, anaesthesia	generalised seizure; broad neuroplastic / neuroendocrine effects	severe / treatment-resistant depression, catatonia, mania	established standard

DEVICE PROFILE

Modality	Invasiveness	Mechanism (in brief)	Main psychiatric use	Status
rTMS (standard)	non-invasive	focal magnetic pulses modulate cortical excitability (LTP/LTD-like)	depression (HF-L DLPFC), OCD	approved
iTBS (theta-burst)	non-invasive	patterned rTMS mimicking endogenous theta; far shorter session	depression	approved (non-inferior to 10 Hz)
SAINT / SNT	non-invasive	accelerated iTBS, fMRI connectivity-guided target, many sessions/day	treatment-resistant depression	approved (2022)
Deep TMS (H-coil)	non-invasive	H-shaped coil reaches deeper / wider cortex	depression, OCD, smoking cessation	approved
tDCS	non-invasive	weak constant current shifts neuronal resting potential (sub-threshold)	depression (adjunct)	investigational (not FDA-cleared)
tACS	non-invasive	oscillating current entrains endogenous rhythms	experimental (mood, cognition)	investigational
tFUS / LIFU	non-invasive	low-intensity focused ultrasound; deep focal neuromodulation	experimental (deep targets)	investigational
MST	convulsive, anaesthesia	magnetically induced, more focal seizure; spares deep structures	depression (ECT alternative)	investigational
FEAST	convulsive, anaesthesia	focal, directional electrical seizure (unidirectional current)	depression (ECT refinement)	investigational
VNS	implanted	chronic left vagal stimulation → brainstem → limbic projections	chronic / recurrent treatment-resistant depression	approved (adjunct, long-term)
DBS	implanted, neurosurgical	chronic high-frequency stimulation of a deep node	treatment-resistant depression, OCD	OCD HDE-approved; depression investigational

THE MODALITY MAP: INVASIVENESS AGAINST MECHANISM



Left to right: non-invasive current/magnetic (tDCS, tACS, rTMS, iTBS, deep TMS, LIFU), then anaesthesia-requiring convulsive therapies (ECT, MST, FEAST), then chronically implanted devices (VNS, DBS). Up the axis = stronger biological footprint on tissue.

QUICK RULE

Approved in psychiatry: **ECT, rTMS, iTBS, deep TMS, SAINT/SNT, VNS**, and **DBS for OCD** (humanitarian device). Still investigational: **tDCS, tACS, LIFU, MST, FEAST**, and **DBS for depression**.

2 Accelerated and patterned TMS

Two advances over standard 10 Hz rTMS: a **shorter pulse pattern** (theta-burst) and a **compressed schedule with a personalised target** (SAINT). Both attack the central weakness of conventional rTMS: a six-week course is slow.

Theta-burst stimulation (TBS)

- **TBS** – bursts of three pulses at ~50 Hz, repeated at ~5 Hz (the theta rhythm). Mimics endogenous hippocampal firing, so it shifts plasticity with far fewer pulses than standard rTMS.
- **iTBS (intermittent)** – short trains with gaps; net **excitatory** (LTP-like). Applied to **left DLPFC** for depression. A session runs about **3 minutes** versus ~37 minutes for 10 Hz rTMS.
- **cTBS (continuous)** – an uninterrupted train; net **inhibitory** (LTD-like). Used to suppress a region.

KEY TRIAL

The **THREE-D** non-inferiority trial (Blumberger et al., *Lancet* 2018) showed iTBS to the left DLPFC is **non-inferior to standard 10 Hz rTMS** for depression, with a fraction of the session time. This is why iTBS has largely replaced conventional rTMS in practice.

SAINT / SNT: accelerated, connectivity-guided iTBS

- **SAINT / SNT** – Stanford Accelerated Intelligent Neuromodulation Therapy (renamed Stanford Neuromodulation Therapy). **Ten iTBS sessions a day** (50-minute inter-session gaps) for **5 days**, delivering a full conventional course of pulses in one week.
- **Personalised target** – the DLPFC site is chosen per-patient by **resting-state fMRI**: the spot most **anticorrelated with the subgenual anterior cingulate (sgACC)**. Network targeting, not a scalp landmark.
- **Higher dose** – ~90,000 pulses across the week (about 5× a standard course), at 90% resting motor threshold.

TRAP TO FLAG

The first open-label SAINT report showed near-90% remission, but the **sham-controlled SNT RCT** (Cole et al., *Am J Psychiatry* 2022, n = 29) found a more modest, real effect (about **~50%** remission at one month, clearly above sham). FDA cleared the protocol in 2022. Quote the controlled figure, not the open-label headline, and note the small sample.

HOLD THIS

iTBS = 3-minute session (non-inferior to 10 Hz, THREE-D). **SAINT/SNT = accelerated iTBS, fMRI-guided to the sgACC-anticorrelated DLPFC, ten sessions/day for five days.**

3 Deeper and focused approaches

Standard figure-of-eight TMS reaches only ~2–3 cm of cortex. Two routes go deeper: a differently wound coil (deep TMS), and, experimentally, an entirely different energy (focused ultrasound) that can reach subcortical targets non-invasively.

Deep TMS (the H-coil)

- **H-coil** – Hesed coil; a winding geometry that produces a broader, deeper field than the standard figure-of-eight, reaching wider prefrontal cortex (at the cost of focality). Marketed as Deep TMS (BrainsWay).

■ **Approved indications** – **major depression**, **OCD** (the first device approved for OCD, 2018, targeting medial PFC / ACC), and **smoking cessation** (2020). For OCD it is paired with symptom provocation before each session.

Low-intensity transcranial focused ultrasound (LIFU / tFUS)

◆ **LIFU** – low-intensity focused ultrasound steers an acoustic beam to a **millimetre-scale deep target** (e.g. amygdala, thalamus) non-invasively. Mechanism is mechanical / thermal-sub-ablative modulation of neuronal membranes; can be excitatory or inhibitory by parameter.

▲ **Status** – **experimental, not routine.** Its appeal is unique: the only non-invasive tool with both *depth* and *focality*. Distinguish from **high-intensity** MRI-guided focused ultrasound (MRgFUS), which *ablates* tissue (used for tremor; capsulotomy for OCD under study). LIFU modulates; HIFU lesions.

● DON'T CONFUSE

Three different "ultrasound" ideas: **LIFU** = low-intensity, reversible neuromodulation (investigational, psychiatry). **MRgFUS / HIFU** = high-intensity ablation (a non-incisional lesion, e.g. thalamotomy, capsulotomy). They are opposite in intent: modulate vs destroy.

4 ECT refinements & seizure-therapy alternatives

ECT remains the most effective acute antidepressant; the advances aim to **keep the efficacy and cut the cognitive cost**. Two levers: refine ECT itself (pulse width, electrode placement), or change the energy used to trigger the seizure (magnetic, or focal electrical).

Ultrabrief-pulse right unilateral ECT

● **Ultrabrief pulse** – pulse width ~**0.3 ms** (vs ~0.5–1.5 ms brief pulse). Closer to neuronal chronaxie, so it triggers a seizure with much less charge, sparing memory.

■ **Right unilateral (RUL) placement** – both electrodes over the non-dominant hemisphere; far less cognitive impairment than bitemporal. **Ultrabrief RUL** markedly reduces memory side effects while keeping useful efficacy, but typically needs a higher dose relative to seizure threshold and may act slightly more slowly. The cognition-sparing combination.

Magnetic seizure therapy (MST)

● **MST** – uses high-frequency, high-intensity **magnetic** pulses (TMS-derived hardware) to induce a therapeutic seizure under anaesthesia. The magnetic field is not impeded by the scalp/skull, so stimulation stays **cortical and more focal**, sparing deeper memory structures (medial temporal lobe).

■ **Claim** – comparable antidepressant effect to ECT in early trials with a **lower cognitive burden** (faster reorientation, better autobiographical memory). Still **investigational**; equipment and seizure-induction reliability are limiting.

Focal electrically administered seizure therapy (FEAST)

● **FEAST** – uses **unidirectional (directional) electrical** current and an asymmetric electrode arrangement to start the seizure focally in the right prefrontal region, aiming to limit spread and cut cognitive effects. An ECT refinement, also **investigational**.

What they share

All four induce a **therapeutic seizure** under general anaesthesia. The goal is constant: retain antidepressant effect, reduce the memory cost by making the seizure **more focal** or the charge lower.

How they differ

Ultrabrief RUL = refine ECT's pulse + placement. **FEAST** = make the electrical seizure focal/directional. **MST** = swap electricity for a **magnetic** trigger (most focal, most cortical). Only ultrabrief RUL is routine; MST and FEAST are experimental.

HOLD THIS

Cognitive sparing, increasing novelty: **ultrabrief RUL ECT** (established refinement) → **FEAST** (focal electrical) → **MST** (focal magnetic). MST and FEAST are not yet routine clinical care.

5 Implanted and closed-loop stimulation

The frontier of treatment-resistant illness: put an electrode in a deep node and stimulate chronically. The story is genuinely mixed; the move now is from **open-loop** (constant) toward **closed-loop** (biomarker-triggered) stimulation.

Deep brain stimulation (DBS)

Indication	Common targets	Evidence / status
OCD	ventral capsule / ventral striatum (VC/VS); nucleus accumbens; STN	Humanitarian Device Exemption (FDA, 2009) for refractory OCD
Depression	subcallosal cingulate (SCG, "Area 25", Mayberg); VC/VS; medial forebrain bundle (MFB)	investigational; pivotal RCTs (BROADEN, the VC/VS trial) failed their primary endpoints

▲ **The mixed trial story** – striking open-label benefit (Mayberg's subcallosal cingulate work) did **not** survive blinded RCTs: the industry-sponsored **BROADEN** (SCG) and the VC/VS depression trial were stopped for futility at the primary timepoint. Long-term open follow-up still suggests benefit in a subset. The lesson examiners want: **open-label promise, RCT disappointment**, with targeting and trial design blamed.

● **Where the field turned** – toward **individualised, tractography-guided targeting** (connectomic DBS) and toward reading a **neural biomarker** of the depressed state to stimulate only when needed.

Responsive / closed-loop (adaptive) stimulation

◆ **Closed-loop DBS** – the device **senses** a pathological neural signature and **stimulates only when it appears**, instead of firing continuously. Proof of concept in depression: a single-patient study (Scangos et al., *Nature Medicine* 2021) detected an amygdala biomarker of low mood and triggered VC/VS stimulation in response.

● **Responsive neurostimulation (RNS)** – the same closed-loop logic is already **approved in epilepsy** (detects seizure onset, aborts it). Psychiatric closed-loop devices borrow this template but remain investigational.

Vagus nerve stimulation (VNS)

● **VNS** – an implanted pulse generator stimulates the **left vagus nerve** (right avoided due to cardiac efferents); afferents reach the nucleus tractus solitarius, then raphe / locus coeruleus and limbic cortex. FDA-approved (2005) as a **long-term adjunct** for chronic / recurrent treatment-resistant depression.

▲ **VNS caveat** – benefit is **slow** (months to a year) and the acute RCT was negative; approval rests on long-term naturalistic data. **Transcutaneous VNS (taVNS)**, stimulating the auricular vagal branch non-invasively, is under study and avoids surgery.

HOLD THIS

Implanted: **VNS** = slow adjunct, approved. **DBS** = approved for **OCD** (HDE), investigational for depression after RCT failures. The future is **closed-loop, biomarker-driven (adaptive)** stimulation.

6 Non-invasive current stimulation

Unlike TMS (which fires action potentials), transcranial electrical stimulation delivers a weak current that **nudges** excitability without directly triggering firing. Cheap, portable, and potentially home-based, but the evidence is softer.

	tDCS	tACS
Current	direct (constant), ~1–2 mA	alternating (oscillating) at a set frequency
Acts by	shifting resting membrane potential (sub-threshold)	entraining endogenous brain oscillations
Polarity rule	anode increases excitability; cathode decreases it	frequency-specific (e.g. targeting alpha, gamma)
Depression use	anode over left DLPFC (adjunct)	experimental

◆ **tDCS polarity** – **anodal = facilitatory**, **cathodal = inhibitory**. It does not cause neurons to fire; it changes how likely they are to fire. This sub-threshold action is the key distinction from rTMS.

● **Home-based tDCS** – portability invites self-administered, remotely-supervised courses. The **DEPRESSION (Woodham et al., 2024)** home-based tDCS RCT reported benefit over sham in major depression, reviving interest, though earlier trials and meta-analyses were inconsistent.

● EVIDENCE CAVEAT

tDCS / tACS are **not FDA-cleared for any psychiatric indication.** The **ELECT-TDCS** trial (Brunoni et al., *NEJM* 2017) found tDCS **inferior to escitalopram** and only modestly better than sham. Effects are small and montage-sensitive. State clearly: promising, low-cost, but **not standard of care**; tACS is earlier-stage still.

7 The state of the evidence

Three things to be able to say cleanly: what is approved versus investigational, why **targeting** is the real revolution, and what is actually **accessible in India**.

Approved versus investigational (say it plainly)

Regulator-approved in psychiatry

ECT (long established) · rTMS · iTBS · deep TMS (depression, OCD, smoking) · SAINT/SNT (2022) · VNS (adjunct) · DBS for **OCD** (humanitarian exemption).

Still investigational / not routine

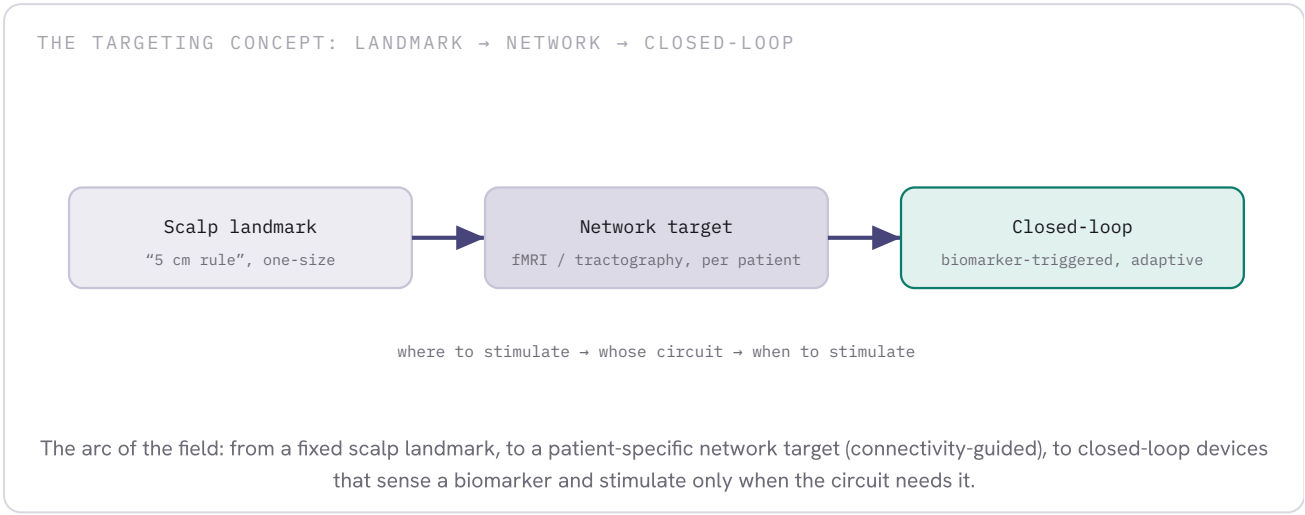
tDCS · tACS · LIFU · MST · FEAST · DBS for **depression** · closed-loop psychiatric DBS · taVNS. Promising signals, but not standard care; trials ongoing.

The targeting revolution

● **From landmark to network** – older protocols used scalp rules ("5 cm rule" for the DLPFC). New work uses **individual functional connectivity** (the sgACC-anticorrelated DLPFC site) and **tractography** to place the field on the patient's own circuit, not a population average.

● **Connectomics** – lesion-network and DBS-connectivity work suggests symptoms map to **networks, not points**; the best DBS responders cluster by the *connectivity* of the stimulated tissue, not its coordinates. This reframes earlier RCT failures as targeting failures.

◆ **Biomarker-driven (adaptive)** – the convergent direction across DBS and TMS: read a neural state, then stimulate **where** and **when** the circuit needs it. Personalised + closed-loop is the through-line of the whole field.



The arc of the field: from a fixed scalp landmark, to a patient-specific network target (connectivity-guided), to closed-loop devices that sense a biomarker and stimulate only when the circuit needs it.

The access picture in India

● **Widely available** – **ECT** is routine across teaching hospitals (modified ECT under anaesthesia; brief-pulse devices standard; the Mental Healthcare Act 2017 bans direct/unmodified ECT and restricts ECT in minors). **rTMS** is available in many academic and private centres.

● **Limited / specialist** – **tDCS** features in Indian research but is not routine therapy. **DBS** exists for movement disorders at major neurosurgical centres; psychiatric DBS is rare and largely research-based. **iTBS** is spreading; **SAINT, MST, FEAST, LIFU** are essentially research-only.

▲ **Practical bottom line** – cost, device availability and trained personnel gate access. For the Indian exam: **ECT and rTMS are the realistic clinical tools**; the rest are mostly academic centres and trials. Present novel methods as **not yet routine**.

QUICK-RECALL · DRILL THESE ONE-LINERS

- **Axes:** non-invasive (tDCS, tACS, rTMS, iTBS, deep TMS, LIFU) → convulsive (ECT, MST, FEAST) → implanted (VNS, DBS). Mechanism = modulate vs seize vs chronic-stimulate.
- **iTBS:** bursts of 3 pulses at 50 Hz, repeated at 5 Hz; intermittent = excitatory (left DLPFC), ~3-minute session; **non-inferior to 10 Hz rTMS** (THREE-D, 2018).
- ★ **SAINT/SNT:** accelerated iTBS, **10 sessions/day × 5 days**, fMRI-guided to the **sgACC-anticorrelated DLPFC**; FDA-cleared 2022; controlled remission ~50% (quote the RCT, not the 90% open-label figure).
- **Deep TMS:** H-coil, deeper/wider field; approved for depression, **OCD** (first OCD device, 2018) and smoking cessation.
- **LIFU:** low-intensity focused ultrasound = the only non-invasive tool with depth + focality; investigational. Don't confuse with high-intensity MRgFUS, which **ablates**.
- **ECT refinements: ultrabrief (~0.3 ms) RUL** = cognition-sparing (routine). **MST** = magnetic, focal, cortical, lower memory cost (investigational). **FEAST** = focal directional electrical seizure (investigational).
- **DBS:** OCD targets = VC/VS, accumbens, STN (**HDE-approved**). Depression targets = subcallosal cingulate (Area 25), VC/VS, MFB; **BROADEN and VC/VS RCTs failed** → investigational.
- **Closed-loop:** sense a biomarker, stimulate only when needed; RNS approved in **epilepsy**; depression proof-of-concept (Scangos 2021, amygdala biomarker → VC/VS).

- **VNS: left** vagus (right avoided, cardiac); approved long-term adjunct for chronic TRD; slow onset, acute RCT negative. taVNS = non-invasive, investigational.
- **tDCS:** weak constant current, sub-threshold; **anode facilitatory, cathode inhibitory**; not FDA-cleared; ELECT-TDCS = inferior to escitalopram; home-based trials reviving interest. **tACS** entrains oscillations, earlier-stage.
- **Targeting:** scalp landmark → individual network (connectomics) → closed-loop. Reframes RCT failures as targeting failures.
- **India:** ECT and rTMS = realistic clinical tools; tDCS/DBS = specialist/research; SAINT/MST/FEAST/LIFU = research-only. Mental Healthcare Act 2017 bans unmodified ECT.

ONE-DAY REVISION · PAPER 4

Recent Advances: Genetics, Biomarkers & Neuroscience

The neuroscience now reshaping psychiatry, and the honest verdict on each piece of it. GWAS and polygenic scores, the immune and gut-brain hypotheses, the biomarker search, and computational psychiatry. The single highest-yield move is to hold each advance against its real clinical readiness: almost all of this is mechanism and research, not yet a test you order on a ward.

● CONCEPT ● RULE ● TRAP ● KEY NUMBER ● MNEMONIC

The colour tells you what kind of fact it is. The recurring exam point: no biomarker yet diagnoses a primary psychiatric disorder.

★ HIGH YIELD TOP 5 IF NOTHING ELSE

1. No biomarker yet diagnoses a primary psychiatric disorder; imaging and bloods are used to *exclude* organic causes, not confirm a diagnosis. The two real clinical exceptions are chromosomal microarray for CNVs in neurodevelopmental workups and anti-NMDA-R (anti-GluN1) antibody testing.
2. GWAS uses a genome-wide significance threshold of $p < 5 \times 10^{-8}$ (Bonferroni on ~1 million tests), which is why it replicates where the candidate-gene era did not; disorders are highly polygenic (schizophrenia 270+ loci, odds ratios ~1.0-1.1).
3. Polygenic risk scores are group/population-level only: case and control distributions overlap heavily, so PRS is *not* validated for individual diagnosis, prediction or screening, and carries a European-ancestry bias.
4. Twin heritability for schizophrenia is ~80% but SNP-based heritability is much lower; the gap is the missing heritability, not proof genes do not matter, and polygenic ≠ deterministic.
5. Anti-NMDA-receptor encephalitis (anti-GluN1/NR1) is the proof of concept that immunity can cause a treatable, reversible psychiatric syndrome: classically a young woman with an ovarian teratoma, psychiatric onset before seizures/dyskinesia/dysautonomia. RDoC and HiTOP are research frameworks, not clinical replacements for ICD/DSM.

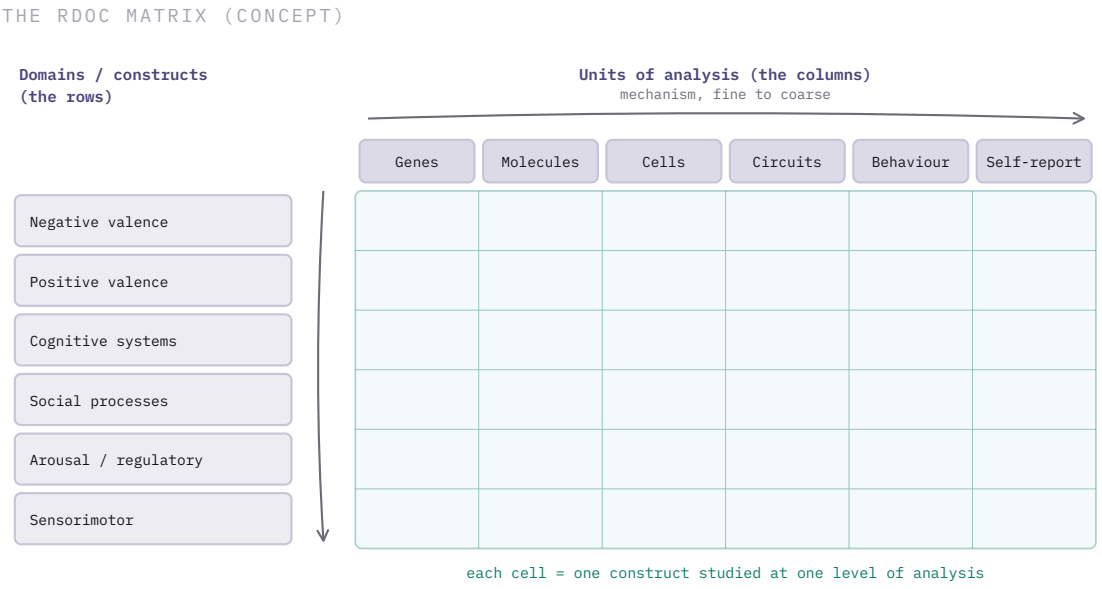
1 The frame: advances and the reframings that organise them

Two forces drive the current syllabus. First, a wave of biological findings (genomic, immune, microbial, imaging, computational). Second, the recognition that DSM/ICD categories cut the brain at the wrong joints, which has produced new **organising frameworks** built around dimensions and mechanisms rather than diagnoses.

The two reframings

- **RDoC** (Research Domain Criteria, NIMH, Insel 2010) – a **research** framework, not a diagnostic system. It studies mechanism across diagnoses using a matrix: **domains/constructs** (rows) against **units of analysis** (columns: genes → molecules → cells → circuits → physiology → behaviour → self-report → paradigms). Dimensional and circuit-based; deliberately agnostic to ICD categories.

- **HiTOP** (Hierarchical Taxonomy of Psychopathology) – a **data-driven, dimensional** classification built from observed covariation of symptoms. Spectra (e.g. internalising, thought disorder, externalising) sit above a general **p-factor** of psychopathology. Replaces categorical boxes with continua; addresses comorbidity and within-diagnosis heterogeneity.
- **The six RDoC domains** – **negative valence**, **positive valence**, **cognitive systems**, **social processes**, **arousal/regulatory systems**, and (added later) **sensorimotor systems**.



RDoC studies a construct (a row) across every unit of analysis (the columns), cutting across DSM diagnoses. It is a research scaffold for mechanism, not a clinic-ready classification.

Centrepiece: each advance against its clinical readiness

Advance	What it offers	Clinical readiness now
GWAS / common-variant genetics	maps the polygenic architecture; hundreds of loci per disorder	Research. No diagnostic or single-gene test in routine psychiatry
Polygenic risk scores (PRS)	a single number summing many small-effect alleles	Research. Group-level only; not validated for individual prediction or clinical use
Copy-number variants (CNVs)	rare, large-effect deletions/duplications	Selective. Microarray used in ID/ASD/dysmorphism workup, not for primary psychiatric Dx
Pharmacogenomics	CYP2D6/2C19 metaboliser status guides dosing	Emerging. Some real-world use; guidelines cautious; not mandated
Inflammatory markers (CRP, cytokines)	stratify an inflammatory subgroup; trial enrichment	Research. No validated diagnostic cut-off; augmentation trials mixed
Structural / functional MRI	group-level differences; circuit dysfunction	Research. Clinically used only to *exclude* organic causes
EEG / event-related potentials	mismatch negativity, P300 as endophenotypes	Research, plus clinical EEG for delirium/seizure exclusion
Machine learning / digital phenotyping	prediction from passive sensing and rich data	Early. Reproducibility and generalisation unproven; ethics unresolved
Anti-NMDA-R / autoimmune encephalitis	antibody assay yields a treatable, reversible cause	Clinical. A genuine, actionable biomarker (a rare exception)

HOLD THIS

The exam answer to "are these clinically useful?" is: **almost all are research tools**. The two real-world exceptions are **chromosomal microarray for CNVs** in neurodevelopmental workups and **autoimmune-encephalitis antibody testing**. Everything else is mechanism, stratification or near-term promise.

● FRAMING TRAP

RDoC and HiTOP are **not** replacements for ICD/DSM in the clinic. RDoC is an NIMH *research* funding framework; HiTOP is a *dimensional research* taxonomy. The categorical systems still govern diagnosis and billing. Examiners reward the candidate who keeps research frameworks and clinical nosology separate.

2 Psychiatric genetics: from candidate genes to the genome

The defining story is a **method shift**. The old candidate-gene era picked one biologically plausible gene (5-HTT, COMT, DRD2) and tested it. Most findings failed to replicate. The genome-wide era tests millions of variants agnostically, in very large samples, with stringent statistics, and is robustly replicable.

The two eras compared

	Candidate-gene (old)	GWAS (current)
Logic	hypothesis-driven; pick a plausible gene	Agnostic; scan the whole genome
Variants tested	one or a few	millions of SNPs
Sample size	small (hundreds)	very large (tens of thousands to millions)
Significance bar	$p < 0.05$	genome-wide $p < 5 \times 10^{-8}$
Verdict	poor replication; largely abandoned	replicable; hundreds of robust loci

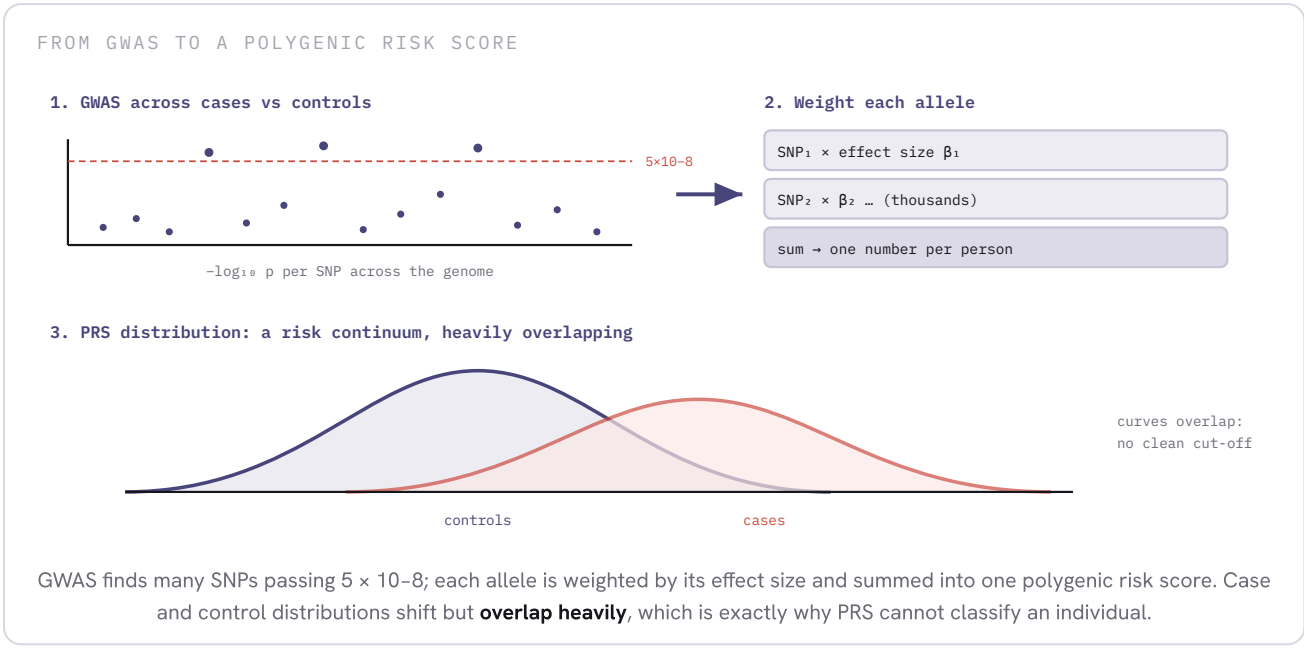
● WHY 5 × 10−8

Testing roughly a million independent common variants demands correction for a million tests. Bonferroni on 0.05 gives the now-standard **genome-wide significance threshold of 5×10^{-8}**. This stringency is exactly why GWAS findings replicate and candidate-gene findings did not.

The polygenic picture

◆ **Polygenicity** – common psychiatric disorders are **highly polygenic**: hundreds to thousands of common variants, each of *tiny* effect (odds ratios typically 1.0–1.1), summing to substantial risk. Schizophrenia GWAS has identified on the order of **270+ loci** (PGC); major depression and bipolar disorder likewise have many.

● **SNP-based heritability** – the proportion of variance explained by measured common SNPs. It is substantial (e.g. roughly a quarter for schizophrenia) but sits well *below* twin-study heritability (schizophrenia ~80%). The gap is the **"missing heritability"** problem: rare variants, gene-by-gene and gene-by-environment interaction, and structural variation are not captured by common-SNP arrays.



GWAS finds many SNPs passing 5 × 10−8; each allele is weighted by its effect size and summed into one polygenic risk score. Case and control distributions shift but **overlap heavily**, which is exactly why PRS cannot classify an individual.

◆ **Polygenic risk score (PRS)** – sums an individual's risk alleles, each weighted by its GWAS effect size, into **one number**. Powerful at the **group/population** level and for research, but the variance explained per person is small and case/control distributions overlap. **Not** clinically validated for individual diagnosis, prediction or screening; ancestry bias (most GWAS are European) further limits transportability.

Rare and structural variation

● **Copy-number variants (CNVs)** – large deletions/duplications, **rare but high-penetrance**. The classic exam example is **22q11.2 deletion** (velocardiofacial / DiGeorge), carrying roughly a 25–30% lifetime risk of schizophrenia. Other recurrent CNVs (1q21.1, 15q11.2, 16p11.2, 3q29, NRXN1) raise risk for schizophrenia, autism and intellectual disability, illustrating shared architecture.

● **Rare coding variants** – exome sequencing implicates rare, often *de novo*, loss-of-function variants. In **schizophrenia**: **SETD1A**, **GRIN2A** and others (SCHEMA consortium) converge on synaptic and glutamatergic/NMDA function. In **autism**: **CHD8**, **SCN2A**, **SHANK3**, **FMR1** (fragile X) and others converge on synaptic and chromatin-remodelling genes.

◆ **Pleiotropy & shared architecture** – the same variants raise risk across diagnoses. There is high genetic correlation between **schizophrenia and bipolar disorder**, and broad cross-disorder overlap among schizophrenia, bipolar, depression, ASD and ADHD (Cross-Disorder Group, PGC). This genomic evidence directly motivates the **transdiagnostic** turn (RDoC, HiTOP, the p-factor).

● TRAP

Do not confuse the two heritabilities. **Twin heritability** for schizophrenia is ~**80%** (high). **SNP-based heritability** (variance from common arrayed SNPs) is much lower. The shortfall is the **missing heritability**, not evidence that genes do not matter. Also: **polygenic ≠ deterministic**; even a high PRS confers risk, not destiny.

3 The immune and inflammatory hypothesis

A large and growing body of work links immune dysregulation to psychiatric illness, most strongly in depression. The frame: chronic low-grade inflammation and microglial activation may drive a subset of cases, and a treatable autoimmune syndrome offers proof that brain-directed immunity can produce psychiatric presentations.

Cytokines and depression

- **The cytokine hypothesis of depression** – a subgroup of depressed patients show raised pro-inflammatory cytokines, classically **IL-6**, **TNF-α** and **CRP**. Supporting strands: **interferon-α** therapy (for hepatitis C/melanoma) induces depression in a substantial minority; **sickness behaviour** (lethargy, anhedonia, social withdrawal) mirrors depressive symptoms; and inflammation is associated with treatment resistance.
- **Proposed mechanism** – cytokines shunt tryptophan down the **kynurenine pathway** (via IDO), reducing serotonin and generating neuroactive metabolites (quinolinic acid, an NMDA agonist). Inflammation also disturbs the HPA axis, monoamine metabolism and neuroplasticity.

Microglia and neuroinflammation

- **Microglial activation** – microglia are the brain's resident immune cells. Activation and aberrant **synaptic pruning** (complement-mediated, e.g. C4) are implicated in **schizophrenia**; the **C4A** finding (Sekar/McCarroll) links a top schizophrenia GWAS signal at the MHC locus to increased complement-driven pruning. PET ligands (e.g. TSPO) probe neuroinflammation in vivo, though results are inconsistent.

Autoimmune encephalitis as proof of concept

- **Anti-NMDA-receptor encephalitis** – the cleanest example of immunity producing psychiatric illness. Antibodies against the **GluN1 (NR1) subunit** of the NMDA receptor cause a syndrome that often *begins* with psychiatric features (psychosis, agitation, behavioural change) before seizures, movement disorder, dysautonomia and reduced consciousness. Classically a **young woman with an ovarian teratoma**. It is **treatable and reversible** with immunotherapy and tumour removal. (See the CNS Infections pack for the full encephalitis workup.)

Why it matters for the exam

It is the proof of concept that a measurable antibody (a genuine biomarker) can yield a **reversible** psychiatric syndrome. Red flags prompting a workup: **first-episode psychosis with neurological signs**, seizures, autonomic instability, abnormal movements, rapid course, or poor response to antipsychotics.

The honest limit

It is **rare**. It does not mean most psychosis is autoimmune. It defines a small, important subgroup to screen for, not a new account of primary schizophrenia.

Anti-inflammatory augmentation

- **The trials** – adjunctive anti-inflammatories (NSAIDs such as **celecoxib**, **minocycline**, statins, cytokine inhibitors, omega-3) have been tested in depression and schizophrenia. Meta-analyses suggest a **modest** benefit, plausibly concentrated in patients with raised baseline inflammation (e.g. CRP). Results are heterogeneous and not yet practice-changing.

QUICK RULE

The inflammatory story is real but **partial**: it explains a subgroup, not all cases. CRP/IL-6/TNF-α are **not** diagnostic tests. Anti-NMDA-R encephalitis is the one place where an immune marker changes management directly.

TRAP

Inflammation in depression is a **correlation** with mixed causal direction: stress, obesity, smoking, poor sleep and the illness itself all raise cytokines. Raised CRP does not diagnose depression, and a normal CRP does not exclude it. Treat the inflammatory hypothesis as a stratification and mechanism story, not a clinic test.

4 The gut-brain axis and the microbiome

A genuinely active research area, and one of the most over-hyped in the popular press. Hold both halves: real bidirectional signalling, but human psychiatric evidence that is still early and preliminary.

The signalling pathways

- **Bidirectional communication** – the gut and brain talk through several routes: the **vagus nerve** (the major neural channel), the **immune system** (cytokines), the **HPA axis** (stress hormones), microbial **metabolites** (short-chain fatty acids such as butyrate), and microbial influence on **neurotransmitter precursors** (gut bacteria affect tryptophan/serotonin availability; most peripheral serotonin is gut-derived).
- **Preclinical foundation** – the strong data are in animals: **germ-free mice** show altered stress reactivity (exaggerated HPA response) and behaviour, partly reversible by recolonisation. These models established that the microbiome *can* influence brain and behaviour.

Human evidence and psychobiotics

- **Human findings** – associations between gut microbiota composition and depression/anxiety exist but are **mostly cross-sectional and small**; causality is rarely established. Interventional trials of **psychobiotics** (probiotics/prebiotics hypothesised to benefit mental health) show small, inconsistent effects. Faecal microbiota transplant in psychiatry is purely experimental.
- **Psychobiotic** – a live organism (or prebiotic) that, when ingested in adequate amounts, is proposed to confer a mental-health benefit via the gut-brain axis. The concept is promising but **not** an established treatment.

● THE OVER-INTERPRETATION TRAP

This is the most common error. The mechanisms are plausible and the animal data are striking, but human psychiatric evidence is **preliminary**: small samples, confounding (diet, drugs, smoking, the illness itself shapes the microbiome), and reverse causation. There is no microbiome test for a psychiatric disorder and no microbiome-based treatment in guidelines. State the promise, then state the caution.

5 Biomarkers and neuroimaging

A biomarker is an objectively measured indicator of a biological process or treatment response. Psychiatry has searched hard for diagnostic biomarkers across imaging, electrophysiology and blood. The honest summary: many group-level differences, no individual-level diagnostic test.

Types of biomarker by purpose

Biomarker type	Question it answers
Diagnostic	does this person have the disorder?
Prognostic	what is the likely course?
Predictive	who will respond to this treatment?
Theragnostic / monitoring	is the treatment working; should we adjust?

The modalities

- **Structural MRI** – replicated **group-level** findings: ventricular enlargement and reduced grey matter in schizophrenia; hippocampal volume changes in depression and PTSD. Effect sizes are small and overlapping, so they cannot diagnose an individual.
- **Functional MRI** – altered activation and connectivity (e.g. amygdala reactivity in mood/anxiety, fronto-limbic circuits). Powerful for mechanism; not a clinical test.
- **EEG / ERPs** – candidate **endophenotypes**: reduced **P300** amplitude and **mismatch negativity (MMN)** in schizophrenia, **prepulse inhibition** deficits (sensorimotor gating). Research markers; clinical EEG is still used to exclude seizures/delirium.
- **Blood-based markers** – inflammatory cytokines, BDNF, cortisol/**dexamethasone suppression**, metabolomic and proteomic panels. None is sensitive or specific enough to diagnose a primary psychiatric disorder.

The connectome and network neuroscience

- **Connectome** – the comprehensive map of the brain's connections. **Network neuroscience** reframes disorders as **dysconnection** syndromes (graph metrics, hubs, the default-mode network, rich-club organisation) rather than single-region lesions. A productive conceptual model; not yet a diagnostic instrument.
- **The single key point** – **no biomarker yet diagnoses a primary psychiatric disorder.** In current practice, neuroimaging and blood tests are used to *exclude* organic and secondary causes (tumour, stroke, demyelination, autoimmune encephalitis, metabolic and endocrine disease), not to confirm a psychiatric diagnosis.

RULE

Distinguish a **biomarker** (objective biological measure) from an **endophenotype** (a heritable, intermediate trait, e.g. P300/MMN, sitting between genes and the clinical phenotype, present in unaffected relatives). Endophenotypes were proposed to be genetically simpler handles on illness; in practice they too have proven polygenic and complex.

6 Computational and digital psychiatry

Two converging strands. **Computational psychiatry** builds formal mathematical models of how the brain computes, to explain symptoms mechanistically. **Digital psychiatry** uses smartphones, wearables and machine learning to measure and predict behaviour in the real world.

Computational frameworks

- **Predictive processing / Bayesian brain** – the brain as a prediction machine that minimises **prediction error** between expectation (priors) and sensory input. Symptoms are recast as faulty inference: **hallucinations** as over-weighted priors overriding sensory evidence; **delusions** as aberrant updating; aberrant **salience** (dopaminergic prediction-error signalling) as a model of psychosis (Kapur).
- **Reinforcement-learning models** – formal models of how reward and punishment shape choice (reward prediction error, learning rate, the explore/exploit trade-off). Used to quantify **anhedonia** and blunted reward learning in depression, and impulsivity/compulsivity in addiction and OCD, with task parameters as candidate markers.

Digital phenotyping and machine learning

- **Digital phenotyping** – moment-by-moment quantification of behaviour using personal devices. **Passive sensing**: GPS/mobility, sleep, screen use, call/text patterns, typing dynamics, voice and speech features. Aim: detect early warning signs (e.g. a manic or relapse prodrome) before they are clinically obvious.
- **Ecological momentary assessment (EMA)** – **active**, repeated real-time self-report in daily life (prompts on the phone). Reduces recall bias and captures variability and context that a clinic snapshot misses; the active counterpart to passive sensing.
- **Machine-learning prediction** – supervised models trained to predict diagnosis, relapse, suicide risk or treatment response from rich, high-dimensional data. Promising in research, but performance often **drops sharply on external validation**.

● REPRODUCIBILITY & ETHICS TRAP

Caveats are heavily examined. **Validity/reproducibility**: small samples, **overfitting**, optimistic in-sample accuracy that collapses out-of-sample, and a replication problem shared with the wider field. **Ethics**: privacy and continuous surveillance, informed consent for passive data, algorithmic bias and equity, data security, the digital divide, and the risk of over-reliance on opaque "black-box" models. Promise is real; deployment must be cautious.

QUICK RULE

Computational psychiatry = mechanism via maths (predictive processing, RL). **Digital** psychiatry = measurement via devices (passive sensing, EMA, ML). Both are early-stage research tools, not validated clinical instruments.

7 Translation and the gaps

The closing, examinable judgement. Despite remarkable mechanistic progress, near-term clinical payoff is modest. A good answer names the obstacles honestly and points to where change is genuinely arriving.

Why translation is hard

- **Heterogeneity** – a single DSM label (e.g. major depression) covers biologically diverse patients. Averaging across that heterogeneity washes out signal; this is the core reason single biomarkers fail and a key motive for stratification and RDoC/HiTOP.
- **Reproducibility** – the replication crisis hit psychiatric neuroscience hard: small samples, flexible analyses, publication bias and overfitting produced many findings that did not hold up. The corrective: **large consortia** (PGC, ENIGMA), pre-registration, and external validation.
- **The transdiagnostic turn** – genomics (pleiotropy), shared circuits and the **p-factor** all argue that mechanism crosses diagnostic boundaries. RDoC and HiTOP operationalise this, aiming at a future psychiatry organised by mechanism and dimension rather than by the present categories.

A realistic near-term appraisal

Genuinely arriving

Chromosomal microarray (CNVs) in neurodevelopmental workups. Autoimmune-encephalitis antibody testing. Cautious pharmacogenomics (CYP2D6/2C19). Inflammation as a **stratifier** for trial enrichment. Digital tools as adjuncts in monitoring.

Not yet here

A diagnostic blood test or scan for a primary psychiatric disorder. PRS for individual clinical decisions. A microbiome treatment in guidelines. A validated ML model for routine relapse or suicide prediction.

◆ **The bottom line** – psychiatry has shifted from candidate genes to the genome, from single regions to circuits and networks, and from categories toward dimensions and mechanism. The science is real and accelerating. But for the foreseeable future, **diagnosis remains clinical**, biomarkers mainly **exclude organic causes**, and the advances are best framed as **stratification and mechanism** rather than ready-made clinical tests.

QUICK-RECALL · DRILL THESE ONE-LINERS

- **Frameworks:** RDoC = NIMH research matrix (constructs × units of analysis), dimensional/circuit, six domains. HiTOP = data-driven dimensional taxonomy, spectra above a general **p-factor**. Neither replaces ICD/DSM in clinic.
- **Genetics shift:** candidate-gene (poor replication) → GWAS (agnostic, huge samples, **5 × 10–8**, replicable). Disorders are highly polygenic; schizophrenia 270+ loci.
- **PRS:** sums small-effect alleles into one number. Group-level only; case/control curves overlap; **not** validated for individual use; European-ancestry bias.
- **Heritability:** twin ~80% (schizophrenia) vs lower SNP-based heritability = the **missing heritability** gap. Polygenic ≠ deterministic.
- **Rare variants:** CNVs rare/high-penetrance (**22q11.2** → ~25–30% schizophrenia risk). Schizophrenia: SETD1A, GRIN2A. Autism: CHD8, SCN2A, SHANK3, FMR1. Pleiotropy → transdiagnostic turn.
- **Immune:** cytokines (IL-6, TNF-α, CRP) raised in a depression subgroup; interferon-α induces depression; kynurenine pathway. C4/complement & microglial pruning in schizophrenia.
- **Proof of concept:** anti-NMDA-R (anti-GluN1) encephalitis – psychiatric onset, young woman + ovarian teratoma, **treatable and reversible**. The one immune biomarker that changes management.
- **Anti-inflammatory augmentation:** celecoxib, minocycline, omega-3 – modest, heterogeneous benefit, maybe in high-CRP patients. Not practice-changing.
- **Gut-brain:** vagus + immune + HPA + metabolites (SCFAs). Strong animal data (germ-free mice); human psychiatric evidence **preliminary**. Psychobiotics inconsistent. Beware over-interpretation.
- ★ **Biomarkers:** structural/functional MRI, EEG (P300, MMN, PPI), blood markers – all group-level. **No biomarker yet diagnoses a primary psychiatric disorder**; imaging is used to exclude organic causes. Connectome = dysconnection view.
- **Computational:** predictive processing / Bayesian brain (hallucination = over-weighted prior; aberrant salience = psychosis); reinforcement learning models reward (anhedonia, addiction).
- **Digital:** digital phenotyping (passive sensing), EMA (active real-time self-report), ML prediction. Caveats: overfitting, poor external validity, privacy/consent/bias ethics.
- **Bottom line:** heterogeneity + reproducibility are the gaps; consortia (PGC, ENIGMA) + pre-registration the fix. Diagnosis stays clinical; advances = stratification and mechanism, not ready tests.

ONE-DAY REVISION · PAPER 4

Evidence-Based Psychiatry & Critical Appraisal

From the answerable question to the bedside decision: the five steps, the hierarchy that ranks evidence, the design that fits each question, and the numbers that tell you whether to believe a result. Every appraisal checklist and association measure here is a recent-advances answer in waiting.

● CONCEPT ● RULE ● TRAP ● KEY NUMBER ● MNEMONIC

The colour tells you what kind of fact it is. Diagnostic-test arithmetic (sensitivity, LR) lives mostly in the Measurements pack; cross-referenced here.

★ HIGH YIELD TOP 5 IF NOTHING ELSE

1. Case-control yields only an odds ratio, never a true RR or incidence (it samples on outcome); the OR approximates the RR only when the outcome is rare, roughly <10%, and exaggerates it for common outcomes.
2. NNT = 1 / ARR (smaller is better); a relative risk reduction hides the baseline, so the same 50% RRR gives NNT 100 at a 2%→1% baseline but NNT 10 at 20%→10%, demand the absolute numbers.
3. Allocation concealment (hides the upcoming assignment, before randomisation, guards recruitment) is not blinding (after assignment, guards conduct); trials without adequate concealment overestimate treatment effects.
4. Intention-to-treat, analyse-as-randomised, is the gold-standard primary analysis for a superiority trial (conservative, preserves randomisation); per-protocol breaks randomisation and risks optimism, and both should agree in a non-inferiority trial.
5. The evidence hierarchy is a default, not a law: best design depends on the question (cohort for prognosis, case-control for rare harm); GRADE rates certainty per outcome with RCTs starting high and observational studies starting low.

1 The frame: evidence-based medicine

Evidence-based medicine (Sackett) is the **conscientious, explicit and judicious use of current best evidence** in decisions about individual patients. It rests on three legs, not one: the best research evidence, the clinician's expertise, and the patient's values and circumstances. Evidence never decides alone.

The five steps (the five A's)

Step	What you do	Tool
1. Ask	convert the clinical problem into an answerable question	**PICO**
2. Acquire	search efficiently for the best evidence	databases, pre-appraised sources
3. Appraise	judge the evidence for validity, importance & applicability	critical-appraisal checklists
4. Apply	integrate the appraisal with expertise & the patient's values	shared decision-making
5. Assess	evaluate your own performance & the outcome; iterate	audit, reflection

● MNEMONIC

"Ask, Acquire, Appraise, Apply, Assess" → the five A's

Five steps, all beginning with A. The cycle closes on itself: step 5 (assess) feeds the next question. EBM is a loop, not a line.

Forming the question: PICO

A vague question ("does therapy help depression?") cannot be searched or answered. PICO forces it into four searchable parts.

Letter	Element	Worked example
P	**Population** / patient / problem	adults with moderate major depression
I	**Intervention** (or exposure / index test)	add CBT to an SSRI
C	**Comparison** (control, alternative, or none)	SSRI alone
O	**Outcome** (the result that matters)	response at 12 weeks

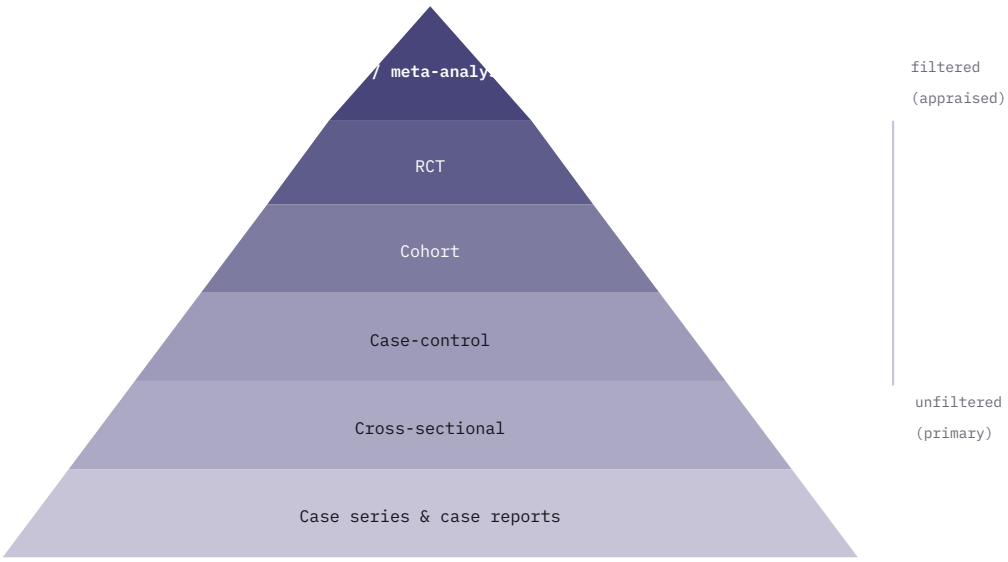
● RULE

Variants extend the core four: **PICOT** adds *Time* (follow-up horizon), **PICOS** adds *Study design*. The question type then selects the best design: therapy → RCT; prognosis → cohort; aetiology/harm → cohort or case-control; diagnosis → cross-sectional with a reference standard.

2 The hierarchy of evidence

Not all evidence is equal. Designs are ranked by how well they guard against **bias** and **confounding**. Higher up means, in general, a more trustworthy estimate, because the design controls more of what could mislead you.

THE EVIDENCE PYRAMID



Apex: synthesised, pre-appraised evidence (systematic reviews and meta-analyses). Then experimental (RCT), then observational analytic (cohort, case-control), then descriptive (cross-sectional, case series and reports), then unsystematic expert opinion at the base.

● IMPORTANT CAVEAT

The pyramid is a **default ranking, not a law**. The best design depends on the question. For *therapy*, the RCT sits above observational studies; but for *prognosis* a cohort is the natural top design, and for *rare harms* a case-control or even a case report may be the only feasible evidence. A well-conducted cohort can outrank a flawed RCT. GRADE (section 6) formalises this: the design sets the starting certainty, then it is up- or down-graded on its actual quality.

3 Study designs at a glance

The centrepiece comparison. For each design, hold three things: **what it answers best**, its **direction** in time, and the **measure of association** it yields.

Design	Answers best	Direction	Measure yielded
RCT	**therapy / intervention** efficacy & causation	prospective; allocation by randomisation	RR, ARR, NNT
Cohort	**prognosis, incidence**, harm of common exposures	prospective (or retrospective): exposure → outcome	RR, incidence; HR (time-to-event)
Case-control	**rare diseases**, long-latency outcomes, aetiology	retrospective: outcome → look back for exposure	odds ratio (OR)
Cross-sectional	**prevalence**, a snapshot, survey, test accuracy	one point in time (no direction)	prevalence; prevalence OR
Case report / series	**novel** presentations, rare events, hypothesis-generating	descriptive, no comparison group	none (descriptive)

The measures, defined

- **Relative risk (RR)** – risk in the exposed / risk in the unexposed. A true *ratio of risks*; needs incidence data, so it comes from cohorts and RCTs, not case-control studies.
- **Odds ratio (OR)** – the odds of exposure in cases vs controls. The natural output of a **case-control** study (where you cannot compute risk because the sampling fixes the disease counts).
- **Hazard ratio (HR)** – the ratio of *instantaneous event rates* over follow-up; from survival / time-to-event analysis (Cox regression, Kaplan-Meier). Used when *when* the event happens matters, not just whether.

● TRAP

The **OR approximates the RR only when the outcome is rare** (roughly <10%). For common outcomes the OR exaggerates the RR (pushes it further from 1). A case-control study can *never* give a true RR or an incidence, because it samples on outcome, not exposure. If a paper reports an RR, it was a cohort or trial, not a case-control study.

Cohort: exposure → outcome

Start with exposed and unexposed groups, follow forward, count who develops the outcome. Gives **incidence and RR**. Good for common exposures and multiple outcomes. Weak for rare diseases (huge n, long wait) and prone to loss to follow-up.

Case-control: outcome → exposure

Start with cases (have the disease) and controls (do not), look **back** for exposure. Gives an **OR**. Efficient for rare diseases and many exposures. Prone to **recall** and **selection** bias; control choice is everything.

4 Critical appraisal of a trial

For an RCT, appraisal asks one question in many forms: **could anything other than the intervention explain the result?** The design features below each close a specific leak.

Allocation: randomisation and concealment

- **Randomisation** – allocating participants to arms by chance. Its purpose is to balance **known and unknown** confounders across groups, so any difference at the end is attributable to the intervention. This is what observational designs cannot do.
- **Allocation concealment** – hiding the *upcoming* assignment from whoever enrols patients, **before** randomisation. Prevents selection bias in who gets recruited into which arm (e.g. steering sicker patients away from the new drug). Distinct from blinding.

CLASSIC TRAP

Allocation concealment happens *before and at* assignment (you cannot foresee the next allocation). **Blinding (masking)** happens *after* assignment (you do not know which arm a patient is in). Concealment guards recruitment; blinding guards what happens afterwards. Empirically, trials without adequate concealment *overestimate* treatment effects.

Blinding (masking)

- **Levels of blinding** – **single** (participant), **double** (participant + assessor/clinician), **triple** (+ data analyst). Blinding the outcome assessor is the most important for subjective endpoints, which dominate psychiatry. An **active placebo** mimics side-effects to preserve blinding.

Analysis: ITT vs per-protocol

Analysis	Who is analysed	What it preserves / tests
Intention-to-treat (ITT)	**everyone**, analysed in the arm they were randomised to, regardless of what they actually received or whether they dropped out	preserves randomisation; pragmatic, **conservative**; the primary analysis for efficacy
Per-protocol	only those who **completed** the protocol as assigned (compliant completers)	estimates effect under ideal adherence; breaks randomisation; risks optimism

HOLD THIS

ITT analyse-as-randomised is the gold standard for a superiority trial: it keeps the balanced groups intact and gives a conservative, real-world estimate. Per-protocol can be reported alongside but never replaces it. **Non-inferiority** trials are the exception, where both ITT and per-protocol should agree.

CONSORT

- **CONSORT statement** – **Cons**olidated **S**tandards **o**f **R**eporting **T**rials. A **25-item checklist** plus a **participant flow diagram** (enrolment → allocation → follow-up → analysis), the standard for *reporting* a parallel-group RCT. Reporting guidelines by design: **CONSORT** (RCT), **STROBE** (observational), **PRISMA** (systematic reviews), **STARD** (diagnostic accuracy).

The five biases (and confounding)

Bias	What goes wrong	Guarded by
Selection	groups differ at entry; who gets in / which arm is non-random	randomisation, allocation concealment

Bias	What goes wrong	Guarded by
Performance	groups treated differently apart from the intervention (extra care, co-interventions)	blinding of participants & clinicians
Detection (ascertainment)	outcomes measured / interpreted differently between arms	blinding of outcome assessors
Attrition	differential dropout / loss to follow-up distorts groups	ITT analysis, complete follow-up
Reporting	selective outcome reporting; only favourable results published	pre-registration, full reporting

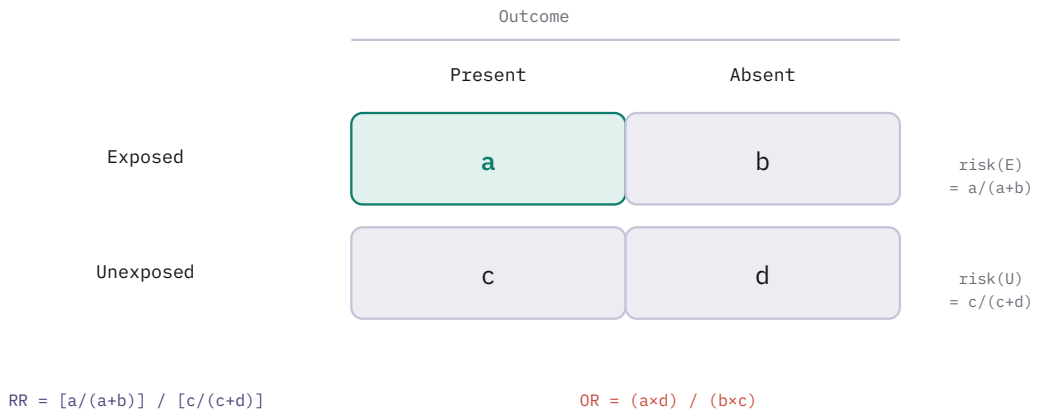
● TRAP · BIAS VS CONFOUNDING

Bias is a systematic error built into the *study process* (selection, measurement) that cannot be fixed by a bigger sample. **Confounding** is a real third variable, linked to both exposure and outcome, that distorts the true association (coffee and lung cancer, confounded by smoking). Confounding can be tackled at *design* (randomisation, restriction, matching) or *analysis* (stratification, multivariable regression). Randomisation handles confounding; it does not, by itself, handle bias from poor conduct.

5 Interpreting the numbers

A result is two questions: **is the effect real** (precision, the CI and the p-value) and **is it big enough to matter** (the size of the effect and the NNT). Statistical significance is not clinical importance.

THE 2×2 TABLE: WHERE THE MEASURES COME FROM



The four cells a, b, c, d generate the lot. RR is the ratio of the two row risks; OR is the cross-product (ad/bc). ARR is the difference of the two risks; NNT is 1/ARR.

The effect measures

Measure	Definition	Reads as
Relative risk (RR)	risk(exposed) / risk(unexposed)	relative; RR 0.7 = 30% lower risk
Relative risk reduction (RRR)	1 − RR	proportion of baseline risk removed; can mislead
Absolute risk reduction (ARR)	risk(control) − risk(treated)	actual percentage-point drop; depends on baseline risk
Number needed to treat (NNT)	**1 / ARR**	how many to treat to prevent one event; **smaller is better**
Number needed to harm (NNH)	1 / absolute risk increase	how many treated for one extra harm; **larger is better**

● CLASSIC TRAP · RELATIVE HIDES, ABSOLUTE REVEALS

"Halves the risk" (RRR 50%) sounds dramatic but tells you nothing about scale. If risk falls from 2% to 1%, the ARR is just 1 percentage point and the **NNT is 100**. The same 50% RRR on a baseline of 20% → 10% gives an ARR of 10% and an **NNT of 10**. Always demand the absolute numbers; RRR is constant across baselines while ARR and NNT track how much actually changes for real patients.

Precision and significance

◆ **Confidence interval (CI)** – the plausible range for the true value; a **95% CI** means that on repeated sampling 95% of such intervals would contain the true parameter. Width = **precision** (narrow is good; widens with smaller n). For a *ratio* (RR, OR, HR), if the CI **crosses 1** the result is non-significant; for a *difference* (ARR, mean difference), the no-effect value is **0**.

◆ **p-value** – the probability of a result *at least this extreme* if the null hypothesis were true. Conventionally significant at **$p < 0.05$**. It is *not* the probability the null is true, and not the size of the effect. A tiny, clinically trivial effect can be highly significant in a huge sample.

◆ **Effect size (Cohen's d)** – the standardised mean difference: (mean difference) / pooled SD. Conventional anchors: **0.2 small, 0.5 medium, 0.8 large**. It expresses magnitude independent of sample size, the antidote to over-reading a p-value. (For binary outcomes the analogous "effect size" is the OR / RR.)

READ A RESULT IN TWO BEATS

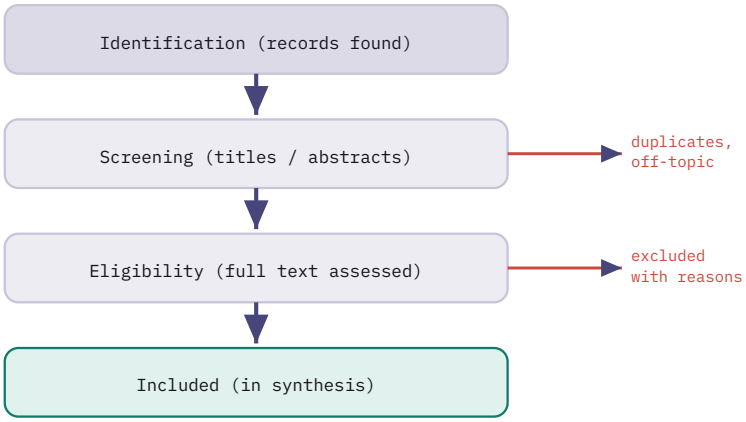
(1) Is it real? Look at the CI, not just p: does it exclude the no-effect value, and how wide is it? **(2) Is it big enough?** Look at the ARR / NNT and the effect size, not the RRR. Significant ≠ important.

6 Systematic reviews & meta-analysis

A **systematic review** answers a focused question by a reproducible, pre-specified search and appraisal of all eligible studies. A **meta-analysis** is the optional statistical step that *pools* their results into one summary estimate with more power and precision. Every systematic review is systematic; not all contain a meta-analysis.

PRISMA: the flow of selection

THE PRISMA SELECTION FLOW



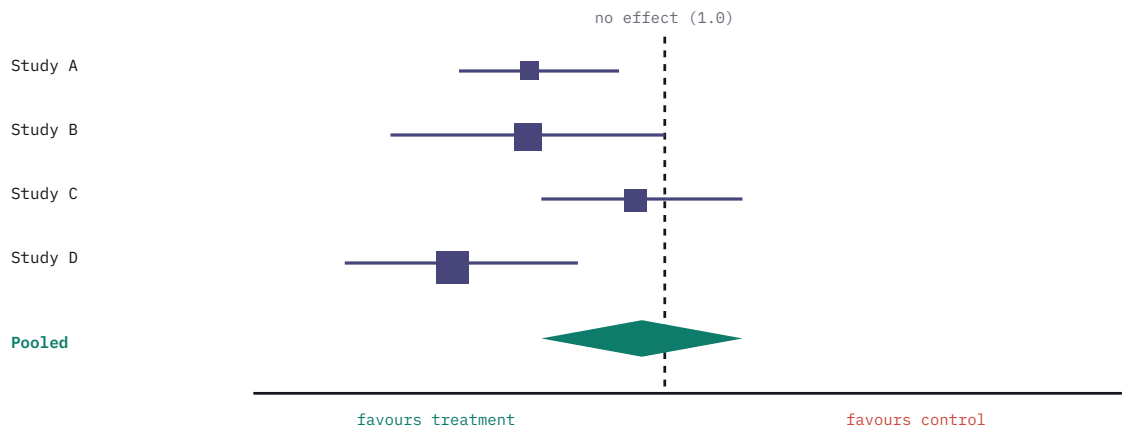
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses): a four-stage flow diagram, identification → screening → eligibility → included, with the count and reasons for exclusions at each stage. The standard for reporting systematic reviews.

Heterogeneity

- **Heterogeneity** – the variability between study results beyond chance. **Clinical** (differing populations / doses), **methodological** (differing design), **statistical** (differing effect estimates). High heterogeneity undermines a simple pooled number.
- **I^2 statistic** – the percentage of total variation across studies due to heterogeneity rather than chance. Rough guide: **<25% low, ~50% moderate, >75% high**. High I^2 argues for a **random-effects** model (assumes a distribution of true effects) over a **fixed-effect** model (assumes one common true effect). Cochran's **Q** is the significance test; I^2 quantifies the magnitude.

The forest plot

HOW TO READ A FOREST PLOT



Each square is one study's point estimate (area = its weight); the horizontal line is its 95% CI. The vertical line is no effect (1.0 for a ratio). The diamond at the bottom is the pooled estimate, its width its CI. A CI touching the line = non-significant. Squares scattered widely from the diamond signal heterogeneity.

Publication bias and the funnel plot

▲ **Publication bias** – positive, significant studies are more likely to be published (and in English, and cited), so a review that finds only published work overstates the effect. Tackled by searching trial registries, grey literature and unpublished data.

● **Funnel plot** – effect size (x) against study precision / size (y). With no bias it is a **symmetric inverted funnel**: small studies scatter widely at the base, large ones cluster at the apex. **Asymmetry** (a missing corner of small negative studies) suggests publication bias. **Egger's test** tests the asymmetry statistically.

GRADE: rating certainty

◆ **GRADE** – **G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation. Rates certainty of evidence *per outcome* as **high, moderate, low or very low**. RCTs **start high**, observational studies start low. Five reasons to **downgrade**: risk of bias, inconsistency, indirectness, imprecision, publication bias. Three reasons to **upgrade** observational evidence: large effect, dose-response, plausible confounding that would reduce the effect.

● RULE

GRADE separates two judgements a guideline must not conflate: **certainty of evidence** (how sure we are of the estimate) and **strength of recommendation** (strong vs weak/conditional). Low-certainty evidence can still ground a strong recommendation when benefits clearly outweigh harms, and high-certainty evidence can ground a weak one when the trade-off is close.

7 Diagnostic tests & applying the evidence

The final two links: judging a **diagnostic test**, then carrying any appraised evidence **to the individual patient**. Evidence ends at the bedside, not the journal.

Test characteristics (cross-reference: Measurements pack)

Metric	Definition	Property
Sensitivity	true positives / all **diseased** = a/(a+c)	fixed; detects disease (rules *out*: SnNOut)
Specificity	true negatives / all **well** = d/(b+d)	fixed; confirms disease (rules *in*: SpPIn)
PPV	true positives / all **test-positive**	varies with prevalence
NPV	true negatives / all **test-negative**	varies with prevalence
LR+	sensitivity / (1 − specificity)	combines both; prevalence-independent
LR−	(1 − sensitivity) / specificity	combines both; prevalence-independent

● TRAP

Sensitivity and specificity are **properties of the test** and do not change with prevalence. Predictive values **do**: the same test applied to a low-prevalence population yields a poor PPV (more false positives), which is why screening an unselected population throws up false alarms. **Likelihood ratios** are the bridge: they combine sensitivity and specificity, stay stable across settings, and move a pre-test probability to a post-test probability (LR+ >10 or LR− <0.1 shifts probability substantially). Full worked arithmetic and the SpPIn/SnNOut rules: Measurements pack.

Clinical practice guidelines

● **Clinical practice guidelines (CPGs)** – systematically developed statements to assist decisions for specific clinical circumstances. Best built by a multidisciplinary panel from a systematic review, with evidence and recommendation strength graded (GRADE), conflicts of interest declared, external review and a planned update. Psychiatry examples: **NICE, APA, IPS, WFSBP, Maudsley**.

▲ **AGREE II** – the instrument for *appraising* a guideline's own quality (rigour of development, stakeholder involvement, editorial independence, applicability). A guideline is evidence to be appraised, not obeyed blindly.

Apply: evidence to the individual

■ **Applicability check** – before transferring a trial result, ask: is **my patient** like the trial's population, or were they excluded (comorbidity, age, severity)? Were **all important outcomes** (including harms) considered? Do the likely benefits, harms and costs fit **this** patient? The relevant number for the patient is the *baseline-risk-adjusted* NNT, not the trial's average.

■ **Patient values & shared decision-making** – the final A. Best evidence plus clinical expertise still has to meet the patient's **preferences, values and circumstances**. Where evidence is uncertain or trade-offs are close (much of psychiatry), shared decision-making is not a courtesy but the method. This closes the EBM triad and the loop back to step 1.

HOLD THIS

EBM is a **three-legged stool**: best evidence, clinical expertise, patient values. Drop any leg and it falls. The hierarchy ranks the evidence leg; appraisal tests it; application weighs it against the other two for one real person.

QUICK-RECALL · DRILL THESE ONE-LINERS

- **Five steps:** Ask, Acquire, Appraise, Apply, Assess (the five A's). Question framed by **PICO** (Population, Intervention, Comparison, Outcome; +T time, +S study design).
- **Hierarchy:** SR/meta-analysis > RCT > cohort > case-control > cross-sectional > case series/report > expert opinion. But *best design depends on the question* (cohort for prognosis, case-control for rare harm).

- **Designs & measures:** RCT → RR, ARR, NNT · cohort (exposure→outcome) → RR, incidence, HR · case-control (outcome→exposure) → OR · cross-sectional → prevalence.
- ★ **OR vs RR:** OR approximates RR only when the outcome is rare (<10%); case-control gives only an OR, never a true RR.
- **HR** = time-to-event (survival / Cox); *when* the event happens, not just whether.
- **Appraisal:** randomisation balances confounders · allocation concealment (before assignment, guards recruitment) ≠ blinding (after assignment, guards conduct).
- **Analysis:** ITT (everyone, as-randomised, conservative, gold standard) vs per-protocol (completers only, optimistic). **CONSORT** = RCT reporting (25-item + flow diagram).
- **Five biases:** Selection, Performance, Detection, Attrition, Reporting. Bias = process error (not fixed by larger n); confounding = a real third variable (fixed by randomisation / adjustment).
- **Numbers:** NNT = 1/ARR (smaller better) · NNH = 1/ARI (larger better). RRR hides baseline risk; demand ARR. CI crossing **1** (ratio) or **0** (difference) = non-significant. Cohen's d: 0.2 / 0.5 / 0.8 = small / medium / large.
- **Meta-analysis:** PRISMA flow (identification→screening→eligibility→included). I^2 >75% = high heterogeneity → random-effects. Forest plot diamond = pooled estimate. Funnel-plot asymmetry (Egger's) = publication bias. **GRADE**: RCT starts high, observational low; high/moderate/low/very low.
- **Diagnosis:** sensitivity/specificity fixed; PPV/NPV vary with prevalence; likelihood ratios are the prevalence-stable bridge. SnNOut / SpPIn. Guidelines appraised by **AGREE II**.
- **Apply:** three-legged stool = evidence + expertise + patient values; check applicability and the patient's baseline-risk-adjusted NNT, then share the decision.