WEAVE SPRINT . PAPER IV

Endocrine psychiatry

The endocrine and metabolic disease a psychiatrist must recognise, investigate and treat: the HPA axis with Cushing syndrome and steroid psychiatry, the thyroid and parathyroid disorders and what lithium does to them, Wilson's disease from copper to chelation, the nutritional syndromes with Wernicke as an emergency, then the metabolic cost of our own prescribing with its monitoring, diabetes and the mortality gap in serious mental illness, the electrolyte and water-balance disturbances led by SIADH, and the hepatic, uraemic and toxic encephalopathies with the reproductive and environmental endocrinology that completes them.

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WEAVE . CENTRE FOR INTEGRATIVE PSYCHIATRY

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Concept / rule Key number Trap

PAPER IV

Endocrine and metabolic psychiatry

Four bands . one complete notes document

The endocrine axes: adrenal, thyroid and parathyroid

1 · Endocrine and metabolic disease for the psychiatrist: what this chapter owns, and what it points to

Every psychiatric syndrome in this chapter can be produced by a gland, a nutrient, a solute, a metal or a drug that a psychiatrist prescribed. The examinable point is not the soft one that hormones influence mood. It is the hard one: a real proportion of psychiatric presentations are generated, sustained or amplified by a disturbance of an endocrine axis, a metabolic pathway, a nutrient store, an electrolyte, an organ of clearance or an environmental toxin, and a large share of those disturbances are correctable. Depression, anxiety, psychosis, catatonia, apathy, cognitive decline and personality change all recur across this chapter, arriving each time from a different organ. The mental state examination alone will not say which organ, and that single limitation is the problem the chapter exists to solve.

The work is therefore not memorising a catalogue of glands and their psychiatric associations. It is learning to hold an ordinary psychiatric presentation and ask a disciplined sequence of questions about the body that produced it: which system could generate this picture, which way causation runs, what in the history or examination points to an organ rather than a mood disorder, which test answers that question, and what changes if it comes back abnormal. The disease sections supply the criteria, investigations, thresholds and treatments. This orientation supplies the **clinical architecture** they sit inside, and the boundary map of what belongs here and what belongs to a neighbouring chapter.

1.1 Traffic runs both ways between body and mind

Most candidates arrive with one model: systemic disease produces psychiatric symptoms. That covers part of the chapter and misreads the rest. The organising discipline is to establish the **direction of causation** first, because it determines who investigates, who treats, and what a good answer looks like.

Systemic disease may present to psychiatry wearing a psychiatric face, referred as depression or psychosis while the disease stays silent, subtle or attributed to the mental illness. Causation also runs the other way, where psychiatric illness and its treatment generate endocrine and metabolic disease: the exposure is a prescription and the outcome is measured in weight, lipids, glucose, prolactin and sodium. The two may also coexist on shared ground, because severe mental illness, poverty, inactivity, diet, tobacco and reduced access to physical healthcare all move metabolic risk the same way, so association establishes nothing about cause. Finally the treatments collide: a psychotropic unsafe in organ failure, a hormone replacement that unmasks an affective episode, an endocrine therapy that alters psychotropic handling.

DIRECTION OF CAUSATION	HOW THE CASE USUALLY ENTERS	THE REASONING IT DEMANDS	WHERE DEPTH FOLLOWS
Systemic disease presenting psychiatrically	Referral for a mood, psychotic or cognitive syndrome	Find the somatic signature; treat the disease, then reassess the mental state	The endocrine axis, nutritional and encephalopathy sections
Psychiatric treatment producing systemic disease	An abnormal weight, waist, lipid, glucose, prolactin or sodium result	Attribute to drug, illness or baseline; switch, add or accept	The treatment-burden and monitoring sections
Shared ground and co-occurrence	A patient with both, and no clear sequence	Resist causal language; treat both, explain neither by the other	The diabetes, obesity and mortality sections
Treatment collision	A prescribing question in organ impairment or hormone therapy	Predict the interaction; choose the agent the failing organ tolerates	The prescribing-in-impairment and reproductive sections

RULE **Name the direction of causation before you name the disease.** The same laboratory abnormality means something different depending on whether the body generated the psychiatric state, the treatment generated the abnormality, or both merely travelled together. Answers that leave the direction unstated read as association-hunting and collapse under one follow-up question in the viva.

1.2 Reversibility is the currency of this chapter

These diseases earn their disproportionate examination weight because of what happens when they are found. Correct the deficiency, replace the hormone, remove the toxin, chelate the metal, restore the solute, and a psychiatric syndrome that looked autonomous may remit, sometimes completely. That converts a screening decision into a clinical duty, and it is why the chapter reads as a set of things not to miss rather than a survey of endocrinology.

Reversibility is not unconditional, and the qualification is where the marks sit. Several diseases here have a **treatment window**: an interval during which correction restores function, beyond which a residual deficit becomes fixed. Others reverse only partially, leaving a remnant to be recognised as sequel rather than pursued as fresh pathology. Others cause harm through the correction itself, so the rate of treatment matters as much as the fact of it. Each belongs to the section that owns it; the rule here is that reversibility is a claim with conditions attached, never a promise.

Axis	Direction	Window	Boundary
THE SYSTEM	THE CAUSAL RUN	THE URGENCY	THE HANDOVER

This governs how cognitive presentations are handled. When a metabolic, endocrine or nutritional disease produces cognitive impairment, this chapter teaches the disease, its cognitive signature and the extent to which it reverses; the dementia syndrome and its workup belong to the Dementias and neurocognitive disorders notes. When systemic disturbance produces an acute confusional state, this chapter teaches the disease and the derangement that drove it, while

delirium as a syndrome, with its criteria, assessment and prevention, belongs to the Stroke, TBI, delirium and focal brain syndromes notes. Keeping that division clean prevents the commonest structural fault here, which is spending half the page rewriting a workup the question did not ask for.

1.3 The mental state cannot name the organ; the body can

Because the psychiatric phenotypes overlap so heavily across the chapter, the discriminating evidence is almost never in the mental state. It is in the **somatic signature**: the physical symptoms, examination findings, temporal features and exposures that point at one organ rather than another. Depression with cold intolerance, hair and skin change and slowed relaxation of reflexes is a different proposition from depression with weight loss, tremor, heat intolerance and tachycardia, and both differ from depression with pigmentation, postural dizziness and salt craving. The affective content may be indistinguishable in all three.

This puts an old-fashioned demand on the psychiatric history and examination. A systematic review of systems is not padding; it is the discriminating instrument. So is a drug history covering prescribed steroids, over-the-counter preparations, traditional and complementary remedies, supplements and anything the patient does not consider a medicine, and an exposure history covering occupation, water source, hobby chemicals, home remedies and cosmetics, alongside nutritional, alcohol, menstrual and reproductive histories and a family history that may carry an inherited metabolic disorder.

Certain features should raise suspicion sharply and are worth carrying as a standing list, because they are the practical trigger for looking beyond the psychiatric diagnosis.

- Onset atypical for the psychiatric diagnosis by age, tempo or absence of a plausible psychosocial context.
- A mixed or shifting picture crossing diagnostic boundaries, especially affective symptoms with psychosis, cognitive change or fluctuating conscious level.
- Prominent physical symptoms the patient has not connected to the psychiatric presentation.
- Failure to respond to adequate psychiatric treatment, or unexpected deterioration during it.
- Neurological signs, movement abnormality, seizures or autonomic instability alongside the mental state.
- A drug, occupational or nutritional exposure with a plausible temporal relationship to onset.

PITFALL

The physical examination that was never done because the patient came through a psychiatric door. Pigmentation, a goitre, a tremor, an abnormal eye sign, a postural drop, a neuropathy or an enlarged liver will not appear in the notes if nobody looked, and the formulation then hardens around an absence of evidence the examination itself manufactured. Record what you found, not what you asked.

1.4 Investigate by question, not by panel

The reflex is to order a broad screen, and it is only half right. Investigation here earns marks when each test answers a question the clinician has already formed. Two ideas are routinely merged: **screening** applies a test to an unselected group because the disease is common enough and missing it serious enough, while **case-finding** applies it to this patient because something in the history or examination raised its probability. The threshold to test is far lower in the second, and a borderline result means something different.

That interpretive difference is the chapter's most reliable trap. A mildly abnormal result in an unselected patient carries a far weaker claim on the diagnosis than the same value in a patient whose history already pointed at that organ. The direction of the abnormality, the pattern across related analytes, the clinical state at sampling, concurrent drugs and the acute illness itself all shift what a number means. The specific interpretations belong to the sections that own them: thyroid function tests to the hypothyroidism and hyperthyroidism section, biochemical confirmation of copper disorder to the Wilson's disease investigation section, the biomarkers probing the stress axis to the Cushing and steroid-psychiatry section.

TRAP **Declaring a borderline abnormality to be the cause of the psychiatric presentation.** Candidates find one deranged value, name it as the explanation and stop. A result at the edge of a reference interval in a patient with no supporting somatic signature is weak evidence, and acute illness of almost any kind perturbs several of these systems transiently. State instead what the result raises, what would confirm or refute it, and what the psychiatric management is meanwhile.

IN INDIA

Investigation strategy here is shaped by who pays and how far the patient travelled. Much of this testing is out of pocket, and a patient who has lost a day of wages to attend is unlikely to return to complete a staged workup. Settle the full question before the patient leaves the room, and be honest about which tests will change management rather than ordering a panel that reassures the clinician. Iodine status, endemic goitre and nutritional deficiency vary sharply by region and diet, so local prevalence should inform the pre-test probability rather than a figure recalled from an imported textbook. Steroids, prescribed and bought without prescription alike, are widely available, which makes the drug history a diagnostic instrument rather than a formality. Where specialist assays or an endocrinology opinion are distant, the psychiatric plan must be safe in the interval, not suspended awaiting a result.

1.5 The iatrogenic axis: what psychiatric treatment does to metabolism

Causation running from treatment to body inverts the clinical posture: here the psychiatrist is not the detective but the exposure. Antipsychotic treatment carries weight, lipid, glucose and prolactin consequences, mood stabilisers and antidepressants carry their own endocrine and electrolyte liabilities, and the resulting **iatrogenic burden** contributes materially to the excess physical morbidity and shortened life expectancy of people with severe mental illness. This is not incidental to psychiatric practice. It is one of its principal harms, and it is prescribed.

The chapter divides the territory carefully, and so should an answer. The receptor-mediated mechanism by which antipsychotic treatment produces metabolic effect is taught in the treatment-burden section, with the comparative liability of individual agents. The monitoring schedule and its cadence are stated once, in the monitoring section; the criteria and thresholds defining metabolic syndrome once, in the metabolic syndrome and mortality section; and management of established metabolic disturbance and raised prolactin in its own section. Drug selection and the receptor pharmacology underlying it belong to the Schizophrenia: management, antipsychotics and adverse effects notes; lithium as a drug, with its pharmacokinetics, therapeutic monitoring and non-thyroid organ effects, belongs to the Mood disorders: pharmacotherapy notes. This chapter takes only the endocrine and metabolic lens on each.

GOOD TO REMEMBER

Metabolic harm from psychotropic treatment is largely front-loaded, so fix the baseline before the first dose rather than discovering a change later without a comparator. Record weight and waist, ask about family history of diabetes and cardiovascular disease, and put the physical starting point in the case record. A patient whose baseline was never documented cannot be shown to have deteriorated, which disadvantages the patient far more than the audit.

1.6 Know what this chapter hands over

A chapter this broad touches many constructs it does not own, and an answer that re-teaches them is both long and wrong for the question. The **boundary map** is worth learning as content in its own right. Beyond the handovers already named, three more matter. The persistent amnestic syndrome that may follow acute thiamine deficiency is taught in the Stroke, TBI, delirium and focal brain syndromes notes; this chapter teaches the acute disease and its treatment window, then hands over the sequel. The basic biology of hormone synthesis, receptor signalling and neuroendocrine measurement is taught in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. The administration and scoring of cognitive and psychopathological instruments are taught in the Psychotherapies, clinical assessment, MSE and nosology notes, so cognitive change is described here in clinical language rather than through reproduced test items.

The habit that keeps the handover clean is to name the neighbouring construct in a clause and move on rather than pausing to define it, while saying explicitly where that chapter would change management. The examiner is testing whether you know the interface exists.

1.7 Managing the patient who has both

Management here is almost always joint, and it becomes coherent when built on the standard spine. **LOCUS** asks where care should happen. Most of this work is outpatient and shared with a physician or endocrinologist, but several presentations are genuine emergencies in which the derangement, not the psychiatric syndrome, dictates management on a medical ward or in critical care with psychiatric input rather than the reverse. Deciding LOCUS early prevents a common

failure: admitting an acutely deranged patient to a psychiatric bed that cannot deliver the monitoring the body needs.

FOCUS asks what is being treated and in what order. Acutely, the target is the derangement that threatens the patient, with enough containment of behaviour and risk to make treatment possible. In the short term it is the underlying disease and the syndrome it drove, on the expectation that the second may improve as the first is corrected. In the medium term it is the residual psychiatric picture persisting after correction, where independent psychiatric treatment becomes justified rather than assumed. In the long term it is relapse prevention, surveillance for recurrence of the systemic disease, and the cumulative physical cost of psychiatric treatment itself.

MODUS asks which modes are available and which are in use. The pharmacological mode covers both the treatment of the systemic disease and the psychotropic prescription, chosen for the organ that must clear it. The psychological and behavioural mode covers adherence support, dietary and activity intervention, tobacco and alcohol work, and psychoeducation the patient and family can act on. The procedural mode covers the surgical, endoscopic and replacement interventions the disease sections describe. The social mode covers the cost of long-term physical treatment, the accessibility of monitoring, family supervision of a complex regimen, and the exposure that may need to change before the illness will. Dosing, eligibility and monitoring intervals belong to the management sections and to current guidelines, not to memory.

1.8 Using the map under examination pressure

When the stem is crowded with physical detail, frame the case before you try to solve it. The scaffold below is a retrieval aid rather than a diagnostic criterion, and it asserts nothing this chapter does not teach. It holds the order of reasoning when the temptation is to seize the first recognisable physical sign and write everything known about the disease it suggests.

MNEMONIC

TRACE

Tempo and trigger: when the mental state changed, and what changed around it, including every drug started or stopped. **R**eversibility: is a treatment window open, and does it make investigation urgent today. **A**xis or organ: which endocrine axis, metabolic pathway, nutrient, solute or organ of clearance could generate this picture. **C**ausal direction: body driving mind, treatment driving body, the two merely travelling together, or treatments colliding. **E**vidence and escalation: which test answers the question actually asked, what would confirm or refute it, and when this patient needs a physician rather than another psychiatric review.

In a long answer, state the construct plainly, then move through the direction of causation, the somatic signature that identified the system, the targeted investigation and its interpretation, the differential within that system, and management by LOCUS, FOCUS and MODUS. In a short note the marks sit in the discriminating features and the test that separates the candidates, so lead with those rather than epidemiology. In a vignette the physical detail is placed deliberately;

read each item as evidence for or against an organ. In a viva, make the reasoning audible: leading formulation, evidence for it, strongest alternative, and the result that would separate them.

The habit worth carrying out of this chapter is a **longitudinal formulation** rather than a fixed label. A hormone level moves with treatment, a deficiency corrects and recurs, a metabolic burden accumulates over years of prescribing, and a syndrome once fully explained by a systemic disease may later be independent of it. Keep revising in the open: retain what remains supported, discard what no longer fits, and be explicit with the patient about which part of the picture is now being treated and why.

> Establish the direction of causation, name the organ from the somatic signature rather than the mental state, ask whether a treatment window is open, test the question rather than the panel, and hand over constructs owned by another chapter.

2 · HPA axis physiology and its role in psychiatric disorders

This is the axis every other endocrine question in psychiatry hangs from. Examiners return to it because it asks for three kinds of knowing at once: physiology recited accurately, laboratory findings among the most replicated in the discipline, and the interpretive discipline that stops those findings being over-read. Get the physiology right and much of what follows in adrenal disease, steroid psychiatry and the biomarker literature becomes derivable rather than memorised. A candidate who cannot say which adrenal output answers to the pituitary cannot explain why one kind of adrenal failure needs mineralocorticoid replacement and another does not.

Begin with what the gland makes, because this axis is only one of several control systems running through it. Kaplan and Sadock's Comprehensive Textbook of Psychiatry frames the adrenal as two organs in one capsule: steroids from the cortex and catecholamines from the medulla. Within the cortex, three hormone classes answer to different masters. Glucocorticoids, principally cortisol, are driven by ACTH from the anterior pituitary under a negative feedback loop; aldosterone, a mineralocorticoid, also arises from the cortex but is controlled by the renin-angiotensin system, itself influenced by body volume and potassium balance. The adrenal androgens, predominantly **dehydroepiandrosterone**, are regulated by the ACTH system and undergo peripheral conversion to sex-determining androgens. Only the first is the HPA axis proper, and keeping the three apart makes the rest of this chapter coherent.

8 AM	ABOUT 15 MIN	20 TO 40%	40 TO 60%
PEAK OF CIRCULATING GLUCOCORTICOID	PLASMA HALF-LIFE OF ACTH	DEPRESSED OUTPATIENTS, RAISED HPA ACTIVITY	DEPRESSED INPATIENTS, RAISED HPA ACTIVITY

2.1 Three modes of regulation

Goodman and Gilman's The Pharmacological Basis of Therapeutics compresses the whole of ACTH regulation into three characteristic modes. Learn them as three, because almost every abnormality you will meet is a failure of one of them.

- **A diurnal rhythm in basal steroidogenesis.** The gland runs to a clock, which is what makes any single measurement meaningless without its timestamp.
- Negative-feedback regulation by adrenal corticosteroids. The product restrains its own drivers, turning an open cascade into a governed system.
- Marked increases in steroidogenesis in response to stress. A designed feature, not a disturbance, and the mode that most often contaminates a clinical measurement.

The framing earns its keep by separating questions that look alike. Whether cortisol is high, whether the rhythm is intact and whether feedback works are three questions needing different measurements under different conditions, and they dissociate. The accompanying figure sets the loop out in the order the modes act on it.

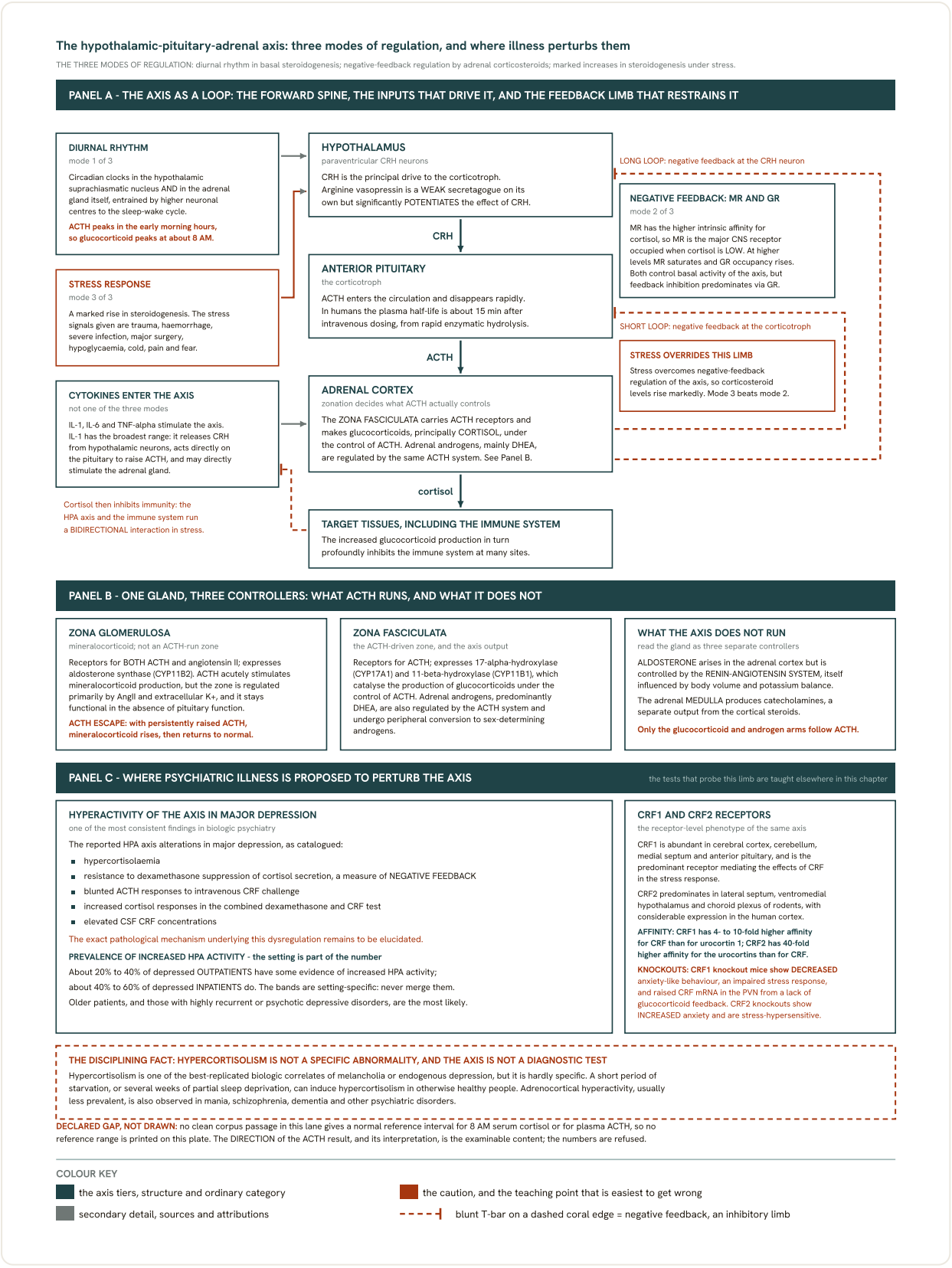

Fig 33.1 The hypothalamic-pituitary-adrenal axis as a loop: the forward spine, the feedback limb, and where illness is proposed to perturb it. Three modes govern the axis: a diurnal rhythm in basal steroidogenesis, negative feedback by adrenal corticosteroids, and a marked rise under stress. Read the feedback limb as the examinable structure: predominantly glucocorticoid-receptor mediated, acting at both the corticotroph and the CRH neuron, and overridden by stress. Hyperactivity of the axis in major depression is consistent but not specific. (Goodman and Gilman's The Pharmacological Basis of Therapeutics; Kaplan and Sadock's Comprehensive Textbook of Psychiatry 2024.)

MNEMONIC

Rhythm, Feedback, Stress

The three modes of physiological regulation, in the order they are usually examined. **R**hythm gives the timing rule, **F**eedback gives the receptor story and the logic of suppression testing, and **S**tress gives the reason a raised value so often means nothing at all.

2.2 The diurnal rhythm and the morning anchor

The rhythm is not generated at one site. It is set by circadian clocks in the hypothalamic **suprachiasmatic nucleus** and in the adrenal gland itself, and the pair is entrained by higher neuronal centres responding to the sleep-wake cycle. Because the adrenal carries its own oscillator, the rhythm is not merely pituitary drive relayed downward; because entrainment runs through sleep and waking, it belongs to the patient's schedule rather than to the wall clock.

The consequence a clinician uses daily is timing. ACTH peaks in the early morning hours and circulating glucocorticoid follows, peaking at about **8 AM**. Every convention about when to draw a cortisol sample descends from that one fact, as does the logic of the suppression testing this chapter takes up where it deals with Cushing syndrome and the HPA biomarkers. Asked why a morning sample is specified, the answer is not tradition: only a measurement at the reproducible peak of a rhythmic variable is comparable between patients or visits.

GOOD TO REMEMBER

Before interpreting any cortisol value, ask what the patient's night looked like. Because the rhythm is entrained by the sleep-wake cycle, a patient who worked a night shift, travelled overnight or slept badly on a ward is not on the schedule the convention assumes. The sample is timed to the clock; the physiology is timed to the patient.

2.3 Negative feedback: a receptor handover, not a thermostat

Cortisol acts centrally through two receptor species, and the logic of feedback rests on the difference in their affinities. The **mineralocorticoid receptor** has the higher intrinsic affinity for cortisol, so during periods of low cortisol it is the major receptor species occupied in the central nervous system. As blood cortisol rises that receptor saturates and occupancy of the **glucocorticoid receptor** increases. Both control basal activity of the axis, but feedback inhibition by glucocorticoids predominantly occurs through the glucocorticoid receptor.

Read it as a handover rather than a switch. At low levels the system runs on the high-affinity receptor and is tuned for maintenance; as levels climb the low-affinity receptor is recruited and the braking function comes on with it. That is why a graded system behaves differently at different set points, and it is the mechanism the Maudsley prescribing guidance uses to explain the neuropsychiatric effects of exogenous steroids, taken up in this chapter under steroid psychiatry. A drug that occupies one receptor species preferentially does not simply raise a level; it changes the balance of the two signals the brain is reading.

RULE **Basal tone is set by both receptors; braking is predominantly a glucocorticoid-receptor job.** The mineralocorticoid receptor is occupied first because its affinity for cortisol is higher, and the glucocorticoid receptor is recruited only as levels rise and the first saturates. Any account of impaired feedback in disease must say which limb of that handover is at fault.

2.4 Zonation: why the two halves of the cortex fail differently

The cortex is not uniformly ACTH-dependent, the most examinable piece of adrenal anatomy. Cells of the **zona glomerulosa** carry receptors for both ACTH and angiotensin II and express aldosterone synthase, the enzyme CYP11B2; ACTH acutely stimulates mineralocorticoid production there, but the zone is regulated primarily by angiotensin II and extracellular potassium and remains functional in the absence of pituitary function. Cells of the **zona fasciculata** carry ACTH receptors and express 17-alpha-hydroxylase (CYP17A1) and 11-beta-hydroxylase (CYP11B1), which catalyse glucocorticoid production under the control of ACTH.

That asymmetry explains a clinical pattern this chapter develops where it deals with adrenal insufficiency: failure at pituitary level removes the ACTH-dependent glucocorticoid limb while leaving largely intact a zone that never needed the pituitary, whereas destruction of the gland removes both. Hold the anatomy and the consequence need not be memorised.

AXIS OF COMPARISON	ZONA GLOMERULOSA	ZONA FASCICULATA
Receptors expressed	ACTH and angiotensin II	ACTH
Characteristic enzymes	Aldosterone synthase (CYP11B2)	CYP17A1 and CYP11B1
Principal product	Mineralocorticoid	Glucocorticoid
Chief regulator	Angiotensin II and extracellular potassium	ACTH
Behaviour without a pituitary	Remains functional	Loses its drive

One further phenomenon is regularly misremembered. With persistently elevated ACTH, mineralocorticoid levels initially increase and then return to normal, a behaviour named **ACTH escape**: the zone responds acutely and then reverts to the control system that actually governs it.

TRAP **Reasoning that chronically high ACTH must produce sustained mineralocorticoid excess.** The premise is right and the conclusion wrong. Candidates correctly recall that the outer zone bears ACTH receptors and that ACTH acutely stimulates mineralocorticoid output, then extrapolate to a chronic effect. Escape is the answer: the initial rise is not maintained, because angiotensin II and extracellular potassium, not the pituitary, are the standing regulators of that zone.

2.5 Driving the axis upward: vasopressin and the stress override

Corticotrophin-releasing hormone is the principal drive to the corticotroph, but it does not work alone. **Arginine vasopressin** is a weak secretagogue for corticotrophs on its own, yet it significantly potentiates the effects of corticotrophin-releasing hormone. It is a modulator rather than an independent driver, so conditions that raise it amplify an axis already being driven.

The larger point about upward drive is that the system is built to be overridden. Stress overcomes negative feedback regulation of the axis and produces a marked rise in corticosteroid levels, and the qualifying signals are mostly not psychological in the everyday sense: trauma, haemorrhage, severe infection, major surgery, hypoglycaemia, cold, pain and fear. A hypoglycaemic, febrile, post-operative or frightened patient has a legitimately elevated cortisol, with nothing in the axis malfunctioning at all.

PITFALL

Sampling the axis in a patient who is acutely unwell, then attributing the result to a primary endocrine or psychiatric process. A raised cortisol drawn during sepsis, uncontrolled pain, hypoglycaemia or the first hours after surgery measures the stress response, not the set point: the physiology says the value should be high. Repeat it when the patient is no longer a stressed patient, or do not draw it at all.

2.6 Corticotrophin-releasing factor receptors and the behavioural phenotype

Receptor pharmacology is where this axis stops being purely endocrine and becomes a plausible substrate for anxiety and mood. Kaplan and Sadock's Comprehensive Textbook of Psychiatry describes two subtypes with different distributions, different ligand preferences and opposite behavioural phenotypes, a contrast favoured by written papers because it is clean enough to test.

AXIS OF COMPARISON	CRF1 RECEPTOR	CRF2 RECEPTOR
Principal distribution	**Cerebral cortex, cerebellum, medial septum and anterior pituitary**	**Lateral septum, ventromedial hypothalamus and choroid plexus in rodents, with considerable expression in human cortex**
Ligand preference	4- to 10-fold higher affinity for corticotrophin-releasing factor than for urocortin 1	40-fold higher affinity for the urocortins relative to corticotrophin-releasing factor
Role in the stress response	Appears to be the predominant receptor mediating the effects of corticotrophin-releasing factor	Not the predominant mediator
Knockout phenotype	Decreased anxiety-like behaviour, impaired stress response, elevated corticotrophin-releasing factor messenger RNA in the paraventricular nucleus from absent glucocorticoid negative feedback	Increased anxiety-like behaviour and hypersensitivity to stress

Two cautions travel with the table. The knockout phenotypes are animal data, and the species caveat is in the source itself: the rodent pattern for the second subtype does not transfer wholesale to humans, where cortical expression is substantial. Nor are the opposing phenotypes a push and pull on one dial, since the elevated messenger RNA in the first knockout is a feedback

phenomenon, a hypothalamic response to missing glucocorticoid restraint rather than a direct effect of losing the receptor.

2.7 The immune interface

Now the part that turns a hormone axis into a systems story. The relationship with the immune system runs both ways, and holding only one direction is the commonest incompleteness in candidates' answers. Among the proinflammatory cytokines, interleukin-1, interleukin-6 and tumour necrosis factor alpha stimulate the axis, with interleukin-1 having the broadest range of actions, and that breadth means action at all three levels at once: interleukin-1 stimulates release of corticotrophin-releasing hormone by hypothalamic neurons, acts directly at the pituitary to increase ACTH release, and may directly stimulate the adrenal to produce glucocorticoids. The return arm closes the loop, since the resulting increase in glucocorticoid production profoundly inhibits the immune system at multiple sites. Goodman and Gilman's The Pharmacological Basis of Therapeutics states the conclusion plainly: axis and immune system are capable of bidirectional interactions in response to stress.

Two consequences matter for a psychiatrist. An inflammatory illness is an endocrine event as well as an infective one, a further reason the acutely septic patient is a poor subject for axis measurement. And this is the mechanistic bridge inflammatory hypotheses of depression are built on, since a route from peripheral immune activation to the hypothalamus is what such a hypothesis requires. That the bridge exists does not establish that it carries the traffic.

2.8 The axis in psychiatric disorder, and the limits of the finding

Hyperactivity of the axis in major depression remains one of the most consistent findings in biological psychiatry. Be precise about what has been reported, because it is a family of observations rather than one. The catalogue comprises hypercortisolemia; resistance to dexamethasone suppression of cortisol secretion, which is a measure of negative feedback; blunted ACTH responses to intravenous corticotrophin-releasing factor challenge; increased cortisol responses in the combined dexamethasone and corticotrophin-releasing factor test; and elevated cerebrospinal fluid corticotrophin-releasing factor concentrations. The tests are set out in this chapter where it deals with the HPA biomarkers; what belongs here is that each probes a different arm of the physiology above, and that the mechanisms underlying the dysregulation remain to be elucidated.

How common is it? The honest answer is setting-dependent, and the two figures must never be collapsed into one. About **20% to 40%** of depressed outpatients show some evidence of increased activity of the axis, against about **40% to 60%** of depressed inpatients. Older patients, particularly those with highly recurrent or psychotic depressive disorders, are the most likely to show it. A single pooled percentage quoted without its setting is not a shorter version of those two numbers but a different and unsupported claim, and the gradient is itself informative: the inpatient population is both more severely ill and more likely to be under the acute stress described above.

The disciplining fact governs everything the biomarker literature may claim. Although hypercortisolism is one of the best-replicated biological correlates of melancholia or endogenous depression, it is hardly a specific abnormality. Two everyday states produce it in people who are entirely well: a short period of starvation, or several weeks of partial sleep deprivation. Nor is it confined to depression among psychiatric populations, since adrenocortical hyperactivity, although usually less prevalent, is observed in mania, schizophrenia, dementia and other psychiatric disorders. Consistency and specificity are different properties, and this finding has a great deal of the first and very little of the second.

TRAP **Treating hypercortisolism as a diagnostic test for depression.** The reasoning is superficially sound: the finding is among the most replicated in biological psychiatry, therefore it must be diagnostically useful. Replication establishes that an association is real, not that it discriminates. A fasting volunteer and a chronically sleep-deprived resident both produce the abnormality, and it appears across mania, schizophrenia and dementia. State the finding, then state its non-specificity in the same breath; an answer that gives only the first half is the answer being tested for.

2.9 Interrogating the axis: what the physiology dictates before any test

Management of the adrenal disorders and of steroid-induced syndromes is set out in this chapter where each condition is taken up; what the axis itself dictates is the assessment logic.

LOCUS decides what is realistically obtainable, more sharply here than for most investigations. In an outpatient clinic a patient can be brought back unhurried and on their usual sleep schedule for a sample timed to the morning peak, which is the condition under which the number means what the convention assumes. On an acute ward sleep is disrupted and the illness that prompted admission is often itself a stress signal, so the convention is met on paper while the physiology it rests on is not. In an emergency setting it should not be interrogated for psychiatric purposes at all, since the setting guarantees a stress response.

FOCUS changes with phase. Before any blood is drawn the target is the timestamp and the state of the patient. Acutely, the only defensible question is whether an adrenal emergency is in play, a medical rather than a psychiatric determination. Over the short and medium term the questions are the ones this chapter's later sections are built on: is the level abnormal, is the rhythm preserved, does feedback still work. Long term, in a patient on exogenous steroid, the question is what sustained occupancy of the two receptor species is doing to mood and cognition.

MODUS is the set of routes available, each mapping onto one regulatory mode. A timed morning sample addresses the basal level at a reproducible point in the rhythm; repeat sampling across the waking day addresses the rhythm itself; pharmacological suppression addresses feedback, and dynamic challenge with corticotrophin-releasing factor addresses pituitary responsiveness. Both of the last two are taught where this chapter deals with the HPA biomarkers. One pre-analytical constraint belongs to the physiology rather than to any protocol: ACTH is readily absorbed from parenteral sites and disappears rapidly from the circulation, with a plasma half-life in humans of about **15 minutes**, primarily from rapid enzymatic hydrolysis. Hence the need to handle an ACTH sample promptly.

IN INDIA

Two divergences bite in routine practice. Cortisol assays are commonly run in-house while plasma ACTH is frequently a send-out test, so the sample is drawn where the patient is and assayed wherever the analyser sits. The same rapid enzymatic hydrolysis that gives ACTH its short plasma half-life is why prompt handling and transport are not optional refinements: a sample that spent the afternoon on a bench yields an uninterpretable number that will nonetheless be acted upon, and where a courier interval cannot be guaranteed it is better to arrange the test through a laboratory that can. Second, reference intervals for these hormones are assay-dependent and are not reproduced in this chapter. Read every result against the interval printed by the performing laboratory, and expect values from two laboratories not to be comparable.

Three modes of regulation, one timing rule and one caveat: rhythm, feedback and the stress override; sample at the morning peak because that is where the rhythm is reproducible; and remember that raised cortisol is consistent in depression but specific to nothing.

3 · Cushing syndrome, steroid psychiatry and the HPA biomarkers

Two clinical realities sit under one heading, and only one is rare. Endogenous hypercortisolism a psychiatrist meets a few times in a career; corticosteroid-induced disturbance is on the wards every week, because exogenous steroid, usually prescribed for a steroid-sensitive medical condition, is the commonest cause of hyperadrenalism overall.

UP TO 70% DEPRESSION IN CUSHING SYNDROME, CONTESTED	**OVER 50%** COGNITIVE IMPAIRMENT IN CUSHING SYNDROME	**22.2** NEUROPSYCHIATRIC CASES PER 100 PERSON-YEARS, FIRST COURSE	**11.5 DAYS** MEDIAN TIME TO ONSET ON CORTICOSTEROIDS

3.1 Where the excess cortisol comes from

Hyperadrenalism is excess adrenocortical corticosteroid. Usually that is ACTH overproduction by the anterior pituitary, most often from a pituitary adenoma, the subset called **Cushing disease**; the remainder is ACTH secretion by a non-endocrine tumour, a primary adrenal neoplasm, and administered steroid.

The somatic picture: hypertension, muscle weakness and fatigue, osteoporosis, cutaneous striae and easy bruising, and obesity of the upper face, back and mesentery giving moon facies, buffalo hump and truncal obesity. Biochemically it declares itself twice: plasma and urinary cortisol are elevated and the normal circadian rhythm of secretion is blunted or absent. Lost rhythm, not a high level alone, is what the tests exploit; the feedback anatomy is taught where this chapter covers the physiology of the hypothalamic-pituitary-adrenal axis.

3.2 The psychiatric signature of endogenous hypercortisolism

The dominant picture is depressive, not psychotic. Depression is the most frequently noted psychiatric symptom, in up to 70% of patients, and may precede the physical features: the patient reaches psychiatry first. Nor is it merely comorbid: it responds to treatment of the underlying cause, the response correlating with the fall in plasma cortisol.

Anxiety is commonly comorbid in up to 50% of those who are depressed, the denominator being the depressed subgroup, not every patient. Elevated mood is infrequent, under 10% in most case series, and delirium is also uncommon, usually marking a supervening infection or another metabolic disturbance such as metabolic alkalosis. New confusion is a reason to hunt a second illness, not to blame the first harder. Delirium as a syndrome belongs to the Stroke, TBI, delirium and focal brain syndromes notes.

Psychosis is where folk teaching misleads. Reports of Cushing syndrome presenting with psychosis and obscuring the underlying condition exist, but that presentation is rare, and psychotic symptoms are almost always **mood-congruent**: delusional beliefs and derogatory auditory hallucinations with depressed mood. Cognition is affected far more often and examined far less: impairment occurs in over 50%, in verbal memory, attention, and visuomotor and visuospatial function.

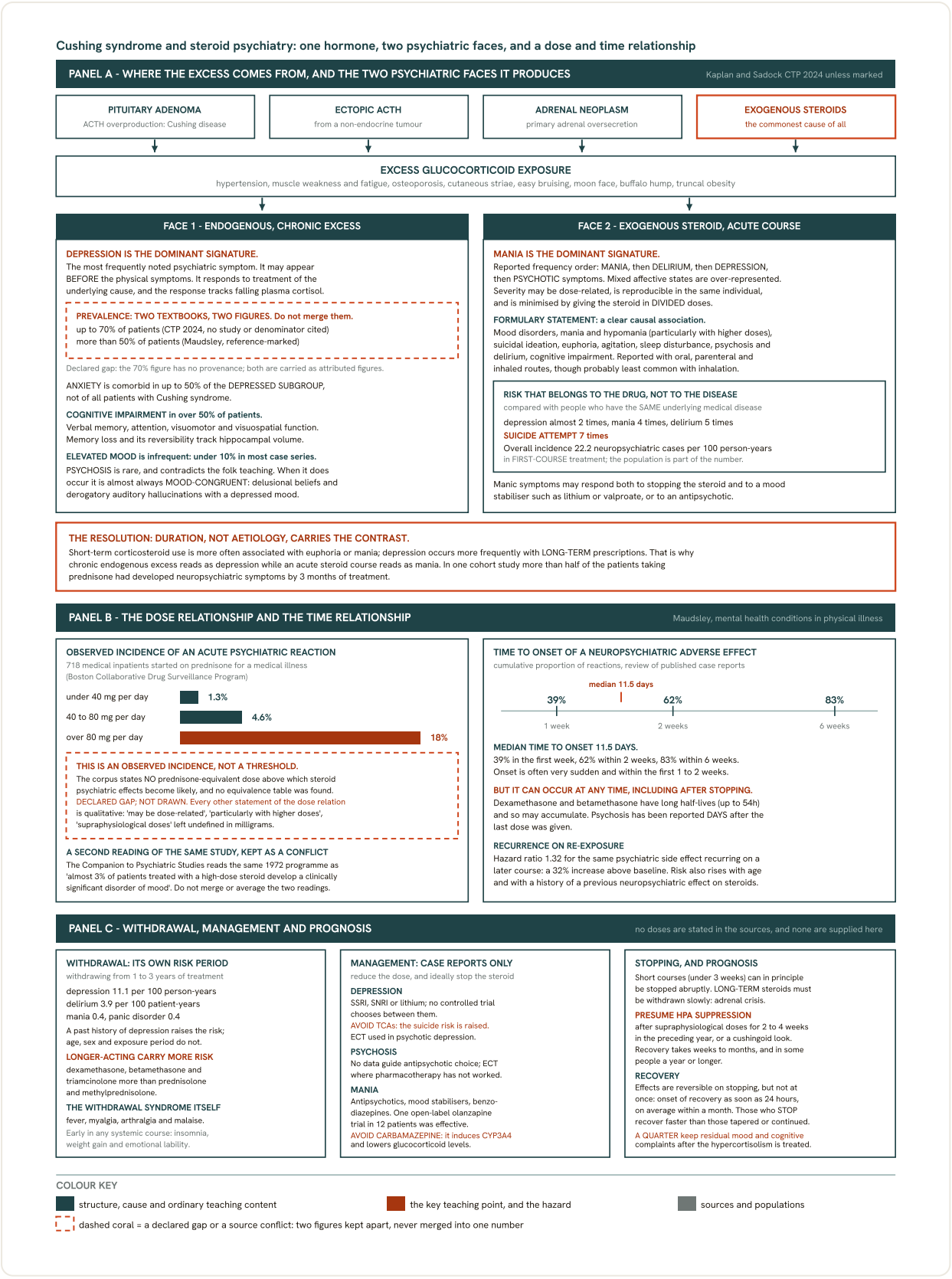

Fig 33.2 Cushing syndrome and steroid psychiatry: two faces of one hormone. Chronic endogenous excess reads as depression with cognitive impairment; an acute exogenous course reads as mania, delirium and mixed states, and duration rather than aetiology carries the contrast. The dose bands are observed incidences in inpatients started on prednisone for a medical illness, not a clinical threshold: no prednisone-equivalent threshold exists in the corpus, and that gap is marked rather than filled. (Kaplan and Sadock CTP 2024; Maudsley; Companion to Psychiatric Studies; Goodman and Gilman.)

The two prevalences do not agree. The Comprehensive Textbook of Psychiatry gives up to 70% with no study, denominator or citation; the Maudsley Prescribing Guidelines for Mental Health Conditions in Physical Illness states instead that depression occurs in more than 50% of patients with Cushing's disease, and does carry a reference. The ranges overlap and the populations differ, so neither is safe as the prevalence: cite each with its textbook and population, or say "the majority".

3.3 Prescribed steroids: a different syndrome, or a different duration?

Swap the disease for a prescribed drug and the affective direction reverses. With exogenous steroid, manic symptoms are most frequently reported, followed by delirium, depression and psychotic symptoms, and mixed affective states appear over-represented. The tidy conclusion, that endogenous cortisol depresses and synthetic steroid elevates, is wrong: the variable is duration. Short-term use is more often associated with euphoria or mania, depression more frequently with long-term prescriptions, consistent with depression being common in Cushing's disease, a disorder of chronic endogenous excess; synthetic corticosteroids have the same effect, and in one cohort study more than half of patients on prednisone had neuropsychiatric symptoms by 3 months.

RULE **Duration, not aetiology, carries the direction of mood change in glucocorticoid excess.** A long course travels from the elevating end of that curve to the depressing end without changing drug; endogenous Cushing syndrome is the chronic arm.

MNEMONIC

Short lifts, long sinks

No threshold in weeks is licensed, because none is stated.

The formulary adds route and severity: recognised glucocorticoid psychiatric adverse effects are mood disorders, mania and hypomania particularly at higher doses, suicidal ideation, euphoria, agitation, sleep disturbance, psychosis, delirium, dementia and cognitive impairment; the causal association is clear and most substantial for depression and mania; they are reported with oral, parenteral and inhaled routes, though probably less common with inhalation, and generally respond to dose decreases. Inhaled steroid is less implicated, not exempt, so respiratory prescriptions belong in the drug history.

3.4 Dose, incidence, and one study read two ways

Risk rises with dose, and the only numeric stratification comes from one surveillance programme. Among 718 medical inpatients started on prednisone for medical illness, acute psychiatric reactions occurred in 1.3% of those on less than 40 mg prednisone per day, 4.6% at 40 to 80 mg per day, and **18%** at more than 80 mg per day. Those are incidences of adverse reaction within dose bands, not therapeutic doses.

TRAP **Two standard textbooks summarise the same surveillance programme with figures differing roughly six-fold, and both circulate in examination answers.** The Maudsley guidelines give the dose-stratified incidences above; the Companion to Psychiatric Studies renders the same programme as corticosteroids increasing the risk of affective disturbance, and of mania or hypomania in particular, in relation to dose, with almost 3% of patients on a high-dose steroid developing a clinically significant disorder of mood. Both cannot describe the high-dose stratum: either the second is an overall cohort rate misattached to that group, or the two count different outcomes, acute psychiatric reaction against clinically significant mood disorder. Do not pick one and do not average them: cite the dose-stratified version with its source and note the second text's almost 3% alongside it.

Two caveats. No source states a prednisone-equivalent threshold above which psychiatric effects become likely; the most direct statement is that severity may be dose-related, reactions are reproducible in the individual, and they may be minimised by divided doses. An observed incidence within a range is not a threshold. Second, elevation is commoner than illness: controlled studies confirm high rates of subclinical mood elevation after 1 week of steroid administration.

Population data give the sturdier framing. A large United Kingdom database study put the incidence of neuropsychiatric outcomes at 22.2 cases per 100 person-years for first-course treatments, its internal comparison attributing the effect to the drug rather than the illness: against people with the same underlying disease, glucocorticoid-treated patients were almost twice as likely to become depressed, four times as likely to develop mania, five times delirium and seven times to attempt suicide. Prior experience counts too: risk rises with age and with previous neuropsychiatric adverse effects on corticosteroids, and one study put the hazard ratio for recurrence of the same side effect on a later course at 1.32, a 32% increase above baseline.

3.5 Timing: onset, the tail, and withdrawal

Timing is what makes this diagnosis on a ward round. Effects can appear at any point, from almost immediately after initiation to some time after treatment has stopped, but most fall in the first few weeks: a case-report review found a median onset of **11.5 days**, with 39% in the first week, 62% within 2 weeks and 83% within 6 weeks. The formulary agrees that onset is often very sudden and within the first 1 to 2 weeks. A new manic or psychotic presentation in a medical inpatient started on steroid a fortnight ago is steroid-related until proven otherwise.

The tail runs longer than intuition allows. Dexamethasone and betamethasone have long half-lives, up to 54 hours, and may accumulate, and psychosis has been reported days after the last dose. A drug chart showing the steroid already stopped does not exonerate it. Withdrawal is its own risk window: in a United Kingdom primary care study of withdrawal from 1 to 3 years of treatment, incident depression ran at 11.1 per 100 person-years, ahead of delirium at 3.9 per 100 patient-years, mania at 0.4 and panic disorder at 0.4; previous depression raised the risk while age, sex and exposure period did not, and the longer-acting dexamethasone, betamethasone and triamcinolone carried more risk than shorter-acting prednisolone and methylprednisolone.

Across a whole course: early therapy brings insomnia, weight gain and emotional lability; high-dose or long-term therapy brings psychosis alongside infection risk, osteoporosis, osteonecrosis, myopathy and suppression of the axis itself; and cessation brings acute hypocortisolism.

3.6 Mechanism, and what does not fully reverse

The honest position is that the mechanism is not clear. The best-articulated account is receptor balance: exogenous corticosteroid activates pituitary glucocorticoid receptors while suppressing adrenal cortisol secretion, depleting endogenous cortisol and reducing mineralocorticoid receptor stimulation, and that imbalance between glucocorticoid and mineralocorticoid receptor activation may underlie the neuropsychiatric effects; high cortisol also inhibits brain-derived neurotrophic factor, low levels of which may contribute to depression and anxiety. The receptor affinities behind the imbalance are taught where this chapter covers the physiology of the axis.

The cognitive picture has an anatomical correlate. The degree of memory impairment and its reversibility correlate with hippocampal volume, implicating the effect of excess glucocorticoid on hippocampal neurons, and a more general reduction in grey matter volume, cortical thickness and white matter integrity can persist after the hypercortisolism is corrected. Imaging converges: smaller hippocampal, cingulate gyrus and medial frontal gyrus volumes, with computed tomography, magnetic resonance imaging and autopsy showing global cerebellar and cerebral volume loss in both endogenously and exogenously exposed patients; a quarter keep residual mood and cognitive complaints after treatment, and brain volume often does not return completely.

> **GOOD TO REMEMBER**
>
> Correcting the cortisol is not the same as restoring the patient. Say so at the outset rather than letting a patient discover it months after curative surgery, and record the cognitive deficits in your own descriptive terms.

3.7 Managing corticosteroid-induced psychiatric syndromes

Guidance comes principally from the Maudsley guidelines, with Goodman and Gilman's The Pharmacological Basis of Therapeutics governing withdrawal and adrenal safety. Neither states a psychotropic dose here, and none should be imported.

LOCUS. Mostly liaison work on a medical ward, because the steroid is treating something that needs treating. Emergency presentation is delirium, acute mania and self-harm risk, real given the seven-fold excess of suicide attempts above. Outpatient work is surveillance and safe tapering on maintenance. The psychiatrist rarely controls the steroid prescription and must negotiate it.

FOCUS. Acutely, agitation, psychotic symptoms, manic elevation and immediate safety. Short term, the steroid dose itself. Medium term, recovery and re-exposure, weighted by the recurrence hazard. Long term, safe withdrawal, adrenal recovery and residual symptoms.

MODUS. The first modality is the offending drug. Dose reduction, and ideally cessation, is the preferable strategy when psychiatric side effects occur; short courses of less than 3 weeks can in principle be stopped abruptly, whereas long-term corticosteroids must be withdrawn slowly to

minimise the risk of adrenal insufficiency and crisis. Pharmacotherapy is evidence-poor and largely a matter of what to avoid. In corticosteroid-induced depression, case reports support SSRIs, SNRIs and lithium with no controlled trials to direct the choice, tricyclics are avoided given the heightened suicide risk, and electroconvulsive therapy has been used in psychotic depression. In psychosis no data guide antipsychotic selection, tricyclics are again avoided since some case series suggest they worsen these psychoses, and electroconvulsive therapy has succeeded where drugs failed. In mania, case reports describe antipsychotics, mood stabilisers, benzodiazepines and combinations, one open-label trial of olanzapine in 12 patients with mania or mixed symptoms found it effective and well tolerated, and carbamazepine is avoided because CYP3A4 induction lowers plasma glucocorticoid concentrations. Lithium as a drug belongs to the Mood disorders: pharmacotherapy notes and antipsychotic selection to the Schizophrenia: management, antipsychotics and adverse effects notes.

Prognosis is good, with a caveat about speed. These effects are reversible on stopping treatment but do not necessarily resolve immediately: recovery from corticosteroid-induced psychosis could begin as soon as 24 hours after either treatment for the psychosis was started or the steroid was stopped, occurred on average within a month, and was quicker in patients able to discontinue than in those tapered or continued. That comparison is the argument to take to the referring team, and the one adrenal risk constrains.

PITFALL

The reflex on seeing steroid-induced psychosis is to stop the steroid today. On a long course that can precipitate adrenal crisis. Patients given supraphysiological glucocorticoid doses for 2 to 4 weeks within the preceding year, or who look cushingoid, should be presumed to have some axis impairment until proven otherwise; acute adrenal insufficiency follows overly rapid withdrawal after prolonged therapy has suppressed the axis, and recovery takes several weeks to months in many and a year or longer in some. Recognise the **glucocorticoid withdrawal syndrome** of fever, myalgia, arthralgia and malaise rather than reading it as somatisation. No source defines supraphysiological in milligrams.

3.8 The dexamethasone suppression test: one name, several tests

Dexamethasone probes negative feedback: a potent synthetic glucocorticoid at night, and a normal axis shuts cortisol output down by morning. Failure to do so is **nonsuppression**. That one idea has been implemented as at least four procedures, and the differences are the examination.

The psychiatric version made the test famous: to confirm a diagnostic impression of major depression, the patient takes 1 mg of dexamethasone by mouth at 11 PM with plasma cortisol at 8 AM, 4 PM and 11 PM, a value above **5 microgram/dL** counting as nonsuppression and therefore positive. The endocrine screen shares the protocol but not the threshold. **The overnight dexamethasone suppression test** is the screening procedure of choice for Cushing syndrome: 1 mg of dexamethasone at midnight with a morning plasma cortisol, a level greater than **200 nmol per litre** indicating a high likelihood of the syndrome; it outperforms urinary

free cortisol on sensitivity and specificity, whereas an isolated plasma cortisol screens inadequately because levels vary considerably across the day.

THE QUESTION BEING ASKED	DOSE TIMING	CORTISOL SAMPLING	THRESHOLD CALLED ABNORMAL	SOURCE
Confirming a diagnostic impression of major depression	11 PM	8 AM, 4 PM and 11 PM	Above 5 microgram/dL	Comprehensive Textbook, glossary
Screening for Cushing syndrome	Midnight	Following morning	Greater than 200 nmol per litre	Comprehensive Textbook, endocrine text
Biochemical evidence of raised cortisol biosynthesis	11 PM	8 AM following morning	Markedly lower than either above; not recoverable from the source	Goodman and Gilman
Research probe of feedback inhibition in depression	Suppression normally lasts 24 hours	8:00 AM, escape at 4:00 PM or 11:00 PM	Nonsuppression, or later escape	Comprehensive Textbook, neuroscience text

TRAP **Quoting a suppression-test cut-off without naming the question the test was asked.** Three textbook passages, two from the same textbook, give three post-dexamethasone thresholds for a test all three call the overnight 1 mg test, and two dosing times; they are not one number in different units. Likeliest is that the psychiatric test of the 1980s and the modern endocrine screen are different tests sharing a protocol, the endocrine threshold set low for sensitivity, but that is a hypothesis and not a resolution: do not harmonise them. The dose is contested the same way: a research probe of feedback inhibition in depression uses dexamethasone at 0.5 to 2.0 mg, whereas the diagnostic protocol in suspected hypercortisolism uses 1 mg of dexamethasone orally at 11 PM with cortisol at 8 AM the following morning. Say 1 mg is the standard clinical protocol and the research literature has used a range; dropping either loses the mark.

A fourth procedure answers a different question. **The high-dose dexamethasone suppression test** determines the aetiology of biochemically documented Cushing syndrome: after 48 hours of baseline cortisol, dexamethasone is given orally as 2 mg every 6 hours for 48 hours, or 8 mg overnight, and in many though not all patients with a pituitary source of ACTH excess cortisol will suppress. The gold standard for establishing a pituitary source remains **inferior petrosal sinus sampling** after CRH administration. This localises within confirmed disease, and is never a screening test nor a psychiatric one.

3.9 The axis as a biomarker, and the other probes

The verdict should anchor everything above: neither the sensitivity nor the specificity of these tests of feedback inhibition is sufficient for use as a diagnostic test, and adrenocortical hyperactivity, although usually less prevalent, is seen in mania, schizophrenia, dementia and other psychiatric disorders. The source gives no sensitivity or specificity figures and none should

be invented. The failure is chiefly one of specificity, since nonsuppression also occurs in major depression, alcoholism, pregnancy, and during acute physical or emotional stress.

- Medication: phenytoin, barbiturates, carbamazepine.
- Endocrine factors: Cushing's disease or pregnancy.
- Metabolic problems: recent withdrawal from alcohol, rapid weight loss, malnutrition, or nausea and vomiting.
- Multiinfarct dementia and increased intracranial pressure.

The enzyme inducers are mechanistically coherent, since drugs or conditions accelerating dexamethasone metabolism, and drugs such as estrogens or conditions such as pregnancy that raise cortisol-binding globulin, compromise the test. Vascular cognitive disorder appears there as a false-positive cause only; the dementia syndrome belongs to the Dementias and neurocognitive disorders notes. Beneath the interpretive problem lies a measurement one: cortisol hypersecretion and dexamethasone nonsuppression correlate only imperfectly, at approximately 60% concordance, so they measure overlapping but different aspects of axis dysfunction.

Where the axis earns its keep is prognostic. Hypercortisolism usually resolves with effective treatment, and when it persists despite it, increased axis activity carries a high risk of relapse, reflecting incomplete resolution of the depressive pathophysiology; such patients respond less well to attention placebo interventions and psychotherapy and may need active pharmacotherapy or electroconvulsive therapy relatively more. A persistently abnormal result after remission is a treatment-intensity signal, not a diagnosis.

Other probes surround the test. **The cortisol awakening response** is the rapid rise about 30 minutes after waking within a rhythm that then declines across the day; research uses its size, that rhythm's slope, stressor reactivity, and total output such as area under the diurnal curve or urinary cortisol. For localisation, **metyrapone** blocks cortisol synthesis and is normally followed by increased cortisol production, produces no such increase in adrenal or ectopic disease, and gives an augmented response in pituitary disease. Ovine CRH, corticorelin, and human CRH are used rarely, mainly to separate pituitary from ectopic ACTH sources during inferior petrosal sinus sampling, since pituitary ACTH production rises with CRH while ectopic does not; CRH after dexamethasone suppression also helps distinguish **pseudo-Cushing states**, as occur with alcoholism and some neuropsychiatric disorders, from true Cushing syndrome.

IN INDIA

Two divergences bite. The exposure history first: since prescribed steroid is the commonest cause of hyperadrenalism and is frequently taken here without a prescription in hand, one question about steroids under-detects it: ask separately about over-the-counter tablets, topical and combination preparations, injections given elsewhere, and unlabelled remedies, and count the inhaled route. Logistics next. The overnight test needs a timed late-evening dose and a timed morning sample, so without dependable outpatient phlebotomy it means a short admission or a failed test, and the shortcut taken instead, one convenient plasma cortisol, is what the source rules out. With phenytoin, barbiturates and carbamazepine in wide use and alcohol withdrawal a routine liaison context, nonsuppression here is more often the confounder than the disease.

The axis has also been a target, not only a marker. **The combined dexamethasone/CRF test** shows increased cortisol responses in major depression, but no protocol or threshold for it is available, so any claimed superiority over the plain test cannot be quantified. And interventions that suppress axis activity, including dexamethasone and the cortisol synthesis inhibitor ketoconazole, are sometimes used in more refractory depressive disorders, while attempts to develop antidepressants directly antagonising central CRH receptors have so far been unsuccessful. The pharmacology behind that failure belongs to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

Endogenous hypercortisolism depresses and impairs cognition while short exposure to prescribed steroid elevates, the direction set by duration rather than aetiology; onset clusters in the first fortnight; dose reduction is the treatment; and a suppression-test result means nothing until you name the question the test was asked.

4 · Adrenal insufficiency and the phaeochromocytoma differential

Two adrenal diseases, two psychiatric masks, one shared reason for being missed. Adrenal insufficiency reaches a psychiatrist as depression with fatigue in a patient who is quietly losing weight. Phaeochromocytoma reaches a psychiatrist as panic in a patient who is quietly hypertensive. Both are uncommon enough that nobody screens for them and consequential enough that missing either can kill.

Hold them as opposites: deficiency against excess, indolent against episodic, psychiatrically broad against psychiatrically narrow. In both the psychiatric label arrives first and the endocrine diagnosis late. Adrenal physiology itself belongs with the account of the hypothalamic-pituitary-adrenal axis elsewhere in this chapter. What is marked here is which presentation turns your attention to the adrenal gland, what you do next, and which of your own prescriptions can precipitate a catastrophe or corrupt the test you rely on.

40% PHAEOCHROMOCYTOMAS THAT ARE PAROXYSMAL	**HIGH ACTH** PRIMARY, NOT SECONDARY, ADRENAL FAILURE	**TWO-THIRDS** OF THE DIVIDED GLUCOCORTICOID DOSE, IN THE MORNING	**24 h OR MORE** FLUDROCORTISONE HALF-LIFE, SO NO DIVIDED DOSING

4.1 Where the lesion sits: primary against secondary failure

Everything downstream follows from the level of the lesion. **Primary adrenal insufficiency, or Addison disease**, comes from structural or functional lesions of the adrenal cortex itself; **secondary adrenal insufficiency** from lesions of the anterior pituitary or the hypothalamus.

The aetiological split is geographical and the most examinable fact here: autoimmune adrenal disease where resources are rich, **tuberculous adrenalitis** where they are not. The rest are short.

- Adrenalectomy, bilateral adrenal haemorrhage, and neoplastic infiltration of the adrenal glands.
- AIDS, which matters wherever tuberculosis matters.
- Inherited disorders of steroidogenic enzymes, and X-linked adrenoleukodystrophy.

Secondary disease behaves differently at the bedside because it generally presents more insidiously than the primary disorder, probably because mineralocorticoid biosynthesis is preserved: aldosterone is not under corticotropin control the way cortisol is, so the patient is spared salt-wasting. That is also why acute decompensation is more commonly associated with disorders of the adrenal than with disorders of the pituitary or hypothalamus.

AXIS	PRIMARY (ADDISON DISEASE)	SECONDARY
Site of lesion	Adrenal cortex, structural or functional.	Anterior pituitary or hypothalamus.
Commonest cause	Autoimmune adrenal disease where resources are rich; tuberculous adrenalitis where they are not.	Pituitary or hypothalamic dysfunction.
Mineralocorticoid	Lost, with the salt-wasting consequences.	Biosynthesis preserved.
Plasma corticotropin	High, from loss of normal glucocorticoid feedback inhibition.	Low.
Tempo	Insidious, but faster to declare itself.	Generally more insidious still.
Crisis liability	The commoner origin of acute decompensation.	Lower, for the same mineralocorticoid reason.

IN INDIA

Tuberculous adrenalitis is the most frequent cause of primary adrenal insufficiency in resource-limited regions. That changes the index of suspicion: the patient with treated or partially treated tuberculosis, or with HIV disease, who becomes apathetic, anorexic and postural is a different proposition from the same presentation in a European textbook.

4.2 The psychiatric phenotype of Addison disease

Onset is usually insidious, with progressive fatigue, weakness, anorexia, nausea, abdominal pain and weight loss, together with cutaneous and mucosal pigmentation, hypotension and

hypoglycaemia. The laboratory correlates are hyponatraemia, hyperkalaemia and metabolic acidosis. Read that list as a psychiatrist and every item is one you have written off before: fatigue, anorexia and weight loss as depression, abdominal pain as somatisation, postural symptoms as an antidepressant side effect.

How often the psychiatric features occur is genuinely unknown. Reports of neuropsychiatric symptoms in Addison disease are uncommon, although the true prevalence is uncertain because of probable under-reporting. No figure is available from the standard sources, and any percentage offered in an answer is invention. What the sources do describe is the shape.

STRATUM	FEATURES	WHAT IT MEANS FOR YOU
Predominant	Depression, reduced motivation and energy, and behavioural change.	What reaches psychiatry, mistaken for a primary mood disorder.
Commonest cognitive disturbance	**Memory dysfunction**.	Formal instruments belong to the Psychometry, Assessment and Descriptive Psychopathology notes.
Less common	Paranoid symptoms and delusions.	Not the modal picture; do not require psychosis before considering the diagnosis.
Rare but dramatic	Catatonia and self-mutilation.	The reason an unexplained catatonia gets a metabolic screen.
Heralding a crisis	Auditory and visual hallucinations, changes in conscious state, irritability, insomnia and nightmares.	A change in trajectory, not a new psychiatric diagnosis.
Established crisis	Frank delirium, coma and seizures.	An emergency; the delirium workup belongs to the Stroke, TBI, delirium and focal brain syndromes notes.

Hyponatraemia and metabolic acidosis may themselves contribute to the delirium and to the cognitive deficits, so part of what you are seeing is electrolyte disturbance rather than cortisol deficiency as such. Thresholds, mechanisms and the risks of correction are set out where this chapter deals with hyponatraemia and with the sodium-correction risk.

4.3 Adrenal crisis: recognising decompensation from the psychiatry ward

Acute adrenal insufficiency, the adrenal crisis, is the life-threatening end of the same disease. It is characterised by gastrointestinal symptoms of nausea, vomiting and abdominal pain, with dehydration, hyponatraemia, hyperkalaemia, weakness, lethargy and hypotension. Two things make it psychiatric. The prodrome is behavioural, in a patient who already carries a psychiatric label. And it can be iatrogenic, because it can follow abrupt withdrawal of glucocorticoids used at high doses or for prolonged periods: any patient on long-term steroids who stops them, or has them stopped during an admission, is exposed.

PITFALL

The insomnia, irritability and nightmares of an incipient crisis are read as psychiatric deterioration and answered with a sedative or a dose increase. What separates them is trajectory plus the somatic signs: falling blood pressure, vomiting, dehydration and clouding of consciousness are not features of a worsening mood or psychotic disorder. A patient with known adrenal insufficiency who becomes more disturbed needs observations and electrolytes before a psychotropic decision.

4.4 Localising the failure: corticotropin, stimulation and suppression

The single test that localises the lesion is the **plasma corticotropin immunoassay**. Its logic is feedback. Patients with primary adrenal insufficiency from intrinsic adrenal disease have high corticotropin levels because normal glucocorticoid feedback inhibition has been lost, whereas patients with secondary adrenal insufficiency from hypothalamic or pituitary disorders have low levels.

The same assay does the reciprocal job at the other end of the axis. In hypercortisolism, normal or high corticotropin levels are seen where the source is pituitary or ectopic, whereas low levels are invariably seen where the source is adrenal. The hypercortisolism syndromes are taught where this chapter deals with Cushing syndrome and steroid psychiatry. One caveat belongs to the assay itself: the specificity of these immunoassays for intact corticotropin can produce falsely low values in patients with ectopic secretion, so a low result in the wrong context is a reason to think again, not to close the case.

Function, as distinct from localisation, needs its own test. **Tetracosactrin testing**, in which an injection of a synthetic corticotropin analogue is given, assesses adrenocortical reserve. Dynamic endocrine tests divide cleanly: a stimulation test asks whether the gland can respond when driven, while **endocrine suppression tests** ask whether feedback is intact or secretion has become at least partly autonomous. Suppression of plasma cortisol by the synthetic glucocorticoid dexamethasone is incomplete in Cushing's syndrome, and suppression of serum growth hormone by an oral glucose load fails to occur in acromegaly. Two diseases, one principle.

The references name the stimulation test and its purpose but supply no usable dose, sampling interval or cortisol threshold, so none is given here. If asked for numbers, say what the test does and quote a threshold only from an endocrine source in front of you.

4.5 Management: replacement, crisis and the perioperative patient

LOCUS is binary. Chronic replacement is outpatient work shared with an endocrinologist, and the psychiatrist's contribution is adherence, recognising undertreatment and not creating a withdrawal crisis. Suspected acute adrenal insufficiency is emergency work: resuscitation with a steroid attached, where the correct psychiatric action is transfer, not titration on the ward. The perioperative patient sits between the two and is managed by protocol.

FOCUS shifts by phase. Acutely the target is circulatory collapse, dehydration and electrolyte derangement, with the neuropsychiatric features expected to follow the physiology. Short term,

stabilisation and step-down; longer term, a regimen that abolishes symptoms without imposing the harms of excess, plus the education that prevents the next crisis.

MODUS is almost entirely pharmacological, and the doses are the examinable content. For glucocorticoid replacement in chronic adrenal insufficiency, hydrocortisone was historically given at 20 to 30 mg per day, but most current guidelines now recommend the lower range of **15 to 20 mg per day**, based on estimates of normal endogenous cortisol production. The downward revision is the point: name both figures with the reason. The alternative agent for chronic replacement is cortisone acetate, inactive until it is converted to cortisol by 11-beta-hydroxysteroid dehydrogenase type 1, used at 25 to 37.5 mg per day. For mineralocorticoid replacement in primary adrenal insufficiency, **fludrocortisone acetate** is used at **0.05 to 0.2 mg per day**.

Both arms are titrated against clinical endpoints, not a target level. Mineralocorticoid dosing in primary adrenal insufficiency is based on resolution of electrolyte abnormalities and of postural hypotension, with reduction of salt craving as another valuable marker; the lower dose is used initially and titrated upward as required by blood pressure, plasma renin and the response to upright posture. Salt craving is the one a psychiatrist is most likely to elicit and least likely to ask about. Dosing frequency differs for a pharmacokinetic reason: fludrocortisone has a half-life of 24 h or more, so divided doses are not necessary, whereas the glucocorticoids are given in divided doses in an effort to mimic the normal diurnal rhythm of cortisol secretion, with two-thirds of the dose in the morning and one-third later in the day.

TRAP **Being asked when the second glucocorticoid dose is given.** The fractions are not in dispute: two-thirds in the morning, one-third later. The timing word is. The running text of the standard pharmacology reference places the smaller dose in the afternoon, while a table tip within the same reference states the evening. This is not pedantry: an evening glucocorticoid dose is precisely the one classically avoided for insomnia and for blunting the nocturnal cortisol nadir. Give the fractions, state the split as afternoon on the running-text reading, and name the variant rather than resolving it by assertion.

In the emergency, dose and route change entirely. **Critical illness-related corticosteroid insufficiency** reflects inadequate cortisol production, and can equally follow abrupt cessation of administered glucocorticoids. For that indication, high-dose intravenous hydrocortisone at 50 to 100 mg every 6 h, or a constant infusion at 10 mg per hour, is needed; prednisone at 1 mg per kg per day is an alternative. Bolus and infusion regimens are separate options and must never be blended into a hybrid figure. As the patient stabilises, the hydrocortisone dose may be decreased to 25 mg every 6 to 8 h, after which treatment proceeds as for chronic insufficiency. For perioperative cover in known adrenal insufficiency, hydrocortisone 100 mg parenterally every 8 h is given, and following surgery the dose is halved each day until routine maintenance levels are reached.

In suspected but unconfirmed acute adrenal insufficiency, **4 mg** of dexamethasone sodium phosphate can be substituted for hydrocortisone, because dexamethasone does not cross-react in the cortisol assay and will not interfere with measurement of cortisol either basally or in response

to the cosyntropin stimulation test. Treatment therefore starts before the diagnosis is secure without destroying the evidence, and failure to respond to cosyntropin in this setting is diagnostic of adrenal insufficiency. The same agent has a patient-held role: patients should carry dexamethasone 4 mg for intramuscular use in the event that severe nausea or vomiting precludes oral medication, and should then seek medical attention immediately.

GOOD TO REMEMBER

Sequencing matters when more than one axis has failed. In adrenal insufficiency associated with panhypopituitarism, glucocorticoids must be given before thyroid hormone is started, because thyroid hormone used in isolation accelerates metabolism of whatever endogenous cortisol remains and may precipitate an adrenal crisis. The temptation runs the other way, since the hypothyroidism is often noticed first. Thyroid replacement is taught where this chapter deals with hypothyroidism and hyperthyroidism; what belongs here is the order.

4.6 The psychiatric symptoms respond to the steroid, not to a psychotropic

The psychiatric literature is unusually strong on this point. The neuropsychiatric symptoms of Addison disease, including those of adrenal crisis, appear largely to resolve once treatment with adequate doses of corticosteroids is commenced, and the use of other psychotropic agents is rarely indicated.

RULE **In diagnosed adrenal insufficiency, persistent psychiatric symptoms are a replacement-dose question before they are a psychotropic question.** Recent data indicate that higher corticosteroid doses reduce the occurrence and severity of neuropsychiatric symptoms, particularly depressive symptoms. The first move when mood and motivation fail to recover is to ask whether replacement is adequate, with whoever manages the endocrine disease, rather than to layer a psychotropic on top.

Hold that direction alongside its mirror image. In replacement, more steroid means fewer psychiatric symptoms; in supraphysiological exposure, which this chapter covers under steroid-induced psychiatric disturbance in Cushing syndrome and in therapeutic corticosteroid use, more steroid means more psychiatric risk. They are not in conflict: they describe different halves of one dose-response curve, correcting a deficiency and imposing an excess. No milligram figure attaches to "higher doses" in the source, so it is a direction of adjustment and not a licence to name a number.

4.7 Phaeochromocytoma: the panic phenocopy

Phaeochromocytomas are catecholamine-secreting tumours that most commonly originate in the chromaffin cells of the adrenal medulla, though they may rarely arise from similar cells in sympathetic ganglia. Familial forms are associated with **multiple endocrine neoplasia syndrome type IIa and type IIb**, and with von Recklinghausen neurofibromatosis. Those are the two associations the standard psychiatric reference names; other syndromic and mutational associations circulate in endocrine practice but are not asserted here.

Catecholamine secretion may be continuous or sporadic, and when sporadic it produces characteristic paroxysmal symptoms: headache, profuse sweating, palpitations, Raynaud

phenomenon, tremor, nausea, vomiting, and abdominal and chest pain. The clinical signs are hypertension, pallor, postural hypotension, and the signs of chronic hypertension such as retinopathy. Read that against the criteria for a panic attack and the overlap is near complete: this tumour is a psychiatric problem before it is a surgical one.

MNEMONIC

Palpitations, Headache, Sweating

The triad of palpitations, headache and profuse sweating is the most sensitive and specific presentation for phaeochromocytoma. All three are symptoms a panicking patient may report, so the triad narrows the field without settling it. The source asserts its discriminating power without attaching sensitivity or specificity values, so quote it qualitatively.

40% of phaeochromocytomas present with paroxysmal symptoms, and the paroxysm may present as a phenocopy of anxiety symptoms, particularly a panic episode, and is often diagnosed as such. The precipitants are informative because several are shared with panic and one is not: episodes may occur spontaneously or be precipitated by exercise, postural change, raised intra-abdominal pressure, or emotional excitement or shock. Raised intra-abdominal pressure has no psychiatric counterpart and is worth asking about. Severity varies between episodes, and anxiety may persist for some time after the attack, so residual anxiety after a paroxysm does not argue for a primary anxiety disorder.

The negative finding narrows the differential. Psychosis and cognitive deficits have not been described in phaeochromocytoma, although there are several case reports of a secretory tumour causing relapse of a previously treated or quiescent psychotic disorder. This is an anxiety-spectrum problem: a first-episode psychosis or a progressive cognitive syndrome is not a phaeochromocytoma presentation.

4.8 Confirming it, treating it, and the psychotropics that intervene

Diagnosis is made by detecting increased urinary secretion of catecholamines or catecholamine metabolites. The psychiatric reference goes no further: no assay named, no sensitivity or specificity given, no cut-off set, so none is stated. Locating the tumour and excising it surgically, under alpha-adrenergic blockade, is effective in resolving most anxiety symptoms if the paroxysmal episodes are terminated. No alpha-blocking agent is named and no preoperative interval is given in these sources, so the teachable content is the sequence and not a drug or a schedule.

TRAP **Reaching for a beta blocker first in the sweating, tremulous, palpitating patient.** Propranolol is a familiar prescription for tremor and performance anxiety, and the reflex is strong. The monograph warning is categorical: do not use propranolol in phaeochromocytoma unless alpha blockers are already being used. The examinable answer is the order: alpha before beta. The source states the prohibition without explaining it, so the safe answer names the sequence and stops there rather than embellishing with a mechanism.

Two of your own prescriptions can corrupt or contraindicate this workup. False-positive results may occur in screening tests for phaeochromocytoma in patients being treated with prazosin, and if an elevated urinary vanillylmandelic acid is found, prazosin should be discontinued and the patient retested after a month. Prazosin is prescribed for nightmares in post-traumatic stress disorder, so this collides with real practice: the traumatised patient with hyperarousal and autonomic symptoms is precisely the one in whom someone orders a catecholamine screen. The second group is contraindicated outright, and the list is a psychiatric one.

- Atomoxetine: do not use if the patient has phaeochromocytoma or a history of phaeochromocytoma, or a severe cardiovascular disorder that might deteriorate with clinically important increases in heart rate and blood pressure.
- Isocarboxazid, phenelzine and selegiline: do not use if the patient has phaeochromocytoma.
- Amisulpride, sulpiride, flupenthixol and pipothiazine: do not use if the patient has phaeochromocytoma.

Atomoxetine is the clinically live entry, a mainstay of non-stimulant attention deficit hyperactivity disorder prescribing in Indian practice. The monoamine oxidase inhibitor entries are mechanistically unsurprising. The last group is the one candidates forget, because the substituted benzamides and thioxanthenes are not drugs anyone associates with catecholamine physiology. Choice among antipsychotics otherwise belongs to the Schizophrenia: management, antipsychotics and adverse effects notes; what belongs here is that this diagnosis removes four of them from the table.

> Adrenal insufficiency presents as depression, apathy and memory failure that respond to adequate corticosteroid replacement rather than to a psychotropic; phaeochromocytoma presents as panic, and in a patient who might have one, alpha blockade always precedes beta blockade.

5 · Hypothyroidism and hyperthyroidism in psychiatry

No gland is asked about more often than this one. The examinable content is not that thyroid disease produces psychiatric symptoms but the shape of the association: which symptoms arrive before the physical features, and what is still there a year after the gland has been corrected. Almost every error here is a caricature. The underactive gland is supposed to produce a slowed, depressed, forgetful patient and the overactive gland a bright, fast, manic one. The first caricature is roughly right; the second is wrong, and the prevalence figures say so plainly enough that examiners build questions on it.

The two diseases are not mirror images. What genuinely inverts between them is the timing relative to the physical illness and the degree to which the biochemistry predicts the psychiatry.

UP TO 50%	APPROXIMATELY 40%	UP TO 30%	2 TO 5%
COGNITIVE DEFICITS IN HYPOTHYROIDISM	DEPRESSION IN HYPOTHYROIDISM	DEPRESSION IN HYPERTHYROIDISM	MANIC SYMPTOMS IN HYPERTHYROIDISM

5.1 Two causal lists, and the test logic that anchors both

Hypothyroidism in adults is overwhelmingly a disease of the gland itself. The commonest cause is **primary autoimmune hypothyroidism related to antithyroid antibodies**, with the remainder made up largely of treatment given for hyperthyroidism, drug-related effects, and iodine deficiency. Causes above the gland, meaning hypothalamic or pituitary dysfunction, account for less than 5% of cases. That proportion carries the interpretive logic of the thyroid function test. Because the great majority is primary, loss of negative feedback drives thyroid-stimulating hormone up while the peripheral hormone falls, so in overt hypothyroidism a raised thyroid-stimulating hormone with a low free thyroxine is the expected pattern. The rare central case breaks it: a low free thyroxine with a thyroid-stimulating hormone that is low or merely unremarkable is a pituitary problem until proven otherwise, and needs the rest of the anterior pituitary examined rather than a prescription for replacement.

Hyperthyroidism has a broader causal list because several different mechanisms produce the same excess. The excessive production of thyroid hormone may arise from a toxic multinodular goitre, from a single functioning adenoma, or from a thyroid stimulator such as the **thyroid-stimulating antibody in Grave disease**. Exogenous thyroid hormone reproduces the picture, as do disorders of thyroid hormone storage consequent to autoimmune thyroiditis. Two matter disproportionately in a psychiatric clinic: the patient taking thyroid hormone for weight control or as an antidepressant adjunct, and the patient whose autoimmune thyroiditis is releasing stored hormone before it burns out into hypothyroidism, so that one gland delivers both syndromes in sequence.

Two boundaries belong to neighbouring material. The numeric definitions that separate subclinical from overt hypothyroidism sit with this chapter's account of subclinical thyroid disease, autoimmunity and Hashimoto encephalopathy, and they are not symmetrical: the hypothyroid side carries an agreed thyroid-stimulating hormone band, the hyperthyroid side has no equivalent, and a candidate who constructs one by mirror image is inventing it. Lithium-induced thyroid dysfunction is taught with the lithium and thyroid material; lithium as a drug, its pharmacokinetics and its non-thyroid organ effects belong to the Mood disorders: pharmacotherapy notes.

5.2 Myxoedema: the examination that makes the diagnosis

The symptoms include fatigue, lethargy, weight gain, constipation, cold intolerance, stiffness and cramping of muscles, hair loss, cognitive slowing and depression. Read that list as a psychiatrist and it is indistinguishable from a moderate depressive episode with somatic features, which is exactly why the examination decides the question.

- General and cardiovascular: hypothermia and bradycardia.

- Skin, hair and face: dry skin, sparse hair and periorbital swelling.
- Mouth and voice: thickening of the tongue, with coarsening and deepening of the voice.

The sign that settles it at the bedside is the **characteristic prolonged relaxation phase of the deep tendon reflexes**, which needs no laboratory and is the one finding a depressed patient cannot produce. Taken together this constellation is what is meant by **myxoedema**.

GOOD TO REMEMBER

The free thyroxine value has no number attached to it in these notes on purpose: report it against the reporting laboratory's own reference interval, since assays and units differ and a remembered range is a good way to call a normal result low. The direction of change, read together with the thyroid-stimulating hormone, carries the diagnosis.

5.3 The hypothyroid ladder: cognition, then mood, then anxiety

Cognitive deficits are the most common neuropsychiatric feature, occurring in up to 50% of cases, with impairment of psychomotor speed, memory and visual-perceptual skills. Difficulty with constructional skills and reduced performance on trail-making and maze tasks point to prominent executive deficits as well, so this is not a pure amnestic picture but a diffuse slowing with an executive edge. How cognition is examined belongs to the Psychotherapies, clinical assessment, MSE and nosology notes, and the dementia syndrome and its workup to the Dementias and neurocognitive disorders notes.

Depression is only slightly less common than cognitive disturbance, reported in approximately 40% of patients, and presents most often as low mood, fatigue, anhedonia, reduced concentration and hypersomnolence. Generalised anxiety symptoms are described in up to 30% of patients, strongly correlated with the depressive symptoms but not with biochemical severity. The mood disturbance is not always unipolar: it may take a **rapid-cycling form**, which is the reason thyroid function is checked in a patient whose bipolar illness has accelerated rather than only in one who looks flat.

MNEMONIC

Think, then feel, then fear, then break

Hypothyroidism descends that ladder in order of frequency: cognitive impairment is commonest, depression next, generalised anxiety next, and frank psychosis is rare. The same four presentations occur in thyrotoxicosis in a different order, so it is the ordering rather than the list that is worth memorising.

The severity of the cognitive disorder is correlated with the degree of biochemical abnormality, and although largely corrected by a return to a euthyroid state, some deficits may remain, particularly in older adults or in those with reduced cognitive reserve. Depression behaves differently: it is less closely related to the severity of the biochemical hypothyroidism. Severe disturbance of consciousness, including coma and delirium, may be encountered, but may be associated with other metabolic changes accompanying the hypothyroid state, such as

hyponatraemia: that sodium pathway is taken up where this chapter deals with SIADH and hyponatraemia, and delirium as a syndrome belongs to the Stroke, TBI, delirium and focal brain syndromes notes.

RULE **Biochemical severity predicts the cognitive picture, not the mood picture, in either direction of thyroid dysfunction.** Cognitive severity tracks the degree of biochemical abnormality in hypothyroidism; depressive severity does not, in either hypothyroidism or hyperthyroidism. A near-normal set of results therefore never excludes a thyroid-driven depression, and a grossly abnormal set never predicts how depressed the patient will be. Anxiety splits between the two: it follows the depression in hypothyroidism and more often follows the thyrotoxic severity in hyperthyroidism.

5.4 Myxoedema madness: the eponym that outlived its epidemiology

Psychotic symptoms in hypothyroidism, including paranoid ideas, misidentification, visual and auditory hallucinations and thought disorder, were originally thought to be common and were described as **myxoedematous madness**, but they likely occur in **less than 5%** of all patients with hypothyroidism and tend to emerge after the onset of the physical symptoms. So a first-episode psychosis in a physically well patient is not myxoedema madness by default.

Indian consultation-liaison practice adds a presentation the standard psychiatric account does not name. Subclinical to moderate hypothyroidism is often associated with depressive symptoms, while severe hypothyroidism can give rise to psychosis, including myxoedema madness, delirium and **catatonia**. That completes a severity gradient: mild and moderate disease is a mood problem, severe disease is a brain-failure problem, and catatonia sits at the severe end alongside the psychosis and the delirium rather than being a separate curiosity.

TRAP **Treating myxoedema madness as a common and early presentation of hypothyroidism.** The historical literature described it as frequent and candidates reproduce that framing. The corrected version is that psychosis occurs in under one in twenty patients with hypothyroidism and follows rather than precedes the physical features. Write the eponym, then correct it in the same breath; that sequence is what earns the mark.

IN INDIA

Two divergences are real here. First, the causal list is weighted differently: autoimmune disease still leads, but iodine deficiency remains a live entry in a way it is not in most Western practice, so a hypothyroid patient from an iodine-deficient area is not automatically an autoimmune one and the dietary and geographic history is worth taking. Second, Indian consultation-liaison teaching explicitly places catatonia within the severe-hypothyroid picture: where a catatonic patient may reach psychiatry before any medical workup, thyroid function belongs in the first set of investigations, and calling a catatonia idiopathic before it has been checked is a decision, not an omission.

5.5 Why the hypothyroid brain becomes depressed

The origin of depression in hypothyroidism appears to relate to the role of thyroxine in serotonergic transmission: reduced thyroid input reduces serotonergic tone and lowers the

threshold toward the development of depressive symptoms, while thyroid replacement restores central serotonin activity in concert with improvement in the depressive symptoms. The same mechanism is thought to underpin the adjunctive antidepressant effect of thyroxine, which is the bridge to thyroid hormone augmentation in resistant depression. That strategy, with its agents and doses, is taught where this chapter deals with lithium, thyroid dysfunction and thyroid hormone augmentation, and none of it should be reconstructed from the physiology given here.

The imaging tells the same story at the level of the whole brain. Functional neuroimaging has demonstrated global hypometabolism, with more specific areas of hypoperfusion in the posterior cingulate, the insula, the fusiform gyrus, and the right parieto-occipital and primary motor cortex. The global finding fits the clinical picture better than any regional one: a diffusely slowed brain produces diffusely slowed cognition, which improves as the metabolic state is restored. The wider principles of functional imaging and neurotransmitter measurement belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

5.6 Hyperthyroidism: depression first, mania last

Here the caricature fails completely. Depressive symptoms are the most common psychiatric feature of hyperthyroidism, occurring in up to 30% of patients, and frequently occur prior to the onset of the other physical features. This includes lowering of mood together with neurovegetative disturbance such as insomnia, reduced libido, weight loss and fatigue. The discriminator is one symptom. As distinct from depression, appetite is invariably increased in hyperthyroidism, so **increased appetite with weight loss**, in a patient who also reports insomnia and fatigue, points at the thyroid until the test says otherwise.

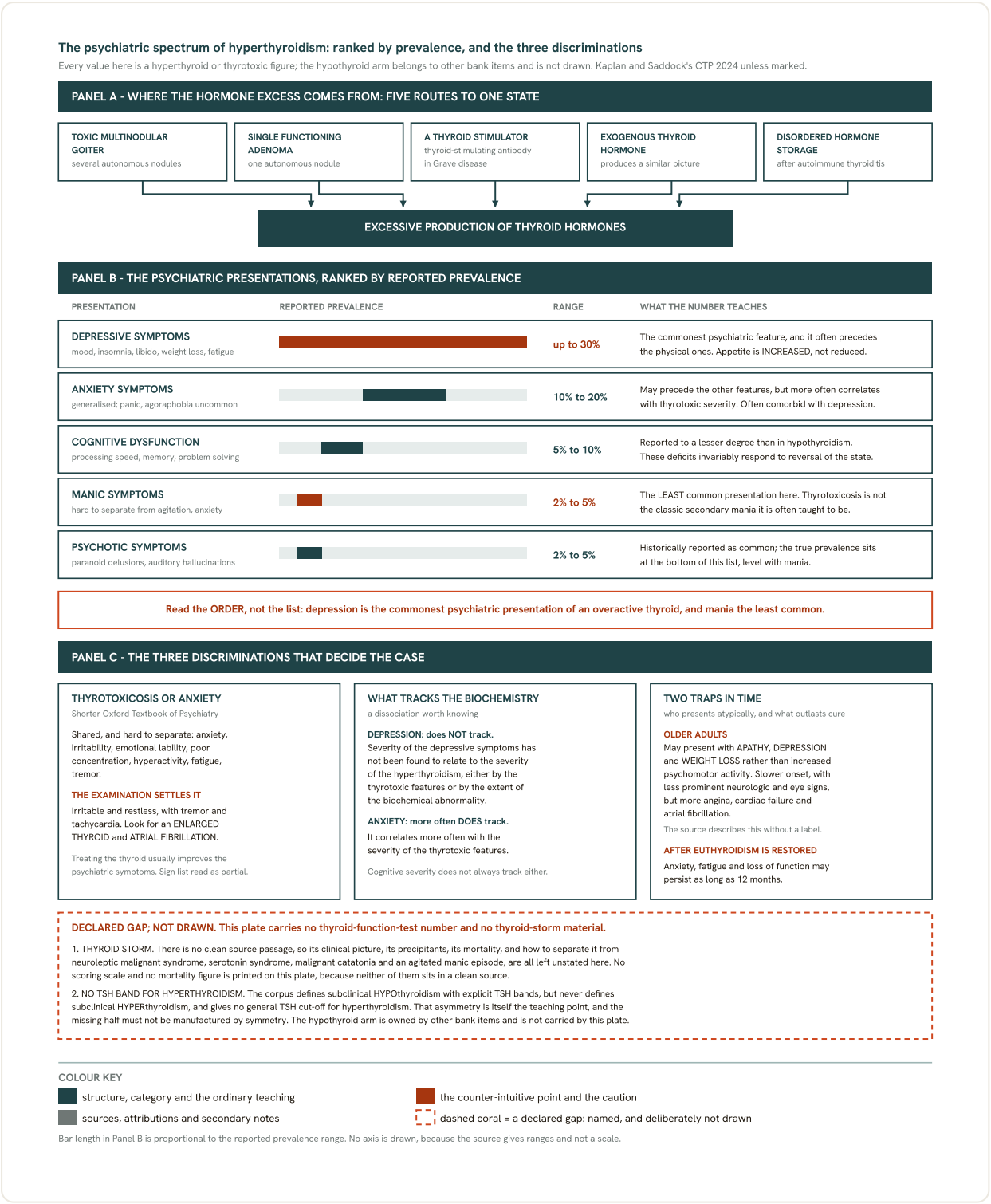

Fig 33.3 **The psychiatric spectrum of hyperthyroidism, ranked by reported prevalence.** The ordering is the teaching: depressive symptoms are the commonest psychiatric feature of an overactive thyroid and frequently precede the physical ones, while manic and psychotic symptoms sit at the bottom of the list, which contradicts the folk teaching that thyrotoxicosis is a classic secondary mania. Appetite is invariably increased, and that is the discriminator from a primary depressive episode. Depressive severity does not track the biochemistry; anxiety more often does. In older adults the presentation may be apathy, depression and weight loss rather than overactivity, an entity the source describes without naming. The hypothyroid arm of the spectrum and every thyroid-function-test band are declared gaps for this item and are not drawn. (Kaplan and Saddock's CTP 2024; Shorter Oxford Textbook of Psychiatry for the anxiety-disorder differential and the examination signs, where the sign list is read as partial.)

The remaining presentations fall in a strict order of frequency below depression.

- Anxiety presenting as generalised anxiety is common, with a prevalence of between 10% and 20%, but panic and agoraphobia are relatively uncommon.
- Cognitive dysfunction is reported in **between 5% and 10%** of patients with thyrotoxicosis, to a lesser degree than in hypothyroidism.
- Manic symptoms are less common, with a prevalence of **between 2% and 5%**, and may be difficult to distinguish from psychomotor agitation and anxiety; psychotic symptoms, including paranoid delusions and auditory hallucinations, were historically reported as common but have a true prevalence of between 2% and 5%.

Timing separates anxiety and depression from everything else. Anxiety, like the depressive symptoms, may occur prior to the other features of hyperthyroidism, but more often correlates with the severity of the thyrotoxic features, and anxiety and depressive features are frequently comorbid. Depression does not behave that way: its severity has not been found to relate to the severity of the hyperthyroidism as measured by the subsequent thyrotoxic features or the extent of the biochemical abnormality.

TRAP **Naming thyrotoxicosis as a classical cause of secondary mania.** It is taught that way in wards and it is the wrong end of the list: mania is the least common of the four psychiatric presentations of hyperthyroidism, sitting alongside psychosis at the bottom, while depression sits at the top at up to three in ten patients. The useful version is the reverse: suspect thyrotoxicosis in the depressed patient with weight loss and a rising appetite, not principally in the elated one.

5.7 The two clinical mistakes: the anxious young patient and the apathetic old one

The first mistake is diagnostic. Hyperthyroidism may present with anxiety, irritability, emotional lability and difficulty in concentrating, and these, together with hyperactivity, fatigue and tremor, can make the differential diagnosis from an anxiety disorder difficult. The resolution is physical rather than psychopathological. The patient may be irritable and restless with tremor and tachycardia, and examination may reveal characteristic signs such as an enlarged thyroid and atrial fibrillation; that list of signs is reliable but not necessarily exhaustive, so a normal thyroid on palpation does not close the question and the biochemistry still decides it. Treatment of the thyroid dysfunction usually results in improvement of the psychiatric symptoms, which is the retrospective proof but no help at the first consultation.

The second mistake is a failure of expectation in older patients. Older adults with thyrotoxicosis may present with predominantly apathy, depression and weight loss rather than increased psychomotor activity, typically with a slower onset and with less prominent neurologic and ophthalmologic features, while cardiovascular events such as exacerbation of angina, cardiac failure and atrial fibrillation are more prevalent. This is the presentation conventionally labelled apathetic thyrotoxicosis, and every element of it points away from the diagnosis. In that patient the thyroid is disclosed by the heart rather than by the eyes.

AXIS	HYPOTHYROIDISM	HYPERTHYROIDISM
Depression	Approximately 40%; low mood, fatigue, anhedonia, reduced concentration, hypersomnolence.	Up to 30%; the commonest psychiatric feature, with appetite increased rather than reduced.
Anxiety	Up to 30%; generalised.	Between 10% and 20%; panic and agoraphobia relatively uncommon.
Cognition	Up to 50%; psychomotor speed, memory, visual-perceptual and executive.	Between 5% and 10%; slow processing, immediate memory, higher-level problem solving, or frank delirium.
Psychosis	Less than 5%.	Between 2% and 5%.
Elevated mood	Mood disorder may take a rapid-cycling form.	Manic symptoms between 2% and 5%; the least common presentation.
Timing versus physical features	Psychosis tends to emerge after the physical symptoms.	Depression frequently precedes the physical features, and anxiety may also precede them.
Tracks biochemical severity	Cognitive severity yes; depression no; anxiety no.	Depression no; anxiety more often yes; mild attention and concentration deficits not always.
After euthyroid state restored	Mood symptoms may reverse but neuropsychiatric problems may persist; some cognitive deficits may remain.	Cognitive deficits invariably respond; anxiety, fatigue and loss of function may persist as long as 12 months.

5.8 Management: correcting the gland, and knowing what correction will not fix

LOCUS. Most of this is outpatient work shared with a physician, where the psychiatrist contributes recognition and sequencing rather than prescription. Inpatient care is for the severe end: the psychosis, delirium and catatonia of severe hypothyroidism, and the patient whose disturbance of consciousness makes safe outpatient correction impossible. Where thyrotoxicosis becomes an acute medical crisis the locus is a medical unit, and the psychiatrist's job is to keep the differential of an agitated, unstable patient open rather than closing it onto a psychiatric label. The authorities here are Kaplan and Sadock's Comprehensive Textbook of Psychiatry for the neuropsychiatric epidemiology and its treatment, the Shorter Oxford Textbook of Psychiatry for the differential against primary anxiety and mood disorder, and Indian consultation-liaison guidance for the severity gradient and the catatonia entry.

FOCUS changes with phase. Acutely the targets are safety, the psychotic or catatonic presentation, and the medical instability that produced them. Over the short term the target is the euthyroid state itself, and this is where restraint earns most: the depressive syndrome seen in hyperthyroidism rarely requires treatment other than that used to restore the euthyroid state. Over the mid term the target is what fails to resolve, since anxiety, fatigue and loss of function may persist as long as **12 months** after a euthyroid state has been achieved. Long term the target

is residual cognition, because replacement therapy may reverse the mood symptoms while neuropsychiatric problems persist, with older adults and those with reduced cognitive reserve the group in whom that residue is most likely.

MODUS begins with the endocrine treatment, which is the effective psychotropic in both diseases, and adds psychiatric treatment only where a specific indication survives it. The psychotic symptoms of hypothyroidism also respond to appropriate thyroid hormone treatment within days to weeks, but rapid titration of hormone doses may exacerbate the psychosis, and careful addition of a low dose of antipsychotic to thyroxine has been reported to be well tolerated and to result in earlier remission of the psychosis. Two instructions sit inside that: go slowly with the hormone in a psychotic patient, and use the antipsychotic alongside it rather than instead of it. No numeric dose of either agent is stated in the source and none should be supplied from memory; the choice of antipsychotic agent and its receptor pharmacology belong to the Schizophrenia: management, antipsychotics and adverse effects notes. The psychological and social modes are load-bearing: explaining to a patient depressed for months that the treatment is for a gland, and warning patient and family that anxiety and fatigue may outlast the biochemistry by many months, prevents the demoralisation that follows a correction which does not feel like a cure.

PITFALL

The residual state after successful treatment of hyperthyroidism gets misdiagnosed twice over. Anxiety and fatigue persisting months after the thyroid is corrected are read as a new primary anxiety disorder and treated as one, or read as inadequate control and used to justify further meddling with the thyroid. These features can persist for up to a year in a properly euthyroid patient, so the correct action is usually to name the timeline, keep reviewing, and not start a new illness on the strength of it.

Depression is the commonest psychiatric presentation of BOTH thyroid diseases, mania is the least common presentation of hyperthyroidism, and biochemical severity tracks the cognitive deficit but never the mood.

6 · Lithium, thyroid dysfunction and thyroid hormone augmentation

Two questions live here and they run in opposite directions. The first is what lithium does to a healthy thyroid, and how to hold a patient on the drug carrying their mood disorder while that thyroid quietly fails. The second is the mirror: what thyroid hormone does to a mood disorder in a thyroid that works. Lithium as a drug belongs to the Mood disorders: pharmacotherapy notes; interpreting thyroid function tests is set out where this chapter deals with hypothyroidism and hyperthyroidism in psychiatry. What is added here is lithium and thyroid function taken together: what those results mean when lithium is why you ordered them.

1.5% PER YEAR	**8% TO 19%**	**UP TO 20%**	**3 TO 4-FOLD**
NEW HYPOTHYROIDISM, ANNUAL INCIDENCE	PREVALENCE, OVERT DISEASE	RISK IN MIDDLE-AGED WOMEN	THYROID LITHIUM VERSUS PLASMA

6.1 Why the thyroid, and by what mechanism

Lithium concentrates in the organ it disables, by the route iodide takes. The **Na+/I- symporter** carries iodide into the follicular cell, where thyroid peroxidase oxidises it and then iodinates selected tyrosine residues on thyroglobulin. Lithium is a substrate for that transporter, so it accumulates: levels in the gland run three to four times higher than in plasma, which is why organ-specific effects appear at ordinary plasma levels. Its actions fall into three groups.

- Release is inhibited: T4 and T3 are held rather than secreted.
- Thyroglobulin conformation is altered, so coupling of its iodinated tyrosine residues to form T4 and T3 is inhibited.
- Binding of T4 and T3 to hypothalamic receptors is altered, downregulating expression of genes for certain receptor isoforms.

MNEMONIC

Release, Reshape, Receptor

Two of the three sit inside the gland, one above it, which is why the picture is not always a clean primary hypothyroidism.

Reassuringly, these effects are largely reversible and lithium is not associated with the development of antithyroid antibodies, though an occasional patient has persistent hypothyroidism after lithium is stopped, for reasons lying elsewhere.

TRAP **Writing that lithium blocks iodine uptake into the thyroid.** Widely reproduced in Indian examination material, and with a real source: Indian consultation-liaison guidance states that lithium interferes with iodine uptake, iodination of tyrosine, thyroglobulin structure and hormone release. The Lithium Handbook contradicts the first element flatly: lithium alters neither iodide uptake nor efflux, being a substrate rather than a blocker. They agree on everything downstream. Name the agreed mechanisms, then flag uptake as disputed rather than asserting either version as settled.

6.2 How common, in whom, and the numbers that get blended

At least four figures for lithium-induced thyroid disease circulate, all of them for hypothyroidism, and each is correct in its own frame. The tightest concerns new disease over time: in long-term follow-up the annual incidence of new hypothyroidism is **approximately 1.5%**, with females affected at three times the rate of males. That is an incidence, new cases per year of exposure: the question a patient asks at initiation.

A prevalence answers something else. The prevalence of **overt hypothyroidism** in lithium-treated patients runs from 8% to 19%, a band restricted to overt disease and so excluding the larger subclinical group. A third is subgroup-bound: the Maudsley Prescribing Guidelines note that in middle-aged women the longer-term risk may reach 20%. Indian consultation-liaison teaching carries a fourth and much broader band, overlapping all of these without matching any.

The recognised predictors group usefully.

- Fixed patient factors: female sex, a predisposition to autoimmune hypothyroidism, family history.
- Age older than 50 years.
- Treatment-related: duration of lithium treatment, and weight gain of more than 5 kg.

The last two are observable without any extra test: a patient who has gained substantial weight over two years of lithium is one whose next TSH deserves attention. For proportion, hypothyroidism does not rank among the leading somatic reasons patients discontinue lithium.

TRAP **Reciting "20%" as the risk of hypothyroidism on lithium.** A candidate who cannot say whether the number is annual or cumulative, overt or subclinical, or in whom, will be taken apart in a viva. Do not average the four. Name the quantity, the population, the period.

6.3 Reading the TSH: reference range and the argument inside it

The normal TSH range is **0.35 to 4.5 mIU/l**, and **subclinical hypothyroidism** occupies 4.5 to 9.9 mIU/l. Resist hardening those edges: the same source records genuine debate about the upper limit, hedges it elsewhere as typically 4.5 or 5.0, and notes the argument that for younger females the upper limit of normal might be as low as 2.5 mIU/l. Subclinical thyroid disease as an entity is developed where this chapter deals with subclinical thyroid disease and Hashimoto encephalopathy.

The source argues for a flexible rather than threshold-driven approach: a patient with a TSH of 4.0 mIU/l and significant hypothyroid symptoms may do better with a TSH nearer 1.00 mIU/l.

Cohort evidence agrees. The investigators who linked lower mean free T4 to more affective episodes and greater depression severity then found that lithium-treated bipolar patients who required treatment for depression had a significantly higher adjusted mean TSH, 4.4 mIU/l, than those who did not, 2.4 mIU/l. Both are group means, not thresholds, and both sit inside the normal range: an argument for a lower threshold to intervene, not for redefining normality.

GOOD TO REMEMBER

Fatigue, weight gain, cognitive slowing and low mood in a lithium-treated patient are the presenting complaints of both a depressive relapse and an underactive thyroid. The discrimination is laboratory, not bedside. Order the TSH before you rework the mood-stabiliser regimen, not after it fails.

6.4 Baseline work-up, and how often to repeat it

Before lithium is started, renal, thyroid and cardiac function should be checked, with estimated glomerular filtration rate, urea and electrolytes and thyroid function tests as the minimum, and a baseline calcium is also helpful. Only a pre-treatment calcium will later separate drug effect from pre-existing disease; the calcium-related syndromes are developed where this chapter deals with hyperparathyroidism and hypoparathyroidism. Once established, two independent sources agree on the interval at which lithium and thyroid function should be re-checked.

SOURCE	ESTABLISHED THERAPY	WHAT IT ADDS
The Lithium Handbook	Serum calcium, TSH and blood pressure every 6 months, with lithium level and estimated glomerular filtration rate on the same schedule.	Frequency changes if an abnormality is found or treatment started.
Maudsley Prescribing Guidelines, fifteenth edition	Plasma lithium, estimated glomerular filtration rate, urea and electrolytes and thyroid function tests every 6 months.	More frequent testing with interacting drugs, in older patients, or in established chronic kidney disease.
Geriatric psychiatry text (dissenting)	Thyroid parameters every 6 to 12 months once established on a stable dose.	Check before initiation and again after every dose adjustment.

Two clean sources against one is why the figure to teach is **every 6 months**; the dissenter is a geriatric source whose surrounding passage is textually damaged. Show the disagreement anyway: older-adult practice may legitimately differ, and the dissenter adds one element the others omit, a re-check after every dose adjustment, contradicted by nothing.

No source here says when the TSH should first be repeated after initiation: the handbook advises discussing when to repeat it without naming an interval, the Maudsley argues for more tests in the first year without a figure. The established-therapy cadence is well grounded; the initiation cadence is local protocol.

6.5 How far to investigate: antibodies, imaging and a live disagreement

Two respected sources take opposite positions on autoantibody testing, both defensible because their scopes differ. The Lithium Handbook rests on an empirical finding. long-term lithium treatment is not associated with an increased prevalence of autoantibodies to thyroid peroxidase, thyroglobulin or the TSH receptor compared with age-matched and gender-matched peers, and carries no increased risk of thyroid tumours. If lithium does not generate autoimmunity, measuring autoimmunity does not measure lithium. Hence there is no indication for routine thyroid ultrasound or autoantibody testing, and any laboratory measure beyond TSH should be dictated by the clinician prescribing L-thyroxine and by the clinical course.

The Maudsley position is narrower. Discussing middle-aged women, it records that a case has been made for testing thyroid autoantibodies in this group before starting lithium, to estimate risk better, and for performing thyroid function tests more frequently during the first year. That is risk stratification in a defined subgroup, not routine surveillance, so the two do not collide head-on. But the reconciliation is only partial: the handbook's evidence undercuts the risk-stratification rationale as much as the surveillance one. The risk-factor list carries a related tension, naming a predisposition to autoimmune hypothyroidism while the handbook finds no lithium-induced rise in antibody rates; both hold if kept apart, since a patient may bring autoimmune vulnerability to lithium without lithium creating it.

PITFALL

Reading a negative thyroid autoantibody panel as reassurance that this patient will not become hypothyroid on lithium. Evidence that lithium does not raise antibody titres is evidence about mechanism, not a negative predictive value for the individual. Antibody status does not replace the TSH, nor licence a longer monitoring interval.

6.6 Managing hypothyroidism without stopping the lithium

LOCUS. Outpatient almost without exception: the test is a TSH, the treatment a tablet, so neither admission nor endocrinology referral is needed. Shared care matters at two points only, when the TSH is low rather than high, and in pregnancy.

FOCUS. Before treatment, a baseline that lets later change be attributed correctly. Acutely, rarely anything. Short and medium term, the symptom overlap. Long term, continuity of the mood-stabiliser treatment, where nearly all the harm in lithium-induced thyroid disease is done.

MODUS. Three sources govern: the Maudsley Prescribing Guidelines for monitoring, The Lithium Handbook for the treatment decision, and the American Thyroid Association pregnancy guidelines for the obstetric adjustment. **L-thyroxine** is the treatment of choice rather than lithium discontinuation, started on the TSH. A prior history of hypothyroidism is no reason to deprive a patient of lithium; where it precedes lithium, treatment begins as lithium commences.

RULE **Hypothyroidism never justifies stopping lithium, new-onset included.** **Professor Michael Gitlin**, in a 2016 review of lithium's adverse effects quoted approvingly in The Lithium Handbook, calls this the most important clinical rule in the area. You would be trading a fully treatable endocrine deficiency for the best-evidenced prophylaxis in bipolar disorder, and the relapse risk that follows discontinuation. Supplement the thyroid, keep the lithium.

The sources that insist L-thyroxine is the treatment of choice give no starting dose, no titration increment, no titration interval, no TSH target, and no weight-based figure appears anywhere in this material. Prescribe from local thyroid guidance and the clinician managing the replacement; do not reconstruct a dose from memory.

Pregnancy is the one place a specific figure is grounded. In a woman already on thyroid supplementation, high-quality evidence supports increasing the levothyroxine dose by 20% to 30% on a positive pregnancy test, with follow-up by her treating clinician: a proportional adjustment to a dose already taken, not a starting dose. Starting thresholds in pregnancy are separate: a strong recommendation, on low-strength evidence, to treat subclinical hypothyroidism above 10 mIU/l; a weak one between the pregnancy-specific upper limit and 10 mIU/l; and in women whose thyroid peroxidase antibodies are diagnostic of Hashimoto's thyroiditis, treatment above that pregnancy-specific limit, with weak consideration above 2.5 mIU/l while still within it. That last figure is pregnancy and antibody-specific, unrelated to the debate about the upper limit of normal in younger women, which uses the same number for a different population.

IN INDIA

Two divergences. First, the recommendation is contested here. Indian consultation-liaison guidance offers switching to a different mood stabiliser where clinically significant hypothyroidism occurs or subclinical hypothyroidism persists for a defined period, and names T3 rather than L-thyroxine as the thyroid supplement. The Lithium Handbook contradicts both halves. Name the disagreement rather than picking a side by tone of voice. Second, feasibility favours the never-stop position: high-sensitivity TSH assays are obtainable at most laboratories and thyroid replacement is among the cheapest, most widely stocked drugs in Indian practice, so a 6-monthly test and a daily tablet are realistic at district level.

6.7 The other direction: a low TSH on lithium

Hyperthyroidism on lithium is uncommon and, on the best evidence, incidental rather than caused. One group compared adults with at least two TSH or lithium measurements over three decades against a very large unexposed population: after adjustment for age, sex and a diagnosis of diabetes, lithium use was not associated with hyperthyroidism, with an odds ratio of 1.22 and a 95% confidence interval of 0.96 to 1.55. That study operationally defined hyperthyroidism as a TSH below 0.2 mIU/l for a database search: a study convention, never the diagnostic threshold.

A low TSH follows the same logic as a high one. In every such instance the lithium continues while further measures such as T4 and T3 are arranged with the primary care physician, a repeat TSH is agreed, and a persistently low result triggers the work-up appropriate to the cause: antithyroid peroxidase antibodies for Hashimoto's disease, **thyroid-stimulating antibodies** for Graves' disease. Treatment then follows the aetiology and is unaffected by the presence of lithium. As with the initiation interval, the source directs you to agree a repeat interval without saying what it is.

6.8 Thyroid hormone augmentation in unipolar refractory depression

The same axis now becomes a treatment, and in unipolar depression the strategy is triiodothyronine augmentation. Thyroid hormone has been added to antidepressants since the 1960s and, like lithium augmentation, has faded in popularity as newer options arrived. Trials comparing thyroid with lithium augmentation directly have generally suggested thyroid is at least as effective, and the few head-to-head trials have tended to favour it. One caveat is often dropped: most of the evidence base was generated with tricyclics rather than SSRIs, though a number of trials support the strategy with SSRIs. Indian consultation-liaison teaching corroborates the indication, describing T3 supplementation as an established strategy for augmenting antidepressants where response is inadequate, without attaching a dose.

The agent is **liothyronine**. Case reports and small studies support 25 to 50 mcg of liothyronine added to various SSRIs as a way of potentiating their antidepressant effect, and Kaplan and Sadock's Comprehensive Textbook of Psychiatry gives the same range for mood-disorder augmentation: **25 to 50 mcg as a single morning dose**, timed to avoid insomnia. T3's short half-life argues for divided dosing, but single daily dosing protects adherence; the

recommendation is written for healthy adults and needs modifying in older patients and in significant medical illness.

That range is not a flat band. For augmentation in refractory depression, 25 microgram per day sits below the replacement dose for the hormone, making thyroid toxicity extremely rare, while 50 microgram per day approaches the daily physiological production range, where symptoms of thyroid excess can appear. Continuous clinical monitoring and TSH assessment are recommended while T3 is being administered, at every dose in the range and not only at the top of it. Separately, and because there are no well-demonstrated dose-response studies for T3, doses in excess of 25 microgram per day should be used with caution. The two ends differ in safety, not merely in strength, but the monitoring floor does not move with the dose.

Among the largest and most systematic trials of thyroid hormone augmentation of an SSRI to date was the **STAR*D trial**, in which patients who had failed citalopram and then bupropion or buspirone augmentation received either triiodothyronine or lithium. About 25% of those given T3 augmentation of citalopram reached a remission-level response, against about 15% of the lithium-augmented patients. Both are approximations, and the trial was open-label with patients able to decline randomisation, which makes the comparison suggestive rather than decisive.

6.9 Bipolar disorder, the dose envelope and the safety limits

Thyroid abnormalities have long been recognised as destabilising in bipolar disorder, associated with rapid cycling, mixed states, depression and refractory mania, and supplementation has been used principally in two states: rapid cycling and bipolar depression. Indian consultation-liaison teaching independently links rapid cycling and lithium refractoriness with clinical and subclinical hypothyroidism. Thyroid hormone augmentation here runs at doses of a different order from the unipolar ones.

INDICATION	AGENT AND DOSE	EVIDENCE BASE
Unipolar refractory depression, added to an antidepressant	Liothyronine 25 to 50 mcg as a single morning dose.	Case reports, small studies, one large open-label augmentation trial.
Bipolar depression, added to an existing regimen	T3 to an average dose of 90.4 mcg.	Retrospective series of 159 patients averaging 14 previous failed trials; Eighty-four percent improved on a Clinical Global Impression scale, 33% in remission.
Rapid-cycling bipolar disorder, supraphysiological T4	Levothyroxine 100 to 300 mcg per day.	Small studies from the 1990s, mostly open-label or small case series.
Bipolar disorder, T4 as adjunctive mood stabiliser	T4 in doses ranging from 150 to 500 microgram per day.	Five case studies or series totalling 30 patients, of whom 27 responded.
Added to lithium, high-dose T4 or T3	Dosed to suppress TSH below 0.1, a figure the source reports without a unit.	A 2018 randomised controlled trial in which T4, but not T3 or placebo, produced less time depressed or mixed and more time euthymic.

Two features of that table are examinable. First, the same textbook gives two ranges for **supraphysiologic doses of levothyroxine** in rapid cycling, in chapters describing overlapping but non-identical evidence sets. They must not be merged: the merged range is one no source states, and it misrepresents the top of the envelope widely. Second, the randomised evidence in bipolar disorder favours T4 over T3, the reverse of the unipolar picture.

PITFALL

Carrying the bipolar T3 average into unipolar augmentation, or a bipolar T4 dose into unipolar refractory depression. That average, roughly double the top of the unipolar range, comes from an uncontrolled retrospective series in an extraordinarily treatment-resistant population: a description of what was done, never a recommendation. The distinct T4 dose for unipolar augmentation is not established here, so the strategy is named and the dose withheld.

The apparent superiority of T3 over T4 in unipolar depression should be held loosely. The literature has not settled it: most studies used T3 and the only head-to-head comparison favoured T3, but it ran for 2 weeks, too short against T4's long half-life to establish superiority, and positive T4 studies exist. On who benefits, responders tend to be female with a history of thyroid abnormality, and one report picked out T3 responders by lower T3 levels and by carriage of a particular allele at a single nucleotide polymorphism for the **deiodinase** converting enzyme, a finding awaiting replication.

Tolerability of thyroid hormone augmentation sorts into three scopes and they must not be merged. Thyroid supplementation has generally been well tolerated in most of the studies to date,

and a transient headache, usually subsiding after one or two days, is the most commonly reported adverse effect on T3. Bound to dose: the potential side effects of high-dose thyroid supplements include osteoporosis, tachycardia, palpitations and tremor. Bound to no dose at all: T3 should be used with great caution in older adults and in patients with various medical disorders, including endocrine and cardiovascular disease, and should be avoided in pregnancy. Bound to duration: long-term thyroid hormone treatment may be associated with bone demineralisation, resulting in osteoporosis in women. That last hazard explains the duration limit: prolonged administration to a euthyroid person is not advisable, and in a depressed patient who has responded, treatment should be **tapered and stopped by 12 weeks**. Two boundaries close the topic. No data support the efficacy of thyroid hormone for depression in children. And nothing in the hypothalamic-pituitary-thyroid axis carries regulatory approval anywhere for treating depression, although thyroid hormones, chiefly T3, do appear in clinical practice guidelines for major depressive disorder: T3 as an augmenting agent in refractory depression and a possible accelerator of antidepressant response, T4 as an unsettled option in refractory depression better placed as an adjunct to mood-stabiliser treatment, particularly in rapid-cycling patients.

> Hypothyroidism on lithium is supplemented, never a reason to stop the drug: TSH and calcium every 6 months, L-thyroxine started on the TSH. In the other direction, T3 is the unipolar augmenting agent and T4 the bipolar and rapid-cycling one, and every thyroid dose you quote must carry its indication with it.

7 · Subclinical thyroid disease, autoimmunity and Hashimoto encephalopathy

This is where a thyroid report stops being reassuring. Overt hypothyroidism and overt thyrotoxicosis announce themselves, and where this chapter deals with hypothyroidism and hyperthyroidism it sets out how the function tests are read. The harder half is the patient whose free hormones are normal, whose report therefore reads as unremarkable, and in whom the thyroid is nevertheless part of the psychiatric problem. Two constructs sit in that gap. The first is **subclinical hypothyroidism**, the psychiatrically important form of subclinical thyroid disease and a family of abnormalities occurring without overt functional hypothyroidism, repeatedly implicated in depression that will not shift on adequate treatment. The second is **Hashimoto encephalopathy**, an uncommon autoimmune encephalopathy that can present to a psychiatrist as psychosis, agitation or a depressive illness, and is treatable when recognised.

AS HIGH AS 10%	9.9 mU/L	>95%	>1,000 IU/l
POPULATION BASE RATE, ANTITHYROID ANTIBODIES	UPPER BOUND, GRADE 1 SUBCLINICAL BAND	SEIZURES IN HASHIMOTO ENCEPHALOPATHY	ANTI-TPO TITRE RAISING ITS LIKELIHOOD

7.1 What "subclinical" actually names

What the word strictly means is biochemical, and Kaplan and Sadock's Comprehensive Textbook of Psychiatry subdivides subclinical thyroid disease into three grades, each with a different investigative anchor. **Grade II hypothyroidism** is an elevated thyroid stimulating hormone without any change in thyroid hormones. **Grade III** is an abnormal thyroid stimulating hormone

response to stimulation with thyrotropin releasing hormone, so it is invisible on a basal panel. **Grade IV** is the presence of antithyroid antibodies with no abnormality of the thyroid hormone system at all.

That sequence is also the order in which the grades become clinically ambiguous: by the fourth you are reading an immunological marker in a person whose thyroid is working.

The word is a poor one: it promises the absence of symptoms, does not deliver it, and is taken sometimes as a reason not to treat and sometimes as a reason not to look further. Yet middle-aged patients carrying subclinical hypothyroidism may have measurable cognitive dysfunction and nonspecific symptoms of the kind that fill psychiatric clinics, fatigue and altered mood in particular. The term describes the laboratory, not the person.

7.2 Two grading schemes, overlapping numerals

This is the most avoidable error in the topic, and purely a matter of vocabulary. The grades above are one scheme. A second labels bands of thyroid stimulating hormone concentration and also begins its numbering at a low integer. **Grade 1 subclinical hypothyroidism**, in the sense used by The Lithium Handbook, is a concentration band: thyroid stimulating hormone lying between the upper limit of the reference range, typically quoted as either 4.5 or 5.0 mU/L, and 9.9 mU/L. The source hedges that lower bound between two values rather than fixing one, which tells you how much weight a single decimal deserves.

LABEL	SCHEME	WHAT DEFINES IT	HOW IT IS FOUND
Grade II hypothyroidism	Kaplan and Sadock	Elevated thyroid stimulating hormone, thyroid hormones unchanged	Basal thyroid function panel
Grade III	Kaplan and Sadock	Abnormal thyroid stimulating hormone response to thyrotropin releasing hormone	Dynamic stimulation test only
Grade IV	Kaplan and Sadock	Antithyroid antibodies present, thyroid hormone system normal	Serology only
Grade 1 subclinical hypothyroidism	The Lithium Handbook	Thyroid stimulating hormone from the upper limit of the reference range to 9.9 mU/L	Basal thyroid stimulating hormone value

TRAP **Answering "grade two" or "grade one" without saying whose grading you are using.** The two schemes are not versions of one another and are not numbered on the same principle: one grades the depth of investigation required, the other a concentration band. A candidate who names neither produces an unmarkable answer, and one who knows only one scheme may map a numeral onto the wrong definition. Whenever you use a grade, name the scheme in the same breath.

7.3 Subclinical hypothyroidism and the depression that will not move

Grade II hypothyroidism has been associated with depressive disorders, and the association runs both ways: patients with major depressive disorder show an increased incidence of it, and some studies find these patients respond poorly to conventional treatment. The stronger formulation the standard reference offers is that Grade II hypothyroidism may itself be a risk factor for major depressive disorder rather than merely a correlate.

The phenomenology is not confined to mood. Cognitive disturbance, memory in particular, and psychotic symptoms have both been reported in Grade II hypothyroidism. The presentations attributed to it include the two symptom domains a psychiatrist is least willing to lay at an endocrine door.

The same association reappears in the antidepressant literature from the other end. There is growing evidence that patients with **mild thyroid abnormalities**, meaning a slightly elevated thyroid stimulating hormone with normal triiodothyronine and thyroxine, are less likely to respond to antidepressants given alone, but may respond to the addition of a thyroid supplement. One demographic signal travels with this: women over the age of 50 appear to show higher rates of response to thyroid augmentation, perhaps because they are the group most susceptible to hypothyroidism. The doses and the choice of agent for augmentation belong where this chapter deals with lithium, thyroid dysfunction and thyroid hormone augmentation.

> **GOOD TO REMEMBER**
>
> The practical consequence is a habit, not a drug. In any depressive episode that has failed an adequate trial of an adequately dosed antidepressant, look at the thyroid stimulating hormone value again rather than at the free hormones. A mildly raised value with normal hormones is precisely the report that gets filed as normal, and precisely the one that predicts the non-response you are trying to explain.

7.4 The same number means different things in different patients

Here the topic stops being a matter of cut-offs and becomes a matter of populations. The Lithium Handbook makes the most examinable argument in the subclinical half of this material. Its Grade 1 band, in the general population, is rarely associated with somatic, cognitive or mood effects. Read alone, that argues for leaving these patients alone. But the same passage immediately qualifies it for one group: the threshold for thyroid supplementation may be different in patients with bipolar disorder, because thyroid stimulating hormone values sitting at the upper limit of the normal range have been associated with more depressive relapse in that population. The same source states the general position elsewhere: the association between hypothyroidism and depression is not robust in the general population, but patients with bipolar disorder are unique in this regard.

Notice what that does to a reference range. The assay is not wrong: a population-derived reference interval was never designed to answer a question about relapse in a mood disorder, and using it as though it were is a category error. Lithium as a drug, its therapeutic range and its non-thyroid organ effects belong to the Mood disorders: pharmacotherapy notes.

RULE **A thyroid number is only interpretable against the population it was measured in.** The subclinical band that is clinically inert in a general medical population is not demonstrably inert in bipolar disorder, and no single threshold can be quoted as universal. Asked for a cut-off, give the band and then the population qualifier; a bare number is a wrong answer wearing a decimal point.

7.5 Should it be treated? The sources do not agree

Whether subclinical thyroid disease should be treated is a live disagreement inside the standard references and must be presented as one. Three positions are on the table.

- The endocrine account in Kaplan and Sadock's Comprehensive Textbook of Psychiatry is cautious. It concedes that there is some evidence of improvement in cognition, mood and psychosis, and then states that treatment of subclinical hypothyroidism remains controversial.
- The therapeutic-indications account in the same textbook is materially more permissive: the presence of depressive symptoms in a patient with subclinical hypothyroidism could itself warrant starting thyroxine. Same book, different chapter, different threshold for acting.
- The Lithium Handbook does not adjudicate between them but reframes the question, arguing that the threshold is population-dependent and that the unsettled debate about normal ranges is itself an argument for a flexible treatment approach rather than a fixed rule.

The third position can be read as a resolution of the first two, and the reading is productive: if the answer depends on whether the patient has bipolar disorder, a cautious general stance and a permissive stance in symptomatic patients are not contradictory. Offer that as a synthesis, not as though a single source said it, because none did.

TRAP **Answering "yes, treat" or "no, do not treat" as though the question were settled.** Candidates reproduce whichever position they read and are marked against the other, because both sit in the same standard reference and neither can be dismissed. The mark is in naming the disagreement, stating that benefit in cognition, mood and psychosis is acknowledged while the treatment question is left explicitly controversial, and then offering the population-dependent reading as a synthesis rather than a citation.

7.6 Antithyroid antibodies: what a positive result is worth

The Grade IV category is where psychiatric reasoning most often goes wrong, and the reason is a base rate. Elevations of **antithyroid autoantibodies** occur in the general population at a rate **as high as 10%**. Against that background a positive antibody in a psychiatric patient tells you very little alone.

The associations define the company this finding keeps. Elevated serum antithyroid antibodies are associated with other thyroid disorders, including Grave disease, de Quervain thyroiditis, primary hypothyroidism and colloidal goitre, and with other autoimmune disorders including diabetes mellitus, Addison disease and pernicious anaemia. A positive result is therefore a prompt to ask what else is autoimmune in this patient and this family.

The second reason for restraint is mechanistic, and applies with most force to the encephalopathy below. The role of antithyroid antibodies is itself controversial: there is no direct evidence that these autoantibodies exert direct effects on central nervous system tissue, and they may be epiphenomena of some other autoimmune process. The antibody is associated with the syndrome and used to identify it, and may have nothing to do with causing it. The third reason is evidential: these sources carry no figure connecting thyroid antibodies and treatment-resistant depression, so a positive serology has no quantified predictive value for antidepressant non-response, and the link you can defend in an examination is the one that runs through subclinical hypothyroidism above.

RULE **An antithyroid antibody is a marker, not a mechanism and not a diagnosis.** Its base rate in ordinary people is high enough that a bare positive explains nothing, and no direct action on central nervous system tissue has been demonstrated. What converts it into information is context: the titre, the thyroid hormone status, the presence of an encephalopathic syndrome, and the company of other autoimmune disease.

7.7 Hashimoto encephalopathy: the syndrome and its striking frequencies

Hashimoto encephalopathy, also described as **steroid-responsive encephalopathy associated with autoimmune thyroiditis**, is best defined as an uncommon autoimmune encephalopathy of unknown aetiology associated with high titres of serum antithyroid antibodies, usually antithyroid peroxidase with or without anti-thyroglobulin. Note that it is defined by antibody titre rather than by thyroid function. The second name is the clinically useful one, because it puts the treatment response into the label.

The syndrome is commoner in women, with a mean age of onset between **45 and 50 years**, and there may be a history of other autoimmune disease. That is the age band where a psychiatrist is otherwise thinking about perimenopausal mood change, an early neurodegenerative process, or late-onset psychosis.

The core picture is an encephalopathy with progressive cognitive decline, although the course may equally be relapsing and remitting, itself a useful discriminator against a steadily progressive degenerative illness.

- Seizures, in more than 95% of cases.
- Stroke-like episodes, in more than 65% of cases, alongside memory dysfunction.
- Visual hallucinations, frequently reported at more than **90%**, with other disorders of perception and delusions also described; agitation and restlessness, apathy and social isolation are the accompanying neuropsychiatric features, and the syndrome may present as a depressive illness.

MNEMONIC

Seizures, Strokes, Slowing, Steroid-responsive

The four features no rival explanation ties together: **seizures** in almost every reported case, **stroke**-like episodes in the majority, electroencephalographic **slowing** tracking severity, and a **steroid**-responsive course. A psychiatric presentation carrying any two deserves the antibody.

The stroke-like episodes are a feature of this disease, not a separate cerebrovascular event to be worked up as one; cerebrovascular syndromes belong to the Stroke, TBI, delirium and focal brain syndromes notes, as does the delirium workup a fluctuating encephalopathy will otherwise trigger. Where the presentation is progressive cognitive decline, the dementia syndrome and its investigation belong to the Dementias and neurocognitive disorders notes. What belongs here is that this cause is treatable.

7.8 Titre, electroencephalogram and the evidence of reversibility

Two investigations carry this diagnosis. The first is the antibody titre, where the base rate does its work. A typical psychiatric presentation such as depression, in a patient with mildly elevated antithyroid peroxidase antibodies, is unlikely to be due to Hashimoto encephalopathy. When those levels are very high, meaning **greater than 1,000 IU/l**, the likelihood of association with a neuropsychiatric Hashimoto encephalopathy is much greater. Read that as a likelihood modifier, which is what the source says, and not as a diagnostic criterion, which it does not.

The second is the electroencephalogram. Routine investigations are often normal, but patients will often show slowing on the electroencephalogram, with the degree of slowing proportional to the clinical severity of the syndrome, and some will show triphasic waves. The proportionality makes the electroencephalogram a severity measure rather than a binary test, and a way of following a treated patient when the mental state is hard to score.

QUESTION	ANTIBODIES WITH NORMAL THYROID HORMONES	HASHIMOTO ENCEPHALOPATHY
Prior probability	Common: base rate as high as 10% in the population	Uncommon
Antibody titre	Not specified by the source for this category	Mild elevation argues against it; greater than 1,000 IU/l makes it much more likely
Thyroid hormones	Normal by definition	Not stated in the source
Clinical picture	Mood, memory and occasionally psychotic symptoms	Encephalopathy with seizures, stroke-like episodes and visual hallucinations
Electroencephalogram	No signature described by the source	Slowing proportional to severity, sometimes triphasic waves
Treatment implication	Contested	Majority respond to corticos-teroid treatment

What makes the syndrome worth chasing is documented reversibility, illustrated in the standard reference by two individual cases rather than a series. In a woman of 38 with psychosis and an antithyroid peroxidase titre of 779, the pretreatment recording showed general slowing with high-voltage delta biphasic and triphasic waves at 2 to 3 Hz; after corticosteroid treatment it returned to alpha frequency with occasional posterior theta waves at 5 to 6 Hz. In a woman of 59 with rapidly progressive cognitive impairment and myoclonus, single-photon emission computed tomography showed gross global hypoperfusion in all nonoccipital regions, and her Mini-Mental State Examination score rose from 20 to 27 over the 6 weeks as she improved significantly. The instruments and their scoring belong to the Psychotherapies, clinical assessment, MSE and nosology notes; the direction and timescale belong here.

PITFALL

Treating the high-titre threshold as a rule-out. The illustrative case above carried a titre of 779, below the level at which the source says likelihood becomes much greater, and she nonetheless had a steroid-responsive encephalopathy with electroencephalographic reversal. The threshold raises probability; it does not close the door. The clinical syndrome, not the titre, puts this diagnosis on the list.

7.9 Management, and the honest limits of what the sources supply

LOCUS. The two halves are managed in different places. Subclinical thyroid disease in a mood-disorder patient is an outpatient problem, worked through over successive visits with repeat biochemistry and, where treatment starts, joint endocrine input. Suspected Hashimoto encephalopathy is not: an encephalopathic patient with seizures and stroke-like episodes needs inpatient assessment with neurology, and where consciousness or seizure control is compromised the locus is acute medical care. The governing authorities are Kaplan and Sadock's Comprehensive Textbook of Psychiatry and The Lithium Handbook, which do not agree on the first question.

FOCUS. In subclinical disease there is no acute target. The short-term target is the correct attribution of fatigue, low mood and cognitive complaint, and confirmation that the biochemical picture is persistent rather than a stray value. In the medium term it is treatment resistance itself; in the long term relapse, which is where the bipolar qualifier bites. In Hashimoto encephalopathy the acute targets are seizure control and the encephalopathy, the short-term target is response to immunosuppression, and the longer-term target is the relapsing and remitting course.

MODUS. For subclinical hypothyroidism the pharmacological mode is thyroxine, on the indication the more permissive textbook position accepts. Where a mild thyroid abnormality coexists with antidepressant non-response, the described mode is adding a thyroid supplement rather than switching; the agents and doses belong where this chapter deals with lithium, thyroid dysfunction and thyroid hormone augmentation. Psychological and social modes are unchanged by the endocrine finding and should not be paused while it is investigated. For Hashimoto encephalopathy the pharmacological mode is corticosteroid treatment: the majority of patients respond to corticosteroid treatment with complete resolution of the neuropsychiatric symptoms.

That sentence is the entirety of what these sources say about treating it. They name no agent, no dose, no route, no duration and no second-line immunotherapy. Neither should you: state the steroid responsiveness and that the regimen is set with neurology, and do not invent a milligram figure for a condition defined by its steroid responsiveness.

IN INDIA

Three practical divergences shape this topic here. First, the antithyroid peroxidase assay is widely available in private laboratories but is often reported qualitatively as positive or negative, and the high-titre threshold depends entirely on a quantitative value in stated units, so the request must specify one. Second, in a self-paying patient the serology and the neuroimaging together cost more than the consultation that generated them, so sequencing matters: in an encephalopathic patient the electroencephalogram is cheaper, more widely available, and the investigation the standard reference actually anchors. Third, iodine status and thyroid autoimmunity vary across regions, so a local reference interval is not interchangeable with a Western textbook one; where a decision hangs on a marginal thyroid stimulating hormone value, use the reporting laboratory's interval and repeat the sample before acting.

Subclinical means the hormones are normal and something else is not; a mildly raised thyroid stimulating hormone predicts antidepressant non-response, an antibody at a population base rate as high as 10% means little on its own, and a very high antithyroid peroxidase titre in an encephalopathic patient means Hashimoto encephalopathy until steroids prove otherwise.

8 · Hyperparathyroidism, hypoparathyroidism and calcium-related psychiatric symptoms

Calcium is the electrolyte psychiatry forgets to measure. The **parathyroid glands** are small accessory glands, anatomically bound to the thyroid but functionally separate from it, and they have one job: to hold serum calcium inside a narrow range so that nerve and muscle work properly. They do it by releasing **parathyroid hormone**, which raises serum calcium by stimulating osteoclasts to liberate it from bone and by increasing its absorption in the gut and the kidney. A control system whose declared purpose is to protect the excitability of the nervous system will, when it fails, fail there first. Too much calcium damps excitability towards apathy, slowed cognition and eventually obtundation; too little releases it towards spasm, seizure and confusion.

The marks sit in four places. The two directions of derangement have different signatures, one indolent and easily missed, the other neuromuscular and dramatic. Both are broadly reversible, which is what makes them worth finding. The link between biochemistry and psychiatric picture is a gradient, not a switch. And lithium sits across the whole topic, with a literature that does not agree with itself.

50%	UNDER 10%	39%	ABOUT 4%
HYPERPARATHYROIDISM, ASYMPTOMATIC	PSYCHIATRIC SYMPTOMS, HYPERPARATHYROIDISM	COGNITIVE IMPAIRMENT, HYPOPARATHYROIDISM	HYPERCALCAEMIA ON LONG-TERM LITHIUM

8.1 The set point, and why a psychiatrist should care

Most endocrine axes interest psychiatry because a hormone acts on the brain. This one is different: the hormone acts on an ion, and the ion determines how readily neurones and muscle fibres fire at all. Two consequences follow. The psychiatric picture is non-specific and syndromally promiscuous, because a drifting calcium produces whichever syndrome that brain is disposed to produce rather than a signature delusion, so the differential is wide and the diagnosis is usually made by the laboratory, not the interview. And the disturbance should track the biochemistry in time, worsening as the calcium drifts and settling as it is corrected. That temporal coupling separates a metabolic presentation from a primary illness running in parallel with an incidental abnormal result.

8.2 Hyperparathyroidism: how it is actually found

The teaching picture is florid. The reality is that hyperparathyroidism is usually diagnosed after an incidental finding of hypercalcaemia on routine blood tests, with half of all patients asymptomatic: a biochemical diagnosis handed to a clinician who was not looking for it. The commonest mechanism is increased parathyroid hormone release from a single functioning adenoma, though multiple adenomas occur as part of **Multiple Endocrine Neoplasia Syndrome**, which is why a young patient with hypercalcaemia earns wider endocrine and family enquiry than an older one.

The somatic symptoms, when they appear, are secondary to the hypercalcaemia rather than the hormone: fatigue, general malaise, proximal muscle weakness, renal colic, abdominal pain and cognitive decline. That list repays memorising precisely because it reads so easily as depression with somatic preoccupation in a tired middle-aged patient.

Background rates set how seriously to entertain it. Hypercalcaemia in the general population runs at approximately 1% to 2%, with 90% of those cases accounted for by primary hyperparathyroidism and malignancy-associated hypercalcaemia together. **Primary hyperparathyroidism** itself ranges from **0.2% to 0.8%** of the general population. Both are **2.5-fold** commoner among women and age dependent, with a 3-fold higher prevalence in patients over 80 years of age than in those aged 20 to 29. These describe the general population, not lithium-treated patients, and that distinction matters later.

8.3 The psychiatric syndrome of hypercalcaemia

The mnemonic is famous and the prevalence behind it is not what it implies. Although a range of psychiatric symptoms have been described in hyperparathyroidism, the overall prevalence is likely to be less than 10%. Hold that against the memorability of the tetrad and you have the shape of the question: the psychiatric limb is the best-known part of a syndrome in which it is the least common.

MNEMONIC

Bones, stones, moans and psychic groans

The symptomatic tetrad of hyperparathyroidism, pointing at the skeleton, the renal tract, the abdomen and the mind. Use it as a recall aid for where to look, never as a statement of frequency: the reference that prints this mnemonic is the same one that deflates the psychiatric prevalence to under a tenth of patients.

Within that minority the pattern is orderly. Affective disorders, predominantly depressive, are the most frequently recorded, with anxiety often comorbid; psychotic disorders are reported but infrequent, with persecutory and paranoid delusions predominating; cognitive changes are common, usually short-term memory loss, disorders of attention and acute confusional states. At the severe end, severe derangement of calcium metabolism may present with somnolence and coma. Symptoms correlate with both the duration and the severity of the hypercalcaemia, so a modest elevation of long standing and a sharp recent rise are different clinical problems.

PITFALL

Neuropsychiatric symptoms are often the initial presentation in older adults or those with limited cognitive reserve, which makes the commonest real-world error here not a wrong answer but an absent test. An older adult with months of low mood, apathy, poor attention and short-term memory loss is an ordinary referral, and the formulation writes itself as a depressive episode with cognitive impairment or an early neurodegenerative process. Both are likelier; only one of the three is fully reversible. The syndromal workup of dementia belongs to the Dementias and neurocognitive disorders notes and the cognitive examination to the Psychotherapies, clinical assessment, MSE and nosology notes, but the calcium is a decision you make.

8.4 Hypoparathyroidism and the neuromuscular signature

Where hyperparathyroidism is usually found by accident, hypoparathyroidism is usually made by a surgeon. The most common cause of impaired parathyroid hormone production in adults is inadvertent surgical removal during thyroid surgery, or excessive removal in the operative treatment of hyperparathyroidism itself. That single fact tells you whom to suspect and gives the history its natural question.

The clinical features follow the hypocalcaemia and are dominated by **neuromuscular excitability**: paraesthesias, muscle cramps, carpopedal spasm and facial grimacing, progressing to laryngeal spasm and convulsions. Examination may reveal **tetany**, reduced or absent deep tendon reflexes, papilloedema and prolongation of the QT interval on the electrocardiogram. Two of those are easy to lose. Papilloedema means fundoscopy, skipped far more often in a psychiatric assessment than performed. The QT prolongation matters twice over here, since it sits in the same column as the drugs a psychiatrist might reach for in a patient presenting with spasm, anxiety and paraesthesias who looks, at first pass, like panic disorder.

Note what the reference does not say. It gives this examination list without naming any eponymous elicited sign, so the two signs every candidate reaches for are not asserted here. Know

the phenomenon, latent neuromuscular irritability made manifest, rather than a name the source does not carry.

8.5 The neuropsychiatric syndrome of hypocalcaemia

The psychiatric yield here is substantially higher than on the hypercalcaemic side, which is the reverse of what most candidates expect. Delirium is now understood to be the most common neuropsychiatric manifestation. Delirium as a syndrome, its criteria, bedside detection and workup belong to the Stroke, TBI, delirium and focal brain syndromes notes; what this chapter owns is that a metabolic cause of it sits in the parathyroid axis and answers to correction of the calcium.

Beyond delirium, one large study demonstrated cognitive impairment in 39% of patients, affective or neurotic symptoms in 12%, psychotic symptoms in 11% and nonspecific affective disturbance in 21%. Those are not small numbers for an endocrine disease, and the overall yield plainly exceeds the under-a-tenth quoted on the hypercalcaemic side. The rank order differs as well: there affective disorders are the most frequently recorded, whereas in this study cognitive impairment is the largest single group. No per-symptom breakdown is published for the hypercalcaemic side, so the two cannot be compared any more finely than that. As on the other side, severity relates directly to the degree of hypocalcaemia and appropriate normalisation resolves the symptoms.

GOOD TO REMEMBER

Persistent psychosis has been noted in hypoparathyroidism where associated **hypomagnesaemia** was not addressed. If you have normalised the calcium and the psychosis has not moved, check the magnesium before you raise the antipsychotic. A failure to respond is information about what has been left uncorrected before it is information about treatment resistance.

8.6 A gradient, not a threshold

This is where the chapter deliberately stops short. Both directions carry an explicit severity statement in the standard reference: the more severe the hypercalcaemia, the more severe the psychiatric disturbance, and on the other side symptom severity relates directly to the degree of hypocalcaemia. Both are made without a single calcium figure attached. There is no value in these sources at which psychiatric symptoms are said to emerge, none at which they worsen, and none at which somnolence and coma supervene.

RULE **Psychiatric severity tracks the calcium, and the calcium is what reverses it, in both directions.** This one principle does the work of a dozen memorised facts: it tells you what to measure, it warns you that a mild derangement with a florid psychiatric picture needs a second explanation, and it predicts that correction is the treatment. What it does not do is give you a number, so teach the gradient qualitatively. A remembered threshold, printed with a citation borrowed from the sentence next door, is how a false figure enters a textbook and survives in it.

Two related absences are worth naming, because both are slots where a plausible number would sit unchallenged. No reference range for total or ionised calcium is stated in these sources, and

neither is the albumin-correction formula, notwithstanding that **albumin-adjusted calcium** is an outcome measure in the lithium literature below.

One further discrimination protects against a real error of attribution. It is the calcium that drives the psychiatric picture, not the parathyroid hormone. When hormone levels are mildly raised in the setting of normocalcaemia, most commonly on the basis of **vitamin D insufficiency**, psychiatric disturbance is uncommon.

TRAP **Treating a raised parathyroid hormone as the psychiatric abnormality.** Candidates make this error because the disease is named after the gland and the hormone is what was measured, so it feels like the causal variable. It is not the one the neuropsychiatric syndrome tracks. The source describes mildly raised hormone with normal calcium, the picture produced by vitamin D insufficiency, as increasingly prevalent in developed countries, and psychiatric disturbance as uncommon there. A stem offering a raised hormone, a normal calcium and a psychiatric syndrome is usually offering a syndrome that belongs to something else.

8.7 Lithium and calcium: a literature that disagrees with itself

Lithium is why this topic appears in a psychiatry paper at all, and the mechanism is better established than the magnitude. Sufficient human and animal data indicate that lithium exposure can induce hypercalcaemia through increased gastrointestinal and renal calcium reabsorption, a direct impact on **calcium sensing**, and secondary or independent effects on parathyroid gland function. Altering the calcium-sensing mechanism can itself produce hyperparathyroidism, so the drug reproduces the endocrine disease rather than merely nudging the ion. Lithium as a drug, its pharmacokinetics, therapeutic range and non-thyroid organ-system adverse effects belong to the Mood disorders: pharmacotherapy notes; taught here is the calcium lens only.

The size of the effect is another matter. Four standard sources address it and they do not line up.

SOURCE	QUANTITY MEASURED	FINDING
2012 systematic review and meta-analysis, n = 699 across 4 cohort, 14 case-control, 36 case-report and 6 cross-sectional studies	Mean change in total calcium and in parathyroid hormone	Total calcium raised by **0.09 mmol/l** (95% CI 0.02 to 0.17, p = 0.009); parathyroid hormone raised by 7.32 pg/ml (95% CI 3.42 to 11.23, p < 0.0001)
Oxford University Hospitals NHS Trust laboratory database, n = 1916	Risk of raised albumin-adjusted calcium	No increased lithium-related risk, OR 1.08, 95% CI 0.88 to 1.34, p = 0.46
Maudsley prescribing guidance	Proportion of lithium-treated patients affected	Hyperparathyroidism causes hypercalcaemia in about 4% of patients
Geriatric psychiatry guidance, meta-analysis of 385 studies	Magnitude of the rise in blood calcium	Blood calcium increased by **10%**

The honest reading is that the direction of effect is agreed and almost nothing else is. Two of these are effect sizes, one an incidence and one a proportional rise; the largest single dataset finds no signal; the two study counts cannot be reconciled from what is printed. The handbook itself

names the discrepancy between the meta-analysis and the larger database study and leaves it open, and a revision chapter that closes it by choosing a favourite is doing what the primary literature declined to do.

TRAP **Reading a proportion of patients and a proportional rise as the same quantity because both wear a percent sign.** About 4% of lithium-treated patients developing hypercalcaemia and a 10% increase in blood calcium answer entirely different questions, and side by side in a revision note they read either as a contradiction needing resolution or, worse, as corroboration. They are neither. Any stem offering a single percentage for lithium and calcium is under-specified until you know whether it counts patients or measures calcium. The same discipline applies to the general-population rates given earlier: those describe everybody, not lithium-treated patients, and the source is explicit that they must not be attached to a lithium patient. No source here states which way that error would run, so do not reason from a direction; counsel a lithium patient from the lithium-treated figure.

One apparent contradiction resolves cleanly. The lithium handbook states plainly that lithium does not cause osteoporosis, while the prescribing guidance lists osteoporosis among the consequences of chronically raised serum calcium. These are compatible if the routes differ: what is denied is a direct skeletal action of the drug, what is asserted is a consequence of sustained hypercalcaemia however caused. State them together without that distinction and you have written a contradiction into your own notes.

8.8 Management: finding it, correcting it, monitoring for it

LOCUS. Almost all of this work is outpatient: incidental hypercalcaemia, surveillance on long-term lithium, and follow-up after thyroid surgery are clinic problems. Inpatient care is needed where the psychiatric syndrome itself is unsafe, meaning the confusional and somnolent presentations of severe hypercalcaemia and the delirious and psychotic presentations of hypocalcaemia, and the medical or endocrine ward is usually the right ward, because the treatment is correction of biochemistry. Emergency presentation belongs to the neuromuscular end of hypocalcaemia, where laryngeal spasm and convulsions are why this is not a problem to observe over a weekend.

FOCUS. Acutely the target is the calcium, not the symptom, and the severity relationship is the reason. In the short term it is the cause: the adenoma on the high side, replacement after surgical loss of the glands on the low side. In the medium term it is the resolution that should follow correction, whose failure to arrive is itself a finding, and where magnesium is checked. In the long term it is surveillance, because the consequences of sustained hypercalcaemia accumulate quietly.

- Renal stones
- Osteoporosis
- Dyspepsia
- Hypertension
- Renal impairment

MODUS. Definitive treatment on the hyperparathyroid side is surgical, and the reference is explicit that symptoms generally respond to appropriate treatment such as parathyroidectomy. Where surgery is not the route, **calcimimetic agents** offer a non-surgical option, which is the relevant sentence where lithium is the driver and an operation is a large ask. Psychiatric treatment is adjunctive and symptomatic, and its principle is restraint: a syndrome expected to resolve on correction of the calcium does not need a durable psychotropic regimen built around it. The psychological and social modes are largely explanatory, since a patient told that months of low mood and forgetfulness had a correctable cause needs that explained if the episode is not carried forward as a psychiatric history.

Monitoring is where the guidance is most usable and least unanimous. Both prescribing sources agree on the principle: routine serum calcium monitoring will identify the adverse effect, with **ionised calcium** and parathyroid hormone used for confirmation, and calcium monitored on long-term lithium. On timing they diverge. The geriatric guidance directs clinicians to measure serum calcium before lithium is initiated and annually thereafter, while the lithium handbook recommends a shorter interval this chapter does not print, not being among the values it can vouch for. Take the baseline, follow whichever interval your local protocol specifies, and treat a calcium before a first lithium prescription as non-negotiable, because without it a later raised value cannot be attributed to anything.

IN INDIA

The divergence here is test ordering rather than pharmacology. Lithium monitoring in most Indian settings reliably captures the lithium level, renal function and thyroid function, and calcium is the parameter most often dropped, partly because the psychiatric consequence is unfamiliar and partly because it is another line on a bill paid out of pocket. The consequence is specific: the incidental route by which hyperparathyroidism is usually diagnosed does not operate unless somebody ordered a calcium, so a patient whose only regular biochemistry is a lithium clinic panel has no incidental route at all. Total calcium with albumin is cheap and widely available; the confirmatory ionised calcium and parathyroid hormone assays sit in tertiary centres and larger private laboratories and often need a send-out, so plan that step when you order the screen. One caution: the source used here attaches the rising prevalence of vitamin D insufficiency to developed countries and offers no Indian figure, so none is manufactured.

Psychiatric severity tracks the serum calcium in both directions and reverses when it is corrected, so a calcium belongs in the workup of any unexplained affective, psychotic or cognitive presentation and in every lithium patient at baseline; no source here gives a threshold at which symptoms begin, and none should be invented.

Metabolic and nutritional disease

9 · Wilson's disease: copper metabolism, genetics and the neuropsychiatric presentation

This is the diagnosis that arrives in a psychiatric clinic wearing someone else's clothes. A young adult with irritability, emotional lability and a falling academic trajectory; or a first psychotic episode; or a tremor dramatic enough to be called functional. The referral is written for a mood disorder, the examination stops above the neck, and a treatable single-gene disorder of copper metabolism runs on unrecognised.

What follows is the neuropsychiatric presentation of Wilson's disease and the genetics behind it. Confirmatory biochemistry and the chelating drugs are treated where this chapter deals with the investigation and management of Wilson's disease.

9.1 What Wilson described, and what has been added since

The condition carries the name of Kinnear Wilson, who first recognised the syndrome in 1912 and included in that original description a high rate of psychiatric abnormality. Psychiatric involvement was in the founding account, alongside the movement disorder and the cirrhosis, not a later refinement.

Cummings identified the role of copper in pathogenesis in 1948. Schenberg and Gitlin described the deficiency of ceruloplasmin in 1952, establishing a test still in use. Bearn established the recessive nature of the disorder definitively in 1960. The molecular basis emerged with linkage to the esterase D locus on chromosome 13 in 1985, and then, in 1993, with discovery of the causative mutations in ATP7B. Note that order: ceruloplasmin deficiency was described four decades before the gene was found, which is why older texts treat it as the primary lesion.

9.2 The gene, the protein and the transport failure

Wilson's disease is an autosomal recessive disorder caused by mutations in a copper transporting ATPase encoded by the **ATP7B** gene on chromosome 13q14.3. Kaufman's Clinical Neurology for Psychiatrists localises the gene to chromosome 13, coding for a protein necessary for copper transport, without naming ATP7B; the sub-band locus comes from the more precise source.

The protein matters more than the locus, because copper metabolism fails at a single step. The **Wilson protein** is an ATPase involved in copper transport whose physiological job is to maintain copper homeostasis by facilitating excretion of copper from hepatocytes into bile. Biliary excretion is the only meaningful route for surplus copper, and that route fails, so that copper accumulates in liver, brain and other tissues, producing hepatic failure together with neurological and psychiatric signs and symptoms, with the basal ganglia appearing particularly affected within the brain.

The order is the whole of the mechanism question. The gene defect leads to accumulation of copper in the liver through impaired copper excretion and impaired binding of copper to ceruloplasmin. Catabolism of the resulting ceruloplasmin produces the low plasma ceruloplasmin

level, with a rise in free copper, and free copper then accumulates in the brain and generates the neurological and neuropsychiatric manifestations.

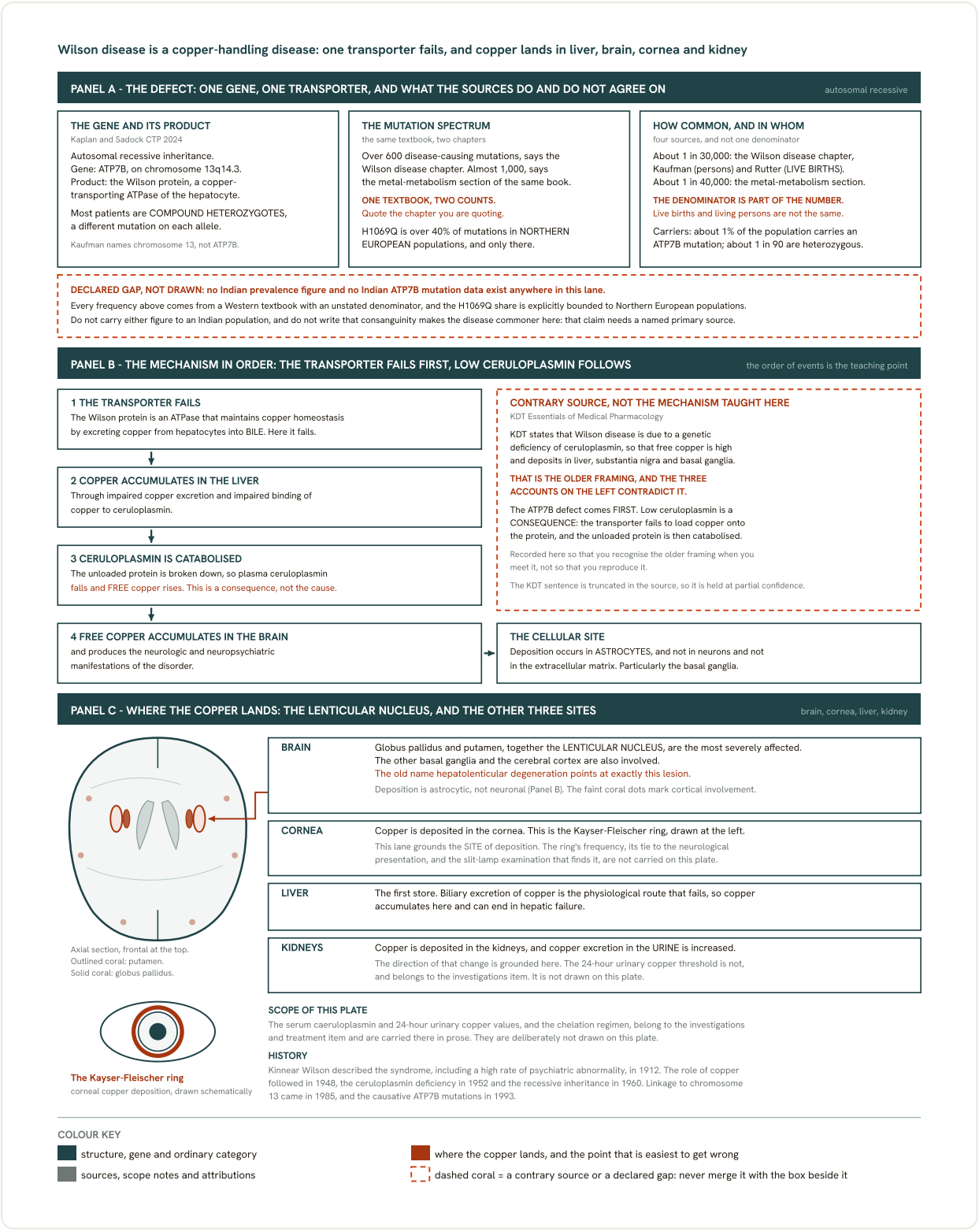

Fig 33.4 Wilson disease as a copper-handling disease: the ATP7B defect, where the copper lands, and the lenticular nucleus. The order of events is the teaching point: the transporter fails first, copper accumulates in the liver because biliary excretion and loading onto ceruloplasmin both fail, the unloaded protein is catabolised, and only then does plasma ceruloplasmin fall and free copper rise. Low ceruloplasmin is a consequence, not the primary lesion, and the older pharmacology framing that reverses this is drawn as a contrary source. Cerebral deposition is astrocytic and falls hardest on the globus pallidus and putamen, which is what the name hepatolenticular degeneration points at. The frequency figures disagree across sources and denominators and are shown unmerged; no Indian figure exists in this lane and none is drawn. (Kaplan and Sadock CTP 2024; Kaufman's Clinical Neurology for Psychiatrists; Companion to Psychiatric Studies; Rutter's Child and Adolescent Psychiatry 6e; KDT Essentials of Medical Pharmacology.)

RULE **Low ceruloplasmin is a consequence of the ATP7B gene defect, not its cause.** Everything downstream follows from surplus free copper, which is why the disease is treated by removing copper and not by replacing ceruloplasmin.

TRAP **Writing that Wilson's disease is due to a genetic deficiency of ceruloplasmin.** This inversion is not invented by candidates, it is printed. KDT's Essentials of Medical Pharmacology states that the disease is due to genetic deficiency of ceruloplasmin, the protein that normally binds and disposes of copper, in whose absence plasma free copper is high and is deposited in liver, substantia nigra and basal ganglia, causing local degeneration. Kaplan and Sadock, the Companion to Psychiatric Studies and Brazis all place the primary lesion in the copper-transporting ATPase, with the ceruloplasmin fall arising secondarily. Name the ATPase account as the current one and the ceruloplasmin-deficiency account as the older framing; drop neither.

9.3 Where the copper lands, and why the disease has two names

Deposition is neither diffuse nor random. The Companion to Psychiatric Studies states that mutation in the copper-transporting P-type ATPase coded on chromosome 13 results in excessive copper deposition in brain, cornea, liver and kidneys, with increased urinary copper excretion, and that the globus pallidus and putamen, together the **lenticular nucleus**, are most severely affected, though the other basal ganglia and the cerebral cortex are also involved. That licenses the older name hepatolenticular degeneration, explains why the syndrome is extrapyramidal rather than pyramidal, and accounts for the cognitive and behavioural layer over the movement disorder.

One cellular detail is a favourite discriminator: copper deposition occurs in **astrocytes**, not in neurons and not in the extracellular matrix, and is particularly evident in the basal ganglia. The figure sets the transport defect, the deposition sites and the ocular sign side by side.

9.4 Mutation spectrum, carrier burden and a frequency figure that will not settle

This is not a one-mutation disease. The dedicated chapter of Kaplan and Sadock records that over 600 disease-causing mutations have been identified in ATP7B; a few are common, with H1069Q accounting for more than 40% of mutations in Northern European populations, while most are rare, so that most individuals with the disease are **compound heterozygotes**, carrying a different mutation on each allele. A negative test for one common variant therefore excludes very little.

Carrier burden is high for a rare recessive disorder. One chapter puts carriage at about 1% of the population, the dedicated Wilson chapter at **approximately 1 in 90 individuals**: close, not identical, from different chapters of one book. The mutation count disagrees more sharply, the first chapter saying almost 1,000 mutations have been identified against the dedicated chapter's count of disease-causing mutations. Identified and pathogenic variants are different denominators, so the two may not be counting the same thing. Quote each in its own wording, and never present the larger number as a count of pathogenic variants.

Disease frequency is the conflict most likely to be asked, and the denominators differ as well as the numerators.

SOURCE	STATED FREQUENCY	DENOMINATOR, EXACTLY AS GIVEN
Kaplan and Sadock, disorders of metal metabolism section	About 1 in 40,000.	General population.
Kaplan and Sadock, dedicated Wilson disease chapter	About 1 in 30,000, with approximately 1 in 90 heterozygous carriers.	Worldwide.
Kaufman's Clinical Neurology for Psychiatrists	1 per 30,000 persons.	Persons.
Rutter's Child and Adolescent Psychiatry	About 1 in 30,000.	Live births.

Three readings give **about 1 in 30,000** and one the higher denominator, which sits in the same textbook as one of the lower ones. Print the commoner one, note the variant, and carry the denominator with the number: a rate per live birth and a rate per general population are not interchangeable in a disease with substantial childhood mortality. Kaufman gives the reason it is quoted at all: despite its infrequent occurrence neurologists routinely test for Wilson disease in adolescents and young adults who develop dysarthria, tremor, parkinsonism, dystonia, atypical psychosis, dementia or cirrhosis. The dementia syndrome and its workup belong to the Dementias and neurocognitive disorders notes; a rare disease is worth testing for when the test is cheap and the treatment works.

IN INDIA

Every frequency figure here comes from Western textbooks, and the only mutation-frequency figure is bounded explicitly to Northern European populations. No Indian prevalence estimate and no Indian ATP7B mutation spectrum can be quoted from these sources. Do not assert that Wilson's disease is commoner in India on account of consanguinity: plausible and widely repeated, it needs a named Indian series before it belongs in an answer. Nor carry the Northern European mutation figure into an Indian population. What travels is the method: in most Indian settings the diagnosis is secured on examination, the slit lamp and biochemistry rather than sequencing, and the highest-yield single step needs only an ophthalmology colleague.

9.5 When it presents, and through which door

The presenting-system split is the most quotable statistic in the topic. About 40% of patients first present with liver abnormalities, about 40% with neurological abnormalities, and up to 20% with primarily psychiatric abnormalities. One patient in five arrives first in a psychiatric clinic, at an age when psychiatric illness is expected and metabolic disease is not.

40%	40%	UP TO 20%	17 YEARS
LIVER FIRST	NEUROLOGICAL FIRST	PSYCHIATRIC FIRST	MEAN AGE OF ONSET

Onset is usually in the second or third decade with a mean age of onset at 17 years, atypical late-onset cases are reported in individuals over the age of 60, and without treatment death may occur

within 5 years, sooner where there is central nervous system disease. Age does not exclude the diagnosis.

Natural history by decade adds the clause that matters most. Hepatic disease is the commonest presentation and occurs anywhere between the first and fourth decades; about 50% of patients are symptomatic by the age of 15; and up to two-thirds present with neurological disease in the second or third decade without clinical evidence of liver disease. Normal liver function tests and an unremarkable abdomen do not exclude the diagnosis in a young patient with a movement disorder or behavioural change, and missed cases are missed on exactly that reasoning.

9.6 The neurological syndromes and the tremor that looks functional

The neurological picture is multifocal, following the deposition pattern. Neurological signs correlate strongly with brain and cerebrospinal fluid copper levels, reflect the multiple brain regions involved, and include dysdiadochokinesis, dysarthria, tremor, dystonia, rigidity, choreoathetosis, bradykinesia, masked facies and micrographia. Seizures occur in 6% of patients. Two phenotypes are conventionally separated, and the separation is prognostically load-bearing.

- The **dystonic form** is the commonest presenting neurological syndrome, with dysarthria, dysphagia, drooling and a rigid open mouth.
- The **pseudosclerotic form** presents with incoordination, clumsiness, unsteadiness of gait or dysarthria.
- As the illness progresses patients may show features of both, with rigidity, tremor and choreic, athetoid or dystonic movements.

The face is distinctive across a consulting room. Brazis records excessive grinning, a sustained open-mouth smile sometimes called the vacuous smile, and a fixed forced smile produced by sustained spasm of the risorius and zygomaticus, termed **risus sardonicus**, alongside slow saccadic eye movements and, rarely, ophthalmoplegia.

The most examined sign is the tremor. The tremor of Wilson's disease, the so-called **wing beating** tremor, may be interpreted as a functional movement disorder. It is characteristically absent at rest and develops after a short period of arm extension; the arms beat in a wide violent arc, and the tremor may be altered by the position of the arms. To a clinician who expects organic signs to be constant, that looks manufactured. It is not. Brazis gives the manoeuvre: a large-amplitude wing-beating tremor may be demonstrated with the shoulders abducted to 90 degrees. Kaufman notes that this hallmark occurs in only about one-third of cases and consists of rhythmic, coarse, up-and-down arm movements based at the shoulders. Keep those figures apart: one is a manoeuvre angle, the other how often the sign is present.

MNEMONIC

Two forms, one arc

Dystonic: mouth, speech and swallow, the commonest presenting syndrome. **Pseudosclerotic**: gait, coordination and speech, the cerebellar-looking one. **One arc**: the wing-beating tremor, absent at rest, appearing on sustained arm extension, and present in a minority of cases, so that its absence excludes nothing.

9.7 The psychiatric presentation, and a disagreement about psychosis

Two-thirds of patients may have psychiatric symptoms by first presentation, and 10% to 20% seek psychiatric treatment before the diagnosis is made, a stage at which the diagnosis is often missed; eventually psychiatric manifestations affect nearly all patients, and the psychiatric profile generally resembles that of Huntington disease. The other chapter reports a range: estimates range from 30% to 100% of symptomatic patients experiencing psychiatric symptoms at some point, up to two-thirds present with psychiatric symptoms, and one-third will have received psychiatric treatment before the diagnosis is made. Print that range as a range: collapsing it to a midpoint destroys what it carries.

What the symptoms are is more consistent across sources than how often they occur. The commonest are personality change, often described as irritability, aggressiveness and emotional lability, and depression ranging from subsyndromal mood change to major depression, at times with suicidality; anxiety disorders, psychotic disorders and individual psychotic symptoms, and catatonia all appear at higher rates than in the general population. The referral pattern follows: the commonest reasons for psychiatric referral are behavioural and personality change, with disinhibition or bizarre or impulsive behaviour in about a quarter of patients and depression in about one-fifth, and personality and behavioural change, but not depression, correlate with the degree of neurological impairment.

That correlation is stated directly elsewhere: psychiatric symptom severity correlates more strongly with neurological deficits than with liver disease, indicating that the psychiatric phenomena arise from brain damage rather than from a psychological reaction to the illness. Cognition follows the same substrate. It has not been well studied; a relatively mild degree of impairment akin to that in other basal ganglia diseases is thought to be present in about 25% of patients, worsening over time and in step with accumulating neurological symptoms. Where there is neurological involvement, the pattern is subcortical, with frontal executive deficits that correlate with the extent of cerebral involvement. Keep the source's own hedge on that figure.

TRAP **Answering that psychosis is a characteristic presentation of Wilson's disease, or that it is rare, as though either were settled.** One chapter of Kaplan and Sadock states that about 10% of patients present with psychosis and are frequently misdiagnosed with primary schizophrenia or bipolar disorder. Another chapter of the same textbook states that although early reports suggested psychotic presentation was a feature of the disease, more recent investigations have shown psychotic symptoms to be relatively rare. This is an intra-textbook contradiction on a load-bearing point. The defensible position is the one both support: personality and behavioural change are the commonest psychiatric presentations in every source, and the frequency of frank psychosis is disputed inside one standard reference.

9.8 The Kayser-Fleischer ring: site, frequency and the word pathognomonic

The **Kayser-Fleischer ring** is the single most important clinical diagnostic sign, consisting of copper deposits in the outer rim of the cornea that appear brown or grey-green on slit-lamp examination. Brazis gives the precise layer: deposition of copper in the **Descemet membrane**, accompanied in some patients by sunflower cataracts. Kaufman adds the caveats: it is most obvious at the superior and inferior corneal margins and usually obscures the fine structure of the iris; a slit lamp is required to see it in its early stages; its size and density correlate with disease duration where the brain is affected; and it dissolves with successful treatment.

Four standard texts describe one sign in four subtly different ways.

SOURCE	SITE AS STATED	FREQUENCY	SPECIFICITY AS STATED
Kaplan and Sadock, disorders of metal metabolism section	Outer rim of the cornea.	About half of patients with hepatic presentation; almost all with a neurological or psychiatric presentation.	Single most important clinical diagnostic sign; pathognomonicity not claimed.
Kaplan and Sadock, physical examination chapter	Limbus of the cornea, brownish-green discoloration.	Not stated.	Stated to indicate Wilson disease sensitively and specifically.
Kaufman's Clinical Neurology for Psychiatrists	Periphery of the cornea, bilateral.	About 70% of cases where the disease affects only the liver; almost 100% where it affects the brain.	Explicitly not pathognomonic, since it also develops in primary biliary cirrhosis and several other liver diseases.
Rutter's Child and Adolescent Psychiatry	On the iris.	Not stated.	Described as pathognomonic.

The iris reading is probably an artefact of appearance: Kayser-Fleischer rings lie in front of the peripheral iris and obscure it. On frequency the sources agree where it matters most to a psychiatrist, because **almost 100%** of patients with brain involvement carry the ring; they disagree only on the hepatic-only denominator, where the populations described are not identical.

TRAP **Writing that the Kayser-Fleischer ring is pathognomonic of Wilson's disease, or that it sits on the iris.** Both errors are printed in respectable texts. The safe answer names the cornea, specifically Descemet membrane, calls the ring the single most important clinical sign, and states on Kaufman's authority that it is not pathognomonic.

GOOD TO REMEMBER

Kayser-Fleischer rings are not reliably visible to the naked eye early on, so a normal-looking iris on ward examination is not a negative result: if Wilson's disease is on the differential, the request is for a slit-lamp examination by an ophthalmologist. They also resolve with treatment, so their absence in a patient already on therapy carries no diagnostic weight.

9.9 Recognising it in a psychiatric clinic, and what changes on Monday

The systemic reach of copper toxicity is wider than the classical triad suggests. Liver dysfunction, the commonest childhood presentation, may appear as mild transaminase elevation, chronic active hepatitis, cirrhosis, or acute and fulminant liver failure; copper toxicity may also produce cardiac arrhythmias, renal disease, rhabdomyolysis, joint disease, anaemia, and thyroid and parathyroid dysfunction. Note the endocrine entry: a movement disorder with a thyroid or parathyroid abnormality in a young patient is two findings that one diagnosis explains.

LOCUS. The neuropsychiatric presentation of Wilson's disease is recognised in the outpatient psychiatric clinic, the consultation-liaison referral, and occasionally the emergency department; confirmation and treatment move into shared care with hepatology and neurology. The psychiatrist's task is the same at each: suspect the diagnosis and arrange the examination that supports it, not complete the workup alone.

FOCUS. Immediately the target is recognition, because the importance of recognising the early psychiatric presentations lies in the proven benefits of early treatment intervention. In the short term, the confirmatory workup and transfer into shared care. Longer term the psychiatric symptoms need treating in their own right; they do not remit the moment a diagnosis is made.

MODUS. No treatment guideline for this disease is quoted here; the sources behind the above are Kaplan and Sadock, Kaufman, Brazis and the Companion to Psychiatric Studies. Clinically, extend the examination: eye movements, tone, gait, speech, the face, and a request for slit-lamp examination. Biochemically, serum ceruloplasmin, urinary copper, the confirmatory sequence and chelation are set out where this chapter deals with the investigation and management of Wilson's disease. Psychiatrically, symptomatic treatment continues alongside; where antipsychotics are involved, their own movement-disorder effects are the subject of the Schizophrenia: management, antipsychotics and adverse effects notes.

PITFALL

Attributing new extrapyramidal signs in a young psychiatric patient to their medication. Diagnostic delay is exacerbated when extrapyramidal movements are attributed to psychotropic medication or interpreted as functional. Both are reasonable on their face and both self-sealing: once the tremor is drug-induced, nobody examines the cornea. Signs that preceded the drug, that persist after it is withdrawn, that come with dysarthria, dysphagia or drooling, or that are unusually dramatic in a young patient, deserve a slit lamp before they deserve an anticholinergic.

Wilson's disease is an autosomal recessive failure of the ATP7B copper-transporting ATPase: biliary excretion fails, ceruloplasmin falls as a consequence and not a cause, and free copper accumulates in astrocytes of the lenticular nucleus and in Descemet membrane of the cornea. Up to a fifth of patients present psychiatrically, almost all of those with brain involvement carry a Kayser-Fleischer ring, and normal liver function tests exclude nothing.

10 · Wilson's disease: investigations (ceruloplasmin, urinary copper) and management (chelation)

No single test makes this diagnosis. Wilson's disease is confirmed on a panel of imperfect measures, and every element has a documented failure rate an examiner expects you to name. The copper-handling defect, the genetics, the Kayser-Fleischer ring and the presentation are set out where this chapter deals with Wilson's disease as a disorder of copper metabolism; what follows is the work-up and the treatment.

The work is worth it: this is one of very few neurodegenerative diseases in which copper accumulation, the fundamental pathogenic process, is itself amenable to treatment, so early consideration of the diagnosis, including in older patients, is essential. The standard references also contradict themselves in four places here; in each, the safe answer names the disagreement rather than picking a side.

95%	10%	UP TO 50%	1 MONTH
CERULOPLASMIN BELOW NORMAL	NORMAL CERULOPLASMIN, HIGH URINE COPPER	NEUROLOGICAL WORSENING, PENICILLAMINE	WINDOW FOR BEST OUTCOME

10.1 Serum ceruloplasmin: the first test, and the ways it misleads

The screening test is **serum ceruloplasmin**, the copper-carrying protein of plasma, which in this illness is low to absent. One mechanism explains both copper tests: the defective transporter fails to load copper onto the apoprotein, the unloaded protein is cleared, and the uncarried copper is excreted, so one lesion lowers the serum protein and raises the urine copper. It is no marker of brain disease, since even where the disease does not affect the brain, ceruloplasmin concentrations fall to very low levels.

Kaplan and Sadock's Comprehensive Textbook of Psychiatry puts the level below normal in 95% of patients, which sounds decisive until the same sentence lists what else lowers it. It is low in newborns and in **20% of heterozygous carriers**, and it may be misleadingly normal in the

setting of infection or inflammation. The mechanism matters: ceruloplasmin is an acute-phase reactant, so sepsis or hepatitis can lift a diagnostic value into the reference range. There the source redirects you, since the absence of serum ceruloplasmin oxidase activity is a useful test. Measuring **ceruloplasmin oxidase activity** rather than protein mass sidesteps it: what is missing is the functional copper-loaded enzyme.

One absence must be stated rather than filled: no source used here gives a numeric cut-off or any units, saying only below normal, low, or low to absent. Take any printable threshold from a named primary hepatology guideline.

RULE **A normal serum ceruloplasmin does not exclude Wilson's disease.** Both chapters of the textbook agree on this while disagreeing on the arithmetic behind it. A patient with a normal result and a fitting picture still needs the urinary copper, the slit-lamp and, if the question stays open, confirmatory testing.

10.2 Urinary copper, and what else raises it

The second core investigation is the **24-hour urinary copper**, and the textbook position is strong: an elevated 24-hour urinary copper concentration is generally considered diagnostic of the disease. Kaufman's Clinical Neurology for Psychiatrists explains why, and why clinicians avoid it, calling it a more cumbersome test, in which the absence of ceruloplasmin greatly increases urinary copper excretion. Cumbersome is the word: an incomplete collection reads falsely low in a patient who has the disease.

Here too the sources give direction and withhold the number: none states a threshold, its units, or a provocation protocol, and that matters more than the ceruloplasmin absence, because the value means nothing without a laboratory reference. The result is less specific than that wording suggests, since urine copper excretion may be elevated for reasons unrelated to Wilson's disease:

- Metal chelation therapy already in progress.
- Acute liver failure, or cirrhosis with cholestasis.
- Nephrotic syndrome.

Hepatic copper has its own mimics: it may be elevated in cholestatic liver disease, where ceruloplasmin is normal or elevated, and in idiopathic childhood cirrhosis, where ceruloplasmin is elevated. The ceruloplasmin direction separates them, which is why the panel is read together. The mimic to memorise is **aceruloplasminaemia**, which produces neurological symptoms but raises liver iron rather than liver copper: what discriminates is the metal, not the missing protein.

PITFALL

Sending the 24-hour urinary copper after chelation has started. It happens whenever a confident diagnosis leads to treatment while confirmatory tests are still in the system, and it destroys the result: chelation is itself a cause of raised urinary copper, so the sample no longer separates disease from drug.

10.3 Confirming the diagnosis: liver biopsy against gene sequencing

Where the copper studies leave the question open, two confirmatory routes exist and the textbook cannot decide between them. Its Wilson disease chapter holds that liver biopsy is the gold standard for diagnostic confirmation, and may show increased hepatic copper concentration with evidence of hepatitis or cirrhosis, though no threshold and no units accompany it anywhere in these sources. Its metal-metabolism chapter measures it differently, giving liver biopsy with staining for total hepatic copper a sensitivity of over 80%, with false negatives arising from sampling error: copper is unevenly distributed through a cirrhotic liver, so a core can miss the loaded parenchyma.

The molecular route is the **ATP7B** gene. Sequencing is confirmatory when disease-causing mutations are identified, but a negative test, absent supportive laboratory data, does not exclude the disease, because the mutations are heterogeneous. The metal-metabolism chapter goes further, calling genetic testing of that gene the gold standard, while noting that it requires direct sequencing of the entire gene and may return variants of unclear significance.

TRAP **Naming one gold standard for Wilson's disease and defending it.** "Gold standard" is the phrase an examiner reaches for, and the same textbook answers it two ways in two chapters. The mark is in the reasoning: say that histological and molecular confirmation are both called the reference test, that each has a stated weakness (sampling error for the biopsy, uninterpretable variants for the sequence), and that they are complementary.

10.4 Neuroimaging and the pathological substrate

Imaging supports the diagnosis and tracks treatment but does not screen: MRI may help diagnose the illness, but characteristic changes often do not emerge until irreparable damage has occurred. A normal scan argues for the copper studies, not against the diagnosis.

The signature to memorise is reduced T1 signal and increased T2 signal in the basal ganglia, thalamus and brainstem. Kaplan and Sadock add generalised atrophy with increased T2-weighted signal in the basal ganglia secondary to copper deposition, sometimes in patients with no clinical evidence of brain disease: the brain may be involved radiologically before clinically. Atrophy may also involve the cerebral cortex, particularly the frontal lobe, and the brainstem and cerebellum; behind the images lies cavitary degeneration of the basal ganglia, with neuronal loss, gliosis and high tissue copper.

Localization in Clinical Neurology is more precise: striatal lesions are the most characteristic lesions found in the brain in patients with neurological symptoms, and MRI demonstrates bilateral symmetric hyperintensities in the putamen, thalami, brainstem and posterior limb of the internal capsule, symmetry discriminating against most other striatal lesions in a young adult. The lesions can be more diffuse, involving the pons, midbrain and dentate nucleus, and less frequently the corpus callosum. A published axial T2 image of an adolescent shows the narrower pattern, bilateral hyperintensity of the thalamus, caudate and putamen.

The eponymous sign needs care: the sources describe it differently and merging them yields a description neither supports. Kaplan and Sadock name the **midbrain panda sign**, common in

the disease but nonspecific, from hyperintense signal around the red nucleus and putamen, while Localization in Clinical Neurology attaches double panda sign to the putaminal, thalamic and brainstem hyperintensity just described. Quote the sign with its source, and carry the qualifier Kaplan and Sadock attach to theirs: suggestive, not diagnostic. Localization in Clinical Neurology states its sign flatly, with no comment on specificity, so the hedge belongs to the first source and should be cited to it.

10.5 Assembling a diagnosis from imperfect tests

Because no test stands alone, someone had to formalise the combination. The **Leipzig criteria** were developed by the European Association for the Study of the Liver, incorporating clinical and laboratory findings, in recognition of how variable both are in this disease. That is all these sources state: no items, no point weights, no total and no interpretation, so a scoring table from memory would be ungrounded. Take the arithmetic from the primary guideline.

TEST	WHAT THE STANDARD SOURCES STATE	THE STATED LIMITATION
Serum ceruloplasmin	Low to absent, even where the brain is unaffected.	Low in newborns and carriers; may be normal in inflammation.
24-hour urinary copper	An elevated concentration is generally considered diagnostic.	Cumbersome. Raised by chelation, acute liver failure, cholestatic cirrhosis, nephrosis.
Liver biopsy	Increased hepatic copper with hepatitis or cirrhosis. Sensitivity over 80%.	False negatives from sampling error.
ATP7B sequencing	Confirmatory when disease-causing mutations are identified.	A negative result does not exclude it. Variants of unclear significance.
MRI	Reduced T1, increased T2 in basal ganglia, thalamus, brainstem.	Characteristic changes often do not emerge until irreparable damage has occurred.

TRAP **Quoting a single sensitivity figure for serum ceruloplasmin.** The same textbook gives two, in two chapters, and they cannot be reconciled. One puts the level below normal in 95% of patients. The other states that low serum ceruloplasmin has high sensitivity, over 80%, with low specificity, and that a normal ceruloplasmin may occur in 10% of patients in the presence of high urinary copper excretion, a sensitivity that is not arithmetically consistent with its own false-negative figure. The two chapters therefore imply different false-negative rates. Give the direction, name both as variants, and land on the consequence both support: you cannot rule the disease out on this test. The passage adds that low serum copper or free copper and high urine copper can be seen but are less reliable.

10.6 The aims of treatment and the agents that serve them

Treatment rests on three aims and every drug maps onto one: to remove accumulated copper, to prevent re-accumulation through maintenance treatment, and to reduce its absorption.

MNEMONIC

Strip, Sustain, Starve

Strip out what is stored with a chelator; **sustain** the gain with maintenance; **starve** the body of new copper by blocking absorption. The agent names the phase your patient is in.

The mainstay chelator is **d-penicillamine**. The Companion to Psychiatric Studies agrees that chelating agents are effective but carry a risk of significant side effects, penicillamine being currently the most widely used, with trientine and zinc acetate as alternatives. KDT Essentials of Medical Pharmacology describes it as dimethyl cysteine, a degradation product of penicillin, used for Wilson's disease from 1956, which selectively chelates Cu, Hg, Pb and Zn, plus the examination favourite: the d-isomer is used therapeutically because the l-isomer and the racemate produce optic neuritis and are more toxic. In practice, penicillamine combined with pyridoxine has been the mainstay of initial treatment, though no source used here states either dose, so neither is printed.

Trientine, or triethylenetetramine dihydrochloride, is an acceptable alternative for patients with Wilson's disease intolerant of penicillamine, and is effective orally. For that indication, copper chelation in penicillamine-intolerant Wilson's disease, Goodman and Gilman gives maxima of **2 g per day** in adults and 1.5 g per day in children, in two to four divided portions on an empty stomach. Those are maxima, not starting doses, and no titration schedule appears in the source.

Zinc acetate serves the third aim by a mechanism that fixes its place: it induces metallothionein in the gastrointestinal epithelium and thereby inhibits copper absorption, and has been used as preventative treatment in presymptomatic patients and for maintenance. The trapped copper is shed with the enterocyte, so zinc blocks rather than de-coppers, which is why it belongs to prevention and maintenance. No zinc dose appears in any source used here. The repertoire is stated once: treatment involves either removing copper by chelation, using D-penicillamine, trientine and tetrathiomolybdate, or blocking copper absorption with zinc salts. Tetrathiomolybdate is named there and nowhere else, with no dose.

TRAP **Writing that trientine is the safer chelator for neurological Wilson's disease.** The sources disagree about which agent carries the risk. One attributes it to penicillamine, whose combination with pyridoxine may lead to a worsening of neurologic symptoms in **up to 50% of patients, which has led to the recommended use of less neurotoxic copper chelators such as trientine**. The other gives it to trientine, which can paradoxically increase neurologic and psychiatric symptoms acutely as hepatic copper is mobilised and deposited in the brain, giving penicillamine a propensity to induce hypersensitivity reactions instead. That mechanism is generic to de-coppering and fits either drug. Name early deterioration on starting chelation as a hazard of de-coppering itself, say the sources differ on which agent carries it, and attribute the up-to-half figure to penicillamine, the agent named by the source stating it.

10.7 Managing the patient: LOCUS, FOCUS, MODUS

LOCUS. Diagnosis and maintenance are outpatient work shared between psychiatry, neurology and hepatology, and the psychiatrist often sees the patient first. Admission is for initiating

chelation in significant neurological disease, where early deterioration is a hazard, and for decompensated liver disease; transplant-centre care belongs to fulminant hepatic failure. The guidance base is thin: the European Association for the Study of the Liver stands behind the diagnostic criteria, but the treatment recommendations come from standard texts, so local hepatology protocols govern the regimen.

FOCUS. Acutely, the copper load and the behaviour that brought the patient in; short term, neurological deterioration as chelation begins; medium term, adherence, where most avoidable harm is done because the patient feels better and stops; long term, re-accumulation, liver monitoring and residual deficit.

MODUS. Drug treatment is the sequence above. Diet is where the sources conflict and both positions must be carried: one chapter holds that restriction of high-copper foods, namely shellfish, liver, chocolate, nuts, beans and mushrooms, is encouraged; the other that except in areas with high levels of copper in the drinking water, dietary restrictions are inadequate to prevent copper overload. Neither says which it means, so if you counsel restriction, say explicitly that it is adjunctive, never a substitute for chelation. Procedurally, orthotopic liver transplantation has proven successful in end-stage liver disease and restores normal copper excretion, though it is limited by lifelong immunosuppression and procedural complexity.

Psychiatric treatment has almost no trial evidence behind it, and saying so is examinable. There are no controlled trials of symptomatic treatment for the psychiatric manifestations, and anecdotal evidence suggests particular vulnerability to the motor side effects of antipsychotics; the prudent course is standard psychiatric treatment, pharmacological and psychotherapeutic, at lower doses, increased slowly, avoiding high-potency antipsychotics. Antipsychotic receptor pharmacology and drug selection belong to the Schizophrenia: management, antipsychotics and adverse effects notes; added here is the reason for the caution, a basal ganglia already loaded with copper and degenerating. No milligram figure attaches to "lower doses" in any source here.

IN INDIA

The copper-restricted food list is written for a Western plate. Nuts, beans and mushrooms are staples in most Indian households and pulses a principal protein source in largely vegetarian diets, so handing it over unmodified either goes unfollowed or does real nutritional harm; counsel specifically, with a dietitian where available. The timed collection is harder where a patient travels a long distance and must return a complete sample, and a partial one reads falsely low. Cost and stock shape the choice of chelator more than any textbook comparison: penicillamine is the cheapest and most widely stocked, and the alternatives are not uniformly available outside larger centres.

10.8 Timing, recovery and what to tell the patient

The strongest argument for psychiatric vigilance is one sentence. Treatment outcomes are best when treatment begins within 1 month after symptom onset; the average symptom duration before correct diagnosis and treatment, however, is about 1 year. The gap is where the

preventable disability is made, much of that year in psychiatric services, because behavioural change and mood disturbance often precede the movement disorder.

Recovery is real but slow, and patients should be told so before they judge the drug a failure. Neurological and psychiatric symptoms improve with copper chelation over 1 to 2 years, with regression of MRI lesions on serial imaging. The counselling figure is a year or two, not weeks, and imaging gives an objective marker of response to a patient who cannot yet feel one.

Outcome differs by phenotype, and the series must be quoted carefully. The best outcomes are seen in patients with the pseudosclerotic form (82% symptom-free), with worse outcomes in patients with chorea (75% of patients), parkinsonism (63%) and dystonia (53%). The source does not repeat "symptom-free" after the first figure, so the denominator of the last three is not explicit; they read as a descending series of symptom-free rates, but nothing says so, and relabelling them would be invention with a citation attached. Teach the ordering: the pseudosclerotic form does best, dystonia worst.

The sources extend early consideration to older patients, and the teaching that this is a disease of the young is what produces the delay. And treatment is lifelong, because copper re-accumulates when the drug stops, so the fully recovered patient is the one at risk of stopping.

A normal ceruloplasmin does not exclude Wilson's disease, and an elevated 24-hour urinary copper is uninterpretable once chelation has begun: send both before the first dose of anything, in any young patient with psychiatric symptoms plus a movement disorder or unexplained liver disease.

11 · Porphyria and the adult-onset inherited metabolic disorders

These are the diagnoses a psychiatrist is structurally placed to miss. An inherited metabolic disorder declaring itself in infancy belongs to the paediatrician; these wait until adolescence or adult life and open with a syndrome psychiatry already names, so the psychiatrist sees them first, the label is defensible the day it is made, and it closes the case. The porphyrias are episodic disorders of heme synthesis in which neurotoxic precursors accumulate under metabolic stress; the storage and remethylation disorders are progressive.

1 IN 20,000 FREQUENCY OF AIP	**1 IN 500** AIP IN 4,000 PSYCHIATRIC INPATIENTS	**1.5 PER 100,000** FREQUENCY OF MLD	**25% TO 40%** PSYCHOSIS, ADOLESCENT AND ADULT NPC

11.1 Acute intermittent porphyria: the defect and who gets it

The porphyrias are disorders in which defects in heme biosynthesis cause excessive urinary secretion of porphyrins and their precursors, several pathway intermediates being neurotoxic. Most porphyrias are dominantly inherited with incomplete penetrance, so the family history is often blank in a carrier.

Acute intermittent porphyria is the one that matters to psychiatry: autosomal dominant and incompletely penetrant, arising from defects in **porphobilinogen deaminase**, the enzyme

converting porphobilinogen to hydroxymethylbilane, and occurring in **1 in 20,000** individuals.

The block accumulates the precursors porphobilinogen and aminolevulinic acid, both thought to be neurotoxic. The deficit is latent: it becomes apparent in situations requiring an increase in heme synthesis, when demand pulls the pathway forward and precursors pile up behind the block. Hence who presents, since the disorder presents most commonly in women of child-bearing age, in whom one such demand recurs monthly.

- Fasting.
- Menstruation.
- Intercurrent medical illness.
- Cytochrome P450 inducers, including alcohol, estrogens, barbiturates and sulfonamides.

In 4,000 psychiatric inpatients the disorder was significantly over-represented at 1 in 500 against a community rate of 1 in 100,000.

TRAP **Quoting "1 in 500" as the prevalence of acute intermittent porphyria.** The population is part of the number: it describes psychiatric inpatients, not any general or outpatient population. A subtler version sits alongside it: the standard reference gives the disorder frequency as 1 in 20,000 and, in the same passage, a community rate of 1 in 100,000. The two do not agree and no source reconciles them. Quote either with its population attached; never average them or invent a reconciliation.

11.2 The attack: a triad, and the two diagnoses it gets instead

The **classical triad** during an episode is abdominal pain, psychiatric disturbance and peripheral neuropathy. The neuropathy is what candidates get wrong: mostly motor and often mimics Guillain-Barre syndrome, not the length-dependent sensory neuropathy met in diabetes or alcohol use.

MNEMONIC

Pain, Psyche, Peripheral nerve

Abdominal **pain**, disturbance of the **psyche**, a mostly motor **peripheral nerve** lesion. Two of the three sit outside psychiatry, and on any visit only one limb may show, since psychiatric symptoms alone may be the single presenting feature. That is why the diagnosis survives several admissions.

Among clinically symptomatic cases, psychiatric disturbance occurs in **up to half of all cases**, and half of those are psychotic episodes, with depression, anxiety and delirium also appearing as the main presenting symptom. The denominator is symptomatic cases, not all gene carriers. Delirium as a syndrome belongs to the Stroke, TBI, delirium and focal brain syndromes notes.

Two misdiagnoses recur. The intermittent character of the attacks invites a misdiagnosis of schizophrenia, and abdominal pain during attacks invites a diagnosis of somatoform disorder. The second is more damaging, because a somatoform formulation discourages further physical investigation, as with the functional movement disorder label misapplied in Wilson's disease, set out where this chapter deals with Wilson's disease and its neuropsychiatric presentation. Beyond

the attacks, the more chronic porphyrias carry elevated rates of anxiety and depression. The periodic madness of King George III has in recent decades been attributed to the disorder, which has also been implicated in illnesses affecting the work of Van Gogh and Soren Kierkegaard; hedged attributions, colour in an answer rather than fact.

11.3 Why the nervous system suffers, and how firmly we can say it

How precursor accumulation produces neuropsychiatric disturbance is unclear, and candidate explanations have included oxidative stress, vascular change and demyelination. Keep that hedge; presenting one hypothesis as established loses credit.

Aminolevulinic acid is structurally similar to gamma-aminobutyric acid, which may impair GABA release from the synapses of inhibitory neurons. Failed inhibition is what agitation, psychosis, seizure risk and autonomic instability look like together. Alongside it, reduced heme-dependent enzymes are proposed to increase serotonin turnover and reduce nitric oxide activity, the second a route to the vascular limb.

11.4 Confirming it: the specimen is half the test

Diagnosis rests on elevated urinary aminolevulinic acid and porphobilinogen together with red cell porphobilinogen deaminase activity. Gross elevations often turn the urine amber or purple in direct sunlight, the classic image and the clue to handling: if light changes the analyte, light destroys the specimen. Hence a 24-hour urine in light-protected containers, correctly preserved.

No cut-off, units or reference band is given for any of the three analytes. Do not reconstruct one; leave interpretation to the reporting laboratory.

Hereditary coproporphyria is the near neighbour: a dominantly inherited deficiency of coproporphyrinogen oxidase that can present identically, with the addition of cutaneous findings: bullous lesions, skin fragility and scarring. The neuropsychiatric picture gives nothing, so the skin discriminates and the laboratory follows it: coproporphyria calls for urinary coproporphyrin levels.

11.5 Managing the acute attack and prescribing around it

LOCUS. An acute attack is emergency inpatient medical work: a motor neuropathy mimicking Guillain-Barre carries a respiratory risk, and the treatments that reverse the biochemistry are intravenous. The psychiatrist's locus is then consultation-liaison: securing the admission, advising on psychiatric symptoms, auditing the drug chart. The independent psychiatric locus is outpatient, in preventing the next attack.

FOCUS. First, correct identification and avoidance of precipitants where possible, the only intervention that changes the trajectory rather than the episode. Acute targets are the biochemical block, the contributing illness and the agitation or psychosis; long term, a regimen that holds the psychiatric disorder without provoking attacks.

MODUS. No dedicated guideline for the psychiatric care of porphyria is available here; what follows rests on Kaplan and Sadock's Comprehensive Textbook of Psychiatry. Attack treatment includes reversal of contributing illnesses, intravenous hydration, carbohydrate loading to inhibit

heme synthesis, and hematin or heme arginate to provide negative feedback to the heme synthetic pathway. The last two signal that heme is abundant, suppressing enzymes upstream of the block so precursors stop accumulating. No dose, route, frequency or duration appears for any of them, and an invented figure here would be one for the definitive treatment of a life-threatening attack.

Psychotropic selection is where the psychiatrist owns the decision. The principle is judicious use of medication that will not worsen the biochemical deficit, and specific agents are named: chlorpromazine and droperidol for psychosis, fluoxetine for depression, lithium for mania, and lorazepam, triazolam and temazepam for anxiolysis and sedation. Lithium belongs to the Mood disorders: pharmacotherapy notes; antipsychotic pharmacology and drug selection to the Schizophrenia: management, antipsychotics and adverse effects notes. One prohibition stands against that list: like the barbiturates, chloral hydrate may precipitate attacks and is contraindicated in porphyria.

PITFALL

Treating that short list of named safe drugs as a complete safety classification, and reading absence from it as evidence of danger. The source does not classify most of the drugs a psychiatrist reaches for, including the anticonvulsant mood stabilisers and the second-generation antipsychotics, and silence about an agent is a verdict in neither direction. Check the specific drug against a maintained porphyria drug-safety database before prescribing.

11.6 Metachromatic leukodystrophy: psychosis with a white matter signature

Metachromatic leukodystrophy is an autosomal recessive, incompletely penetrant deficiency of the lysosomal enzyme arylsulfatase A, occurring in 1.5 per 100,000 individuals and first described in 1933. Inheritance changes here: these disorders are recessive, so consanguinity and affected siblings become relevant. **Arylsulfatase A** hydrolyses sulfatides, including sulfate-containing lipids of the central nervous system; sulfatide accumulates in brain, peripheral nerve, kidney and gallbladder, particularly in myelinated structures, seen as metachromatic granules on histology with widespread myelin loss. A disease of myelin presents as a disconnection syndrome, not a focal deficit.

In younger patients seizures and motor symptoms predominate; in adults psychiatric manifestations and dementia frequently precede motor symptoms, particularly with the I179S mutation, and severity is inversely correlated with residual enzyme activity. More residual enzyme means later onset and a more psychiatric, less motor picture. The adult form appears to cleave into two phenotypes.

- A predominantly motor, cerebello-pyramidal presentation.
- A predominantly psychiatric presentation.

Up to half of patients with onset between 10 and 30 years of age present with psychotic symptoms, including auditory hallucinations, systematised delusions, formal thought disorder, catatonic posturing and inappropriate affect. That is a complete description of schizophrenia in a

patient whose neurological examination will initially be normal. The figure is bound to that onset band.

Time supplies the clues. Seizures, chorea or dystonia supervene, and dementia is an inexorably progressive component presenting first as attentional disturbance, reduced processing speed and executive impairment, which may present as a phenocopy of frontotemporal dementia, or, where disinhibition is prominent, as a phenocopy of hypomania. A first manic episode dominated by disinhibition, in a young adult slowly losing executive function, should trigger this thought; the dementia syndrome itself belongs to the Dementias and neurocognitive disorders notes. Diagnosis is by reduced enzyme activity in leukocytes or skin fibroblasts, MRI supporting rather than confirming: it generally shows periventricular white matter change sparing the subcortical U-fibers, often with a frontotemporal preponderance.

11.7 Niemann-Pick type C: the eye sign that changes the diagnosis

Niemann-Pick disease type C is an autosomal recessive neurovisceral lipid storage disorder with a frequency of 1 in 100,000 live births, in which **95%** of patients have aberrations on NPC1 at 18q11-12 and 5% on NPC2 at 14q24.3. One discrimination is examined: it is biochemically and phenotypically distinct from types A and B, which result from lysosomal sphingomyelinase deficiency.

NPC1 and NPC2 handle the cyclical movement of sterols within cells, and their impairment causes late endosomal accumulation of cholesterol and gangliosides. Excess GM2 and GM3 gangliosides alter neuronal ultrastructure, and disrupted cholesterol metabolism alters tau and beta-amyloid processing, with Alzheimer-like neurofibrillary tangles, startling in a young patient. The regional pattern explains the sequence: axonal structures are affected early, then cerebellar Purkinje cells, basal ganglia and thalamic neurons, with hippocampal and neocortical regions later, the most fulminant loss being cerebellar and producing early cerebellar signs.

Clinically the disorder may present in infancy, adolescence or adulthood, but its core features are dementia, dysarthria, ataxia, vertical supranuclear ophthalmoplegia and hepatosplenomegaly, with seizures, dysphagia and pyramidal signs as it progresses. Psychosis occurs in 25% to 40% of adolescent and adult-onset cases and may precede motor and cognitive disturbance by many years. The band is bound to adolescent and adult-onset cases, and the lead time makes this a psychiatric problem: there are years in which the patient is simply a person with a psychotic illness.

RULE **Vertical gaze palsy plus psychosis means Niemann-Pick type C until proven otherwise.** The co-occurrence of vertical gaze palsy and psychosis should prompt the clinician to consider this disorder, so that appropriate treatment can be instituted. It is the highest-yield rule in this group, because **vertical supranuclear ophthalmoplegia** is easy to miss and easy to elicit. A routine examination follows a finger horizontally, which will not find it: ask for voluntary downgaze and look for a saccadic abnormality rather than gross restriction.

Confirmation runs through cell biology: a low esterification rate of exogenous cholesterol in fibroblasts, or filipin staining for lysosomal accumulation of free cholesterol, with oxidised

plasma cholesterol and direct NPC1 sequencing used more recently. **Filipin staining** is the classic confirmatory test. Imaging often shows diffuse cerebral or cerebellar atrophy, striatal, hippocampal and thalamic atrophy and callosal thinning, none of it specific alone. One published case shows what confirmation looks like: a 26-year-old man presented with movement disturbance and dysarthria after a 10-year history of treatment-resistant psychosis, with gait ataxia, jerky saccades and grossly impaired downgaze. Filipin staining showed 60% to 70% of cells with perinuclear staining against a normal figure of less than 5%, and the cholesterol esterification rate was mildly abnormal at 2.9 pmol/hr/mg on a scale where less than 2 is abnormal, 2 to 3 equivocal and greater than 3 normal, with NPC1 compound heterozygosity for G992R and R1186H. Treat that esterification band as one laboratory's reported figure inside a published case, not a general threshold.

Treatment is why the rule exists. Psychosis may require higher antipsychotic doses and a combination of antipsychotics and mood stabilisers. That direction runs opposite to the antipsychotic advice in Wilson's disease, set out where this chapter deals with Wilson's disease investigations and management. Beyond symptomatic treatment, substrate reduction therapy with the imino sugar miglustat, which crosses the blood-brain barrier and reduces ganglioside accumulation, has shown promise in reversing motor and cognitive deficits and may reduce or prevent psychiatric disturbance, with trials under way of intrathecal and intravenous cyclodextrin and acetyl-L-leucine. No dose, frequency or titration is given for any of these.

11.8 The homocystinurias: one analyte up, the other in either direction

Disorders raising blood and urinary homocysteine are grouped as the homocystinurias. The classic form is autosomal recessive, caused by a defect in the chromosome 21 gene coding for cystathionine beta-synthase, the enzyme converting homocysteine and serine into cystathionine, leading to accumulation of both homocysteine and methionine. **Cystathionine beta-synthase** sits on the transsulfuration exit, so methionine rises alongside homocysteine.

Presenting features are usually developmental delay or intellectual disability with optic lens dislocation within the first 10 years; lens dislocation is seen in almost 100% of patients older than 10, with cataract, glaucoma and optic nerve atrophy as further complications, and intellectual disability in about half of patients, declining slowly. Patients may appear Marfanoid, with arachnodactyly, kyphoscoliosis and pectus excavatum, and clotting abnormalities with increased platelet adhesiveness cause occlusion and thromboembolism with very high mortality. Intellectual disability and the thrombotic tendency discriminate from Marfan syndrome, and the thrombosis is what kills.

Early reports linked homocystinuria with psychosis, but large case series report personality disorder, behavioural disturbance such as aggression, depression and obsessive-compulsive disorder as the most common findings, with aggression and behavioural disturbance more common in those with intellectual disability. Answering "psychosis" reproduces the impression those series overturned. Diagnosis rests on elevated plasma methionine with elevated plasma and urine homocysteine; treatment works when early: methionine restriction and cysteine supplementation will generally prevent long-term sequelae if the disorder is diagnosed at birth,

and oral pyridoxine, which remethylates homocysteine to methionine, reduces both analytes in about half of patients, with folic acid and vitamin B12 possibly of further benefit. No dose is stated, and the quantities used run far above ordinary supplement doses.

The second mechanism group inverts one of the two analytes. Other autosomal recessive homocystinurias arise from defects in an alternative remethylation pathway, in which homocysteine is catalysed to methionine by either methionine synthetase or methylenetetrahydrofolate reductase; an inherited defect in methylcobalamin, the cofactor for methionine synthetase, also produces homocystinuria together with methylmalonic aciduria. These deficiencies give high homocysteine but, in contrast to cystathionine synthase deficiency, low methionine.

FEATURE	CLASSICAL HOMOCYSTINURIA	REMETHYLATION DEFECTS
Enzyme or cofactor	Cystathionine beta-synthase, chromosome 21.	Methionine synthetase, MTHFR, or methylcobalamin.
Homocysteine	Elevated, plasma and urine.	High.
Methionine	Elevated in plasma.	Low.
Extra marker	None distinctive.	Methylmalonic aciduria with a methylcobalamin defect.
Psychiatric signature	Personality disorder, behavioural disturbance, depression, OCD.	Psychosis with the less severe MTHFR form.

TRAP **Assuming every homocystinuria raises methionine.** Homocysteine is high in all of them, so it cannot separate the mechanism groups. Methionine discriminates: high in the classical transsulfuration block, low where the defect lies in remethylating homocysteine back to methionine. Candidates lose the mark by reasoning from the disorder's name, which points only at homocysteine. Reason from the pathway: block the exit and substrate dams up behind it with the product it would have become; block the recycling arm and that product cannot be made at all.

Methylenetetrahydrofolate reductase is the one member with a population-level psychiatric footprint. The less severe form of the deficiency has been strongly associated with psychosis in adolescents and adults, possibly through alterations to dopamine synthesis and myelination, and the C677T variant, which causes a 35% reduction in enzyme function, is an independent risk factor for the development of psychosis. Read that **35%** correctly: it is the reduction in enzyme function attributable to the variant, not an effect size for psychosis risk.

The clinical course and MRI findings in the methionine synthetase and methylcobalamin disorders can resemble the childhood leukodystrophies, and neuropsychiatric symptoms figure most prominently among presenting symptoms in methylcobalamin deficiency, with delays of up to 13 years between onset of neuropsychiatric symptoms and the eventual diagnosis. A delay of **up to 13 years** is a career-length misdiagnosis in a treatable disorder. This is an inherited cofactor defect, not the acquired dietary deficiency set out where this chapter deals with vitamin B12 and folate deficiency.

IN INDIA

Access to the confirming test diverges here, not access to the drug. Every disorder in this section is confirmed by an assay a district or medical college laboratory does not perform: red cell porphobilinogen deaminase, arylsulfatase A in leukocytes or cultured fibroblasts, filipin staining, plasma methionine and homocysteine, gene sequencing. These are send-away tests routed to a handful of metabolic centres, with transport, cold chain and turnaround working against the referring psychiatrist, and largely paid out of pocket. Free bedside discriminators therefore carry disproportionate weight, and the porphyria specimen instruction becomes a live failure point rather than a formality, since a light-protected, correctly preserved 24-hour collection is hard to obtain reliably in a busy general hospital.

11.9 Pattern recognition: when to stop and think metabolic

The standard reference maps each storage and metabolic disorder to its characteristic psychiatric presentation, and psychosis and mood disorder recur across the storage disorder rows. They are not the whole group's vocabulary: the same table gives Wilson's disease personality change, rarely psychosis, and the large case series in classical homocystinuria report personality disorder, behavioural disturbance, depression and obsessive-compulsive disorder as the most common findings instead. The accompanying sign, never the psychiatric presentation alone, makes the diagnosis.

DISORDER	PSYCHIATRIC SIGNATURE	WHAT DISCRIMINATES IT
Acute intermittent porphyria	Psychotic episodes, depression, anxiety, delirium; episodic.	Abdominal pain, mostly motor neuropathy; urinary aminolevulinic acid and porphobilinogen.
Hereditary coproporphyria	Identical to acute intermittent porphyria.	Bullous lesions, skin fragility, scarring.
Metachromatic leukodystrophy	Psychosis.	White matter change sparing U-fibers; enzyme activity in leukocytes or fibroblasts.
Niemann-Pick type C	Mood disorder, psychosis.	Vertical gaze palsy, ataxia, hepatosplenomegaly; filipin staining.
Classical homocystinuria	Personality disorder, behavioural disturbance, depression, OCD.	Lens dislocation, Marfanoid habitus, thromboembolism; high plasma methionine.
GM2 gangliosidosis and adrenoleukodystrophy	Psychosis and mood disorder in both.	Named in the source summary only; not developed further here.

Wilson's disease belongs in the same reflex and is set out in full where this chapter deals with its copper metabolism, genetics and neuropsychiatric presentation, and separately with its investigation and management. Triggers for pausing a routine formulation: a first psychotic or manic episode in a young adult, treatment-resistant from the outset; any psychiatric syndrome with a movement disorder, gait abnormality, neuropathy or eye sign; unexplained abdominal

pain running with episodic disturbance; cognitive decline that does not recover between episodes; consanguinity or an affected sibling.

GOOD TO REMEMBER

A two-minute addition to the examination of any young adult with a first psychotic episode. Test voluntary vertical eye movements, particularly downgaze. Watch the patient walk. Look at the light-exposed skin. Ask about abdominal pain and consanguinity. None of it costs anything.

The metabolic diagnosis is made by the company the psychosis keeps: abdominal pain with a motor neuropathy means acute porphyria, vertical gaze palsy means Niemann-Pick type C, white matter change sparing the U-fibers means metachromatic leukodystrophy, and lens dislocation with a Marfanoid habitus means homocystinuria, in which high methionine marks the classical form and low methionine the remethylation defects.

12 · Wernicke encephalopathy and the Korsakoff boundary

This is the one condition in metabolic psychiatry where the correct response to uncertainty is to treat, not to test. A malnourished drinker is admitted confused. The house officer orders a computed tomography scan, waits for a normal report before settling on a diagnosis, and writes thiamine up for the morning drug round. Ordering the scan is reasonable; waiting on it is not, and the morning drug round is not defensible at all in an emergency this fragment treats as one. Both failures are the same failure: investigation and diagnostic uncertainty are allowed to set the hour at which treatment starts, and that deferral is the standard route to a permanent amnestic syndrome.

The chronic syndrome's phenomenology and prognosis belong to the Stroke, TBI, delirium and focal brain syndromes notes; the beri-beri syndromes belong where this chapter deals with pellagra and the other vitamin deficiency syndromes.

12.1 The disease, the vitamin and the three ways deficiency happens

Wernicke's encephalopathy is an acute and reversible neuropsychiatric condition resulting from thiamine deficiency, occurring mainly but not exclusively in people with alcohol use disorders who are malnourished, and also in those with malabsorption or with repeated vomiting and diarrhoea. Reversible is the source's own word, and the emergency logic rests on it.

Thiamine is an essential co-factor for many enzymes of the glycolytic and pentose phosphate pathways, so tissues wholly dependent on aerobic glucose metabolism, holding no reserve, decompensate first, which is why an encephalopathy rather than a myopathy presents. Deficiency arises by exactly three routes: low thiamine intake, impaired thiamine absorption, or impaired thiamine utilization. The first is the drinker whose diet has been displaced by alcohol, the second malabsorption and the gut complications of drinking, the third inherited susceptibility.

Kaplan and Sadock's Comprehensive Textbook of Psychiatry states that some people are at higher risk than others for this condition because of a genetically influenced transketolase

deficiency. Two patients drinking comparably need not both develop the syndrome: intake and absorption are necessary, not sufficient.

12.2 The classical triad, and how seldom it is complete

The syndrome is taught through its **classical triad**. Saunders and colleagues in Addiction medicine describe one or more symptoms or signs from the classical triad: oculomotor abnormalities, meaning nystagmus and ophthalmoplegia with paralysis or weakness most commonly affecting lateral or upward gaze and often with diplopia, reflecting the external recti as in a sixth nerve palsy; cerebellar dysfunction, meaning ataxia; and confusion of recent onset, with disorientation, inattention and poor responsiveness. The threshold is one or more of the three, not all three.

It has to be, because the complete triad is uncommon. The full triad is seen in only **16 to 20%** of cases, and the diagnosis is often missed. Autopsy data make the point from the other direction: Wernicke's pathology is 20 times more common than the classical triad, and is found in 12.5% of people who misuse alcohol and in 0.4 to 2.8% of the general population. Those two percentages are not interchangeable and neither should be quoted without its population attached. The cost of missing it: Wernicke's encephalopathy constitutes a medical emergency with an estimated mortality of 10 to 20% if untreated, and is easily reversible with the timely administration of adequate doses of parenteral thiamine.

16-20%	12.5%	10-20%	48-72 H
HAVE THE FULL TRIAD	AUTOPSY PATHOLOGY, ALCOHOL MISUSE	MORTALITY IF UNTREATED	WINDOW BEFORE IRREVERSIBILITY

12.3 Where the lesion sits, and what imaging can and cannot settle

The lesion is periventricular and paramedian. Tasman's Psychiatry records that the condition is characterised pathologically by haemorrhage in the **mammillary bodies** and the dorsomedial nuclei of the thalamus, with patients presenting clinically with delirium, with or without nystagmus and ataxia, and left with an amnesia once the delirium clears. Kaplan and Sadock name pathological alterations in the mammillary bodies and thalamus as the substrate of that amnesia; imaging of the combined syndrome adds a third structure: volume loss of the mammillary bodies, medial thalamus and periaqueductal grey matter. Delirium as a syndrome belongs to the Stroke, TBI, delirium and focal brain syndromes notes.

Imaging follows the anatomy, and its role is confirmatory. Where Wernicke's encephalopathy is clinically suspected, treatment with high-dose intravenous thiamine should commence before any investigations are carried out. A normal computed tomography scan of the brain does not rule out the diagnosis. Magnetic resonance imaging supports it by showing structural change in the region of the hippocampus, the mammillary bodies, the mammillothalamic tract and the thalamus.

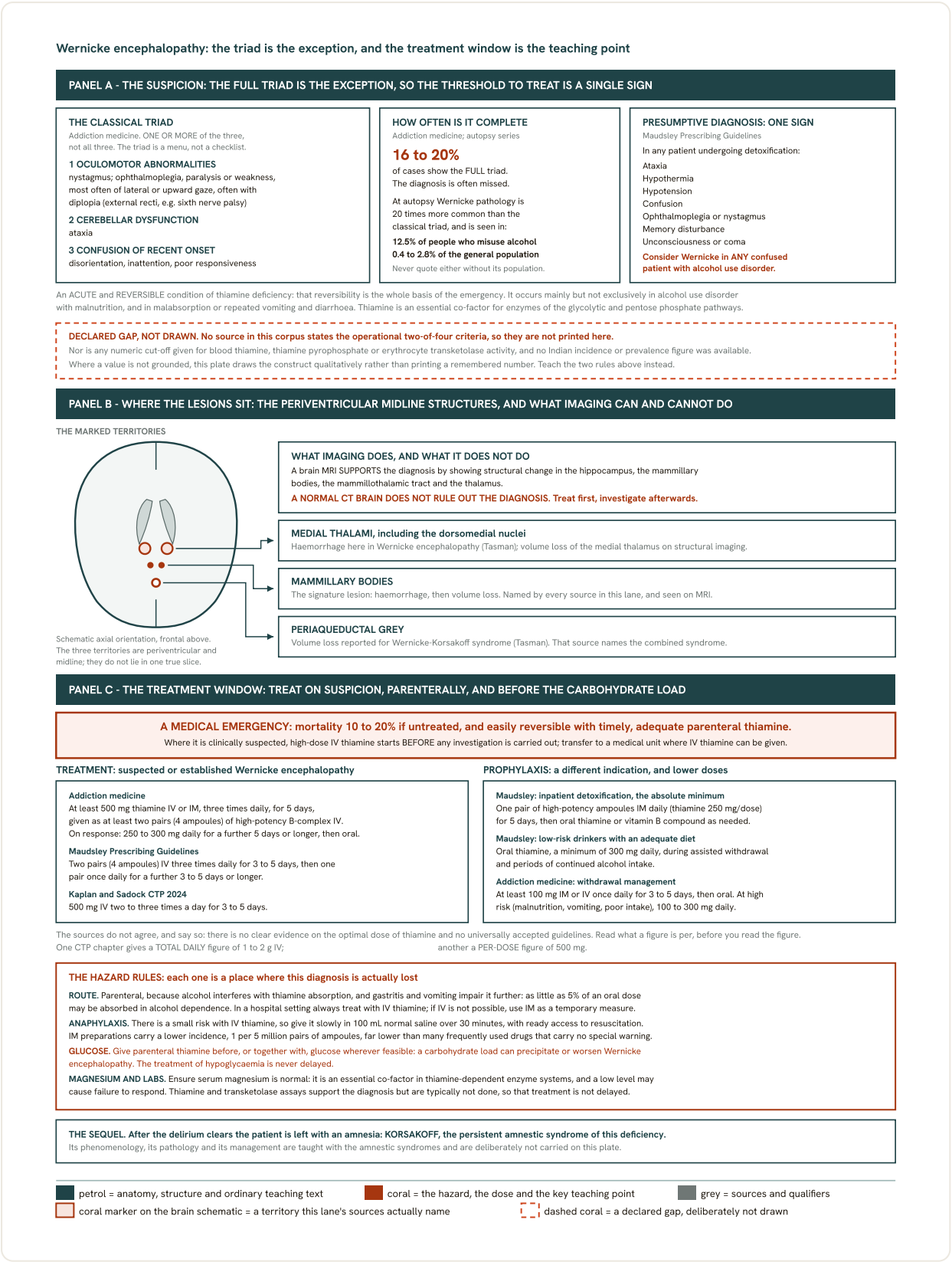

Fig 33.5 Wernicke encephalopathy: the classical triad, the periventricular midline territories, and the thiamine treatment window. The complete triad is the exception, so the threshold to treat is a single sign in a patient at risk, and treatment precedes investigation. Doses differ between sources and the sources say so; read the unit and the indication before the number, and never carry a prophylaxis dose across to treatment. Korsakoff, the persistent amnestic sequel, is named here and taught with the amnestic syndromes. (Addiction Medicine, Saunders et al.; The Maudsley Prescribing Guidelines; Kaplan and Sadock CTP 2024; Tasman, Psychiatry.)

12.4 Who to suspect it in, and the presumptive rule that replaces the triad

The operational threshold is therefore very low. Addiction medicine holds that there should be a high index of suspicion of Wernicke's encephalopathy and Wernicke-Korsakoff syndrome in patients with alcohol use disorders, and that the diagnosis should be considered in any confused patient with an alcohol use disorder until proved otherwise. The Maudsley Prescribing Guidelines convert suspicion into an explicit single-sign rule. Noting that the classical triad is rarely present and the syndrome is much more common than is recognised, they hold that a **presumptive diagnosis** should be made in any patient undergoing detoxification who experiences any one of the following:

- Ataxia, or ophthalmoplegia or nystagmus.
- Confusion, or memory disturbance.
- Hypothermia, or hypotension.
- Unconsciousness or coma.

Any history of malnutrition, recent weight loss, vomiting or diarrhoea, or peripheral neuropathy should also be noted. Hypothermia and hypotension are not in the triad at all, which is why the observations chart matters on a detoxification ward as much as the eye signs. The risk factors in alcohol dependence are acute withdrawal, malnourishment, decompensated liver disease, attendance at an emergency department, hospitalisation for a co-morbid condition, and homelessness. Three of those six are contextual rather than clinical: the syndrome concentrates where care is fragmented.

Kaufman's Clinical Neurology for Psychiatrists notes that thiamine deficiency, whatever its cause, generally leads to absent deep tendon reflexes and loss of position sensation, deficits that may remain asymptomatic unless the patient walks in the dark; in the Wernicke-Korsakoff syndrome, amnesia, dementia and cerebellar degeneration accompany the neuropathy associated with alcoholism. Hutchison's Clinical Methods tabulates the same vitamin B1 signature: nystagmus, sixth cranial nerve palsy and ataxia, with symmetrical peripheral neuropathy as the peripheral counterpart. The dementia syndrome and its workup belong to the Dementias and neurocognitive disorders notes.

12.5 Investigations: what confirms it, and why you will not wait

Addiction medicine is explicit about the thiamine assays: low blood thiamine or thiamine pyrophosphate levels and low **erythrocyte transketolase activity** support the diagnosis, but these are typically not done, because it is important not to delay treatment while awaiting the results. No numeric cut-off or reference range for any of the three appears in the standard references drawn on here: know the tests by name and by direction of abnormality, and quote no threshold value.

One laboratory value does change management. Serum magnesium should be checked and normalised, because magnesium is an essential co-factor in many thiamine-dependent enzyme systems and low magnesium levels may result in failure to respond to thiamine therapy.

PITFALL

Escalating the thiamine dose in a non-responder without ever checking a magnesium level. The reasoning feels sound: right diagnosis, therefore too low a dose. But in a malnourished drinker with vomiting and diarrhoea, hypomagnesaemia is close to expected, and non-response is not evidence against the diagnosis.

12.6 Three orders that must not be reversed

The route is not negotiable, and the reason is pharmacokinetic. In a hospital setting always treat with intravenous thiamine, because alcohol interferes with thiamine absorption and the medical complications of drinking, such as gastritis and vomiting, further impair it. As little as **5%** of an oral dose may be absorbed in alcohol dependence. If the intravenous route is not possible, use intramuscular thiamine as a temporary measure. Kaplan and Sadock supply the pharmacodynamic half: high-dose intravenous thiamine is currently considered superior to oral supplementation in preventing and treating Wernicke's, because high serum concentrations are needed to drive thiamine across the blood-brain barrier.

The second order is the one every examination tests. It is imperative that parenteral thiamine is given before a dextrose drip, because a carbohydrate load has the potential to precipitate or exacerbate Wernicke's encephalopathy. The Maudsley makes it a standing rule: as thiamine is required to utilise glucose, a glucose load in a thiamine-deficient patient can precipitate the encephalopathy, and parenteral B-complex must be given before glucose in all patients presenting with altered mental status. That clause is not restricted to known drinkers: those who most need it are the ones whose history is not yet known. Read both statements for what they are, which is an ordering rule. What each source fixes is which of the two goes in first, not whether the other is given at all. The third order was given above: treatment precedes investigation.

Note the limit of what these sources address. Both state the ordering rule and stop there. Neither takes up the patient who is at once thiamine-deficient and hypoglycaemic, and no claim drawn on in this fragment says what to do when a documented low glucose and an undrawn thiamine make their demands at the same moment. That silence is a gap in the sources, not a permission granted by them: nothing quoted above licenses withholding or delaying the treatment of hypoglycaemia, and a candidate should not read the ordering rule as though it did. Answer the examination question with the order the sources give. The competing case is a matter for acute medical practice and is settled by no sentence printed here.

MNEMONIC

Parenteral before oral, thiamine before glucose, treatment before tests. Sequence, not omission: these sources are silent on the patient who is also hypoglycaemic, and nothing in them permits delaying treatment of a documented low glucose.

RULE **Suspicion, not confirmation, is the threshold for treatment.** The triad is complete in a minority, autopsy prevalence far exceeds clinical diagnosis, untreated mortality is substantial, and the treatment is a water-soluble vitamin. Both prescribing sources therefore set the threshold at a single sign in a patient at risk rather than at a criterion count. Treat first, parenterally, before glucose and before imaging. Before is a statement about sequence, not about omission: it fixes which of two things goes in first, not whether the other is given.

12.7 Treating it: locus, focus and modus, and three regimens that disagree

LOCUS. The diagnosis is made wherever the confused drinker presents: emergency department, acute medical ward, consultation-liaison referral, detoxification unit. Treatment has one location: if Wernicke's encephalopathy is suspected, the patient should be transferred to a medical unit where intravenous thiamine can be administered. A psychiatric ward that cannot give intravenous thiamine with resuscitation cover is not a treatment location.

FOCUS. First hours: the encephalopathy itself, confusion, eye signs and ataxia, aiming at complete reversal. Next days: consolidating that response and correcting the co-factor deficiencies that limit it. Longer term: preventing relapse into deficiency and the amnestic sequel.

MODUS. The three standard references agree on the magnitude of parenteral dosing and on loading followed by continuation, and disagree on frequency and duration.

SOURCE	REGIMEN FOR SUSPECTED OR ESTABLISHED WERNICKE ENCEPHALOPATHY	WHAT DIFFERS
Addiction medicine	At least 500 mg of thiamine intravenously or intramuscularly, three times daily, for 5 days, given in the United Kingdom as at least two pairs of ampoules, that is four ampoules, of high-potency B-complex vitamins.	Frequency fixed; duration flat.
The Maudsley Prescribing Guidelines	On an acute medical ward, at least two pairs of high-potency intravenous ampoules, that is four ampoules, three times daily for 3 to 5 days, then one pair once daily for a further 3 to 5 days or longer, until no further response is seen.	Frequency fixed; duration a range.
Kaplan and Sadock, substance-use chapter	500 mg of intravenous thiamine two to three times a day for 3 to 5 days, or 100 mg of oral thiamine a day usually given for many months.	Frequency given as a band; a per-dose figure in milligrams.
Kaplan and Sadock, amnestic-disorders chapter	High doses of thiamine, 1 to 2 g intravenously daily.	A total daily figure in grams.

The continuation phase is more consistent. If it responds, Addiction medicine continues with 250 to 300 mg of thiamine daily for another 5 days, or longer if improvement continues, followed

by oral thiamine and multivitamin supplementation thereafter and as an outpatient, adding that for patients with enduring ataxia, polyneuritis or memory disturbance, high-potency vitamins should be given for as long as improvement continues. That rider makes continued improvement, not the calendar, the stopping rule.

TRAP **Answering as though one of these regimens is the regimen.** A stem offering four dose options and expecting one is testing a consensus that does not exist. Addiction medicine says there is no clear evidence on the optimal dose and no universally accepted guidelines; the Maudsley notes insufficient randomised evidence as to best dose, frequency or duration. One textbook even holds two formulations, milligrams per dose in one chapter and grams per day in another. Do not average them or silently pick one: state the magnitude, give each source's frequency and duration, and name the absence of consensus.

12.8 Prophylaxis, and a minimum that two sources set differently

Most thiamine given in psychiatry is preventive, and dosing is tiered by risk and route.

INDICATION	REGIMEN AS STATED	SOURCE
Prophylaxis, low-risk drinker with adequate diet and no neuropsychiatric complications	A minimum of 300 mg of oral thiamine daily during assisted alcohol withdrawal and periods of continued alcohol intake.	The Maudsley Prescribing Guidelines
Prophylaxis, inpatient alcohol detoxification	One pair of high-potency intramuscular ampoules daily, containing thiamine 250 mg per dose, for 5 days, then oral thiamine or vitamin B compound as needed; stated as the absolute minimum for all inpatients.	The Maudsley Prescribing Guidelines
Prophylaxis, alcohol withdrawal management	At least 100 mg of thiamine intramuscularly or intravenously once daily for 3 to 5 days then orally, or at least 300 mg of thiamine per day orally, maintained on oral thiamine 100 mg daily with multivitamins.	Addiction medicine
Prophylaxis, patient at high risk of Wernicke encephalopathy	In malnutrition, vomiting or poor oral intake, 100 to 300 mg daily of intramuscular or intravenous thiamine, with the warning that these are prevention doses and higher doses are used for treatment.	Addiction medicine

Both sources cost a pair of high-potency ampoules at the same 250 mg of thiamine per dose, so the disagreement is about the recommended floor, not the product. Their oral arms agree exactly.

TRAP **Quoting a prophylactic minimum as though there were one, or using a prevention dose to treat.** The Maudsley calls its inpatient parenteral regimen an absolute minimum for all inpatients; Addiction medicine calls its own, materially lower per dose, a minimum too. Both are grounded, so a stem asking for the minimum parenteral prophylactic dose has more than one defensible answer. The second error is worse clinically: a patient with a single presumptive sign has crossed into the treatment column, and the dose must cross with them.

IN INDIA

No Indian incidence or prevalence figure for Wernicke's encephalopathy appears in these standard references, so every epidemiological number above comes from Western autopsy and clinical series and should not be silently naturalised. Both prescribing sources dose in pairs of a United Kingdom high-potency parenteral B-complex preparation and name no Indian equivalent. Prescribe in milligrams of thiamine with route and frequency written out, using the sources' own figure of one pair containing thiamine 250 mg per dose, rather than an ampoule count the ward stock will not match. A normal computed tomography scan does not exclude the diagnosis, which weighs more where magnetic resonance imaging means a wait, a transfer and an out-of-pocket cost. Give the thiamine while the scan is being arranged.

12.9 The boundary: the reversible window and its irreversible sequel

Everything above earns its urgency from one sentence about time. Addiction medicine states that most patients who do not recover promptly within the first **48 to 72 hours** develop Korsakoff's syndrome with irreversible memory loss. Note what the source does not say: whether the window runs from symptom onset or from the start of thiamine. Neither should a candidate. It fixes the scale, days rather than weeks.

On the far side sits **Korsakoff's syndrome**, described as a persistent alcohol-induced amnestic confabulatory neurocognitive disorder and a sequel to untreated or inadequately treated Wernicke's encephalopathy, with an estimated 20% of affected individuals requiring long-term institutionalised care. Undertreatment is what the source blames: an oral prescription or a course stopped early is itself a mechanism of the chronic syndrome. The Maudsley states it bluntly: if untreated, Wernicke's encephalopathy progresses to Korsakoff's syndrome. Tasman adds the nosological caution that although the term is often used for all cases of chronic anterograde amnesia with a retrograde component, it is properly reserved for the form occurring secondary to thiamine deficiency. The syndrome in full belongs to the Stroke, TBI, delirium and focal brain syndromes notes.

The boundary is pharmacological as well as temporal: high-dose intravenous thiamine is likely to partially or completely reverse Wernicke encephalopathy, but its benefits in the chronic stages are not established. That asymmetry is why the acute intervention is framed as prophylaxis against the irreversible sequel: patients in alcohol withdrawal with suspected Wernicke encephalopathy should be given high-dose thiamine intramuscularly or intravenously, since oral absorption is very poor, to prevent progression to Korsakoff syndrome, and more broadly prevention of cognitive impairment is possible in those at risk of thiamine deficiency, from long-standing

alcohol misuse or severe malnutrition, through vitamin B1 given particularly in intravenous form.

Symptoms of Wernicke's encephalopathy may be mixed with those of Korsakoff's syndrome as a result of repeated episodes of clinical or subclinical thiamine deficiency, which is why the combined term **Wernicke Korsakoff syndrome** exists at all. The boundary is therefore a gradient rather than a line, and each unremarked episode moves the patient along it before anyone has recorded a sign.

TRAP **Quoting a single recovery figure for the Korsakoff amnestic syndrome.** Kaplan and Sadock's amnestic-disorders chapter states that about 25% of patients with Korsakoff syndrome recover, while the rest continue to suffer varying degrees of memory impairment and a significant minority need permanent placement, and Tasman corroborates it exactly: on long-term follow-up about one-quarter eventually recover, half show some improvement, and in the remaining quarter none is seen. The same textbook's substance-use chapter, however, calls the syndrome permanent in at least a partial form in about 50% of the people affected, implying a very different recovery rate. Two of the three readings agree, so print that distribution and name the substance-use chapter's wording as the discrepant reading rather than suppressing it.

GOOD TO REMEMBER

Do not let the anaphylaxis warning become a reason to withhold or to delay. There is a small risk of anaphylaxis with intravenous thiamine, so slow administration in 100 mL of normal saline over 30 minutes is recommended, with ready access to resuscitation measures; intramuscular preparations carry a lower incidence than intravenous ones, at 1 per 5 million pairs of ampoules, far lower than many frequently used drugs that carry no special warning.

Wernicke's encephalopathy is an acute, reversible thiamine-deficiency emergency in which the complete triad appears in a minority, so treat any confused patient at risk on a single sign with high-dose parenteral thiamine, before glucose and before imaging, check the magnesium if there is no response, and note that most of those not recovering promptly within the first 48 to 72 hours go on to the permanent amnestic syndrome thiamine can no longer reverse. Before means sequence, not omission: on the patient who is at once thiamine-deficient and hypoglycaemic the sources are silent, and nothing here licenses delaying treatment of a documented low glucose.

13 · Vitamin B12 and folate deficiency: cognitive and psychiatric manifestations

These two vitamins are the reason a psychiatrist orders blood tests at all. They are the standing example of a treatable cause of psychiatric illness hiding inside an ordinary presentation. Both are cofactors in the same stretch of one-carbon chemistry, both produce a macrocytic marrow, both produce cognitive and affective change, and only one of them damages the spinal cord. Everything examinable descends from that asymmetry.

The marks sit in four places: a phenotype wide enough to fit almost any primary psychiatric disorder; a laboratory of non-interchangeable thresholds and a confirmatory metabolite; the

discrimination between the two deficiencies; and treatment, where the classic error is a right drug given alone.

200-250 pg/mL	400 pg/mL	1.5% TO 15%	ABOUT 20%
B12 LABORATORY LOWER LIMIT	SCREEN-FURTHER THRESHOLD	B12 DEFICIENCY, OLDER ADULTS	FOLATE INSUFFICIENCY, US SURVEY DATA

13.1 Two vitamins, one stretch of chemistry

Folate matters to psychiatry entirely as an enzymatic cofactor, and the processes it serves are neuropsychiatric ones: neurotransmitter synthesis, central nervous system phospholipid synthesis, and homocysteine metabolism. B12 works alongside it in the same reactions, which is why the two deficiencies overlap so heavily in the blood and in the mind. That overlap is the mechanism, not a nuisance.

When B12 is absent the reactions it serves stall and their substrates accumulate, so that both homocysteine and methylmalonic acid rise. That is the entire basis of confirmatory testing: a metabolite piling up behind a blocked step is a more faithful witness to functional deficiency than the circulating vitamin. And because folate can substitute for B12 in one reaction but not the other, giving folate alone repairs part of the picture and lets the rest progress.

The supply routes differ, and the difference is load-bearing. B12 is essentially found only in animal products, and deficiency can arise either from decreased intake or from failure of absorption, since intrinsic factor is a gastric protein required to facilitate dietary absorption. One dietary class plus an obligatory gastric chaperone gives two independent failure modes, and a history establishing one does not exclude the other. Folate has no such chaperone, so its deficiency is driven by intake, demand and drugs rather than anatomy.

13.2 Who becomes deficient

Learn the two risk profiles separately, because they overlap less than the clinical pictures do. For B12, risk rises with older age, a vegan or vegetarian diet, pernicious anaemia, the malabsorption syndromes, and chronic use of metformin, proton-pump inhibitors and histamine-2 receptor antagonists. The drug triad deserves attention: all three are prescribed long term, for reasons unrelated to the nervous system, and none is likely to be flagged as a neuropsychiatric risk. The malabsorptive causes group anatomically.

- Gastric bypass surgery
- Inflammatory bowel disease
- Celiac disease
- Small intestinal bacterial overgrowth
- Ileal resection

The yield of testing older patients is real: estimates of B12 deficiency in older adults range from 1.5% to 15%, and low B12 status has been linked to depression and cognitive dysfunction. Treating this as a disease of the elderly is now questionable, because deficiency may be increasing in younger adults, and the Framingham Offspring Study found similar deficiency rates across the

age bands 26 to 49 years, 50 to 64 years, and 65 years and older. Read that precisely: it does not extend the prevalence band to the young, it says the assumed age gradient was absent in that dataset.

Folate runs on different drivers: inadequate diet, excessive alcohol intake, women of childbearing age, non-Hispanic black women, pregnancy, dialysis, celiac disease, inflammatory bowel disease, and methylenetetrahydrofolate reductase gene mutation. Two psychiatric populations are picked out there without being named: low folate levels are found in patients who abuse alcohol or who have poor nutrition, which covers much of any general caseload, and two drugs are specified: methotrexate and phenytoin can both lead to folate deficiency. The methotrexate link is firm enough that a standard clinical-methods text lists it as the named deficiency syndrome for folic acid, with macrocytic anaemia, thrombocytopenia and a megaloblastic bone marrow as the principal signs.

13.3 The psychiatric presentation

The psychiatric syndrome of B12 deficiency has no signature. What it has is breadth: depression, irritability, insomnia, cognitive slowing and psychosis. Every item is an ordinary reason for referral and no combination of them points at a vitamin. Folate produces a narrower version, with cognitive impairment and depression as its symptoms, and low folate levels associated with major depressive disorder, dementia and schizophrenia. Across both vitamins the nutritional deficiencies have been implicated in dementia, delirium, psychosis, fatigue and personality changes.

A list that wide is useless as a prompt and valuable as a rule. If no phenotype triggers the test, something else must: age, the drug list, the diet, or policy for unexplained presentations. Delirium as a syndrome belongs to the Stroke, TBI, delirium and focal brain syndromes notes; what this topic supplies is the correctable nutritional cause sitting behind a share of it.

> **GOOD TO REMEMBER**
>
> Personality change is the item most often handled as a formulation rather than a symptom. Relatives describing a patient as irritable, apathetic and unlike themselves over months, with disturbed sleep and slowed thinking, present a shape that attracts an interpretive explanation more readily than a blood test. Either vitamin can produce it.

13.4 The nervous system and the blood: what B12 damages

The neurology is what separates B12 from folate, and it is best held anatomically. B12 deficiency affects multiple levels of the nervous system, and may present as peripheral neuropathy, myelopathy, or a cognitive syndrome. The underlying lesion is demyelinating: B12 deficiency causes demyelination in the posterior tracts of the spinal cord, in the cerebrum and in other areas of the central nervous system, and it causes dementia and a peripheral neuropathy. Name the tract and you have the cord syndrome, the neuropathy, and the reason the two coexist.

The named cord syndrome is **subacute combined degeneration of the spine**, which travels in the standard tables with **macrocytic anaemia** under the deficiency syndrome **pernicious**

anaemia. That triad is the classical teaching picture, correct as far as it goes; its limitation is the subject of the next section.

Absorptive failure dominates in practice. B12 deficiency is usually the result of poor absorption due to pernicious anaemia or gastric disease, the clinical expression of the point about **intrinsic factor**. It also predicts something counter-intuitive: if the lesion is absorptive, oral repletion ought to fail. Why it does not is taken up under management.

13.5 Cognitive decline, and how far it reverses

This is where the received teaching is least reliable. Two propositions are carried forward together and both need qualifying. The first is that macrocytosis is the tripwire. It is not: B12 deficiency is often suggested by the presence of a macrocytic anaemia, but B12 deficiency dementia may occur in the absence of both macrocytosis and anaemia. The same holds on the other side, where folic acid deficiency is a very rare cause of dementia which likewise can occur in the absence of anaemia. A normal full blood count excludes neither, and this is the commonest route by which the diagnosis is lost.

The second proposition is reversibility, more heavily qualified than most candidates expect. Although neurologists often cite B12 deficiency as the quintessential cause of "reversible dementia", several studies have found that the dementia resists B12 repletion. Hold both halves: the disease belongs on every list of treatable causes of cognitive decline, but the promise that treating it restores cognition is not one the literature fully honours. That argues for testing early, not against testing. The dementia syndrome and its workup belong to the Dementias and neurocognitive disorders notes, and cognitive instruments to the Psychotherapies, clinical assessment, MSE and nosology notes; this topic owns the disease, its cognitive signature and the limits of its reversibility.

> **PITFALL**
>
> Ordering a full blood count as the screen for B12 deficiency in a patient with cognitive decline. The error is logical: the classical association is haematological, and a normal mean corpuscular volume feels like reassurance. It is not, because the deficiency dementia occurs without macrocytosis and without anaemia. If the question is neuropsychiatric, the assay has to be the vitamin.

13.6 Reading the laboratory: which threshold does which job

Marks are lost here by treating several different numbers as one cut-off. B12 status is measured in serum or plasma, with **200 to 250 pg/mL** as the lower limits used by most laboratories, while some suggest that levels up to 400 pg/mL should be screened further for deficiency. The higher figure exists precisely because a value inside the reference interval does not exclude functional deficiency.

Folate has its own set. Deficiency is defined as a serum folate below **3 ng/mL**, while **folate insufficiency** sits at approximately below 7 ng/mL, a level that matters because insufficiency in women of childbearing age is a risk factor for neural tube defects in offspring. A pharmacology reference adds the exclusion figure and the red cell measure.

VALUE	WHAT IT IS	WHAT IT IS NOT
B12 200 to 250 pg/mL	Laboratory lower limit of normal	Not a functional deficiency threshold
B12 400 pg/mL	Threshold for screening further	Not a diagnosis, not a treatment trigger
Serum folate below 3 ng/mL	The definition of folate deficiency	Not applicable to red cell folate
Serum folate approximately below 7 ng/mL	Folate insufficiency, carrying the neural tube defect risk	Not the deficiency definition
Serum folate above 5.0 ng/mL	Level above which folate deficiency can be excluded, though 2% to 5% of healthy adults fall below it	Not a target, not a deficiency cut-off
Red cell folate above 140 ng/mL	Reference range for chronic folate status, less affected by acute ingestion than the serum level but more time consuming and costly to measure	Not a deficiency cut-off; none is stated here

The last row carries an examinable absence: the serum figures cannot be transposed onto red cell folate, because the two measure different things over different timescales.

13.7 The metabolic intermediaries, and what each discriminates

When the vitamin level is equivocal the question moves from concentration to function. Sensitivity in determining B12 deficiency may be enhanced by measuring intermediate metabolites such as methylmalonic acid and serum homocysteine. The indication is specific: they are useful particularly when vitamin levels are in a borderline range where deficiency cannot definitely be ruled in or out. They are not a first-line screen.

The discriminating rule is the one thing here that must be automatic. B12 and red blood cell folate levels constitute the screening tests, followed up by homocysteine and methylmalonic acid: homocysteine is elevated in both B12 and folic acid deficiency, while methylmalonic acid is elevated in B12 deficiency alone. A pharmacology reference states the same independently, that **serum homocysteine** is elevated in both while **serum methylmalonic acid** is elevated only in B12 deficiency, and it follows mechanically from the coenzyme chemistry above.

MNEMONIC

Both rise together; methylmalonic rises alone

Homocysteine is the shared metabolite and rises in either deficiency, so it says something in the pathway is missing but not which. Methylmalonic acid sits behind a step only B12 serves, so a rise points at B12 specifically.

For the confirmatory figure, one source gives an explicit boundary: in borderline cases methylmalonic acid is recommended as a more sensitive measure of B12 status, with an elevated

level above **0.271 micromol/L** serving as a reliable cut-off indicating deficiency. A second standard reference prints an upper reference limit for the same analyte falling immediately below that value.

TRAP **Reading a reference limit as a diagnostic cut-off because the two numbers coincide.** Kaplan and Sadock give a cut-off for methylmalonic acid, above which deficiency is indicated. Goodman and Gilman give an upper reference limit for the same analyte, landing in essentially the same place. The coincidence looks like corroboration. It corroborates a number, not a category: a reference limit comes from a healthy population and answers whether a result is unusual, a cut-off is derived against a diagnosis and answers whether it means deficiency. A stem offering one and asking for the other is testing exactly this. A second layer: the printed units for these metabolite ranges differ between the two texts by orders of magnitude, a typesetting artefact rather than a disagreement about biology.

No numeric homocysteine threshold appears in this chapter, and the omission is deliberate: the available reference figures carry units irreconcilable with any clinical assay as printed, and the alternative candidate value sits in a text fragment whose subject cannot be established. Learn the direction, not a number.

13.8 Management: repletion, the masking trap, and folate in depression

LOCUS. Almost all of this is outpatient: detection in clinic while investigating cognitive change, treatment-resistant depression or an unexplained psychosis, and repletion in clinic too. Inpatient care is driven by the psychiatric syndrome rather than the vitamin, principally the psychotic and confusional presentations. There is no emergency limb here as the encephalopathies have one, but there is a time limb: the cord and the cognitive syndrome do not wait for a convenient appointment.

FOCUS. Acutely the target is the deficiency, not the psychiatric symptom, which is downstream. In the short term it is the cause, since a dietary deficiency, an absorptive failure and a drug effect need different follow-ups. In the medium term it is the neurological deficit, watched with the reversibility caveat in mind. In the long term it is maintenance: an absorptive lesion does not resolve, and a patient who stays on the offending drug stays at risk.

MODUS. Two evidence anchors carry the pharmacological limb, both frequently misquoted. For repletion in vitamin B12 deficiency, a 2018 Cochrane review graded the evidence low quality and found that daily oral supplementation at **1,000 to 2,000 mcg per day** is as efficacious and safe as, and potentially more cost-effective than, intramuscular supplementation. The grading is part of the finding. The parenteral route keeps a role where repletion must be rapid: rapid repletion of vitamin B12 is usually accomplished by intramuscular administration daily for a week, then weekly for the first month, followed by monthly maintenance therapy. The schedule is the examinable part; the quantity attached to it in the source cannot be reconciled with any plausible clinical dose and is therefore not printed rather than silently corrected from memory. The paradox of treating an absorptive disease by mouth resolves cleanly, since chronic oral repletion is possible even in patients with low intrinsic factor activity, through a low-affinity uptake mechanism.

RULE **Never replete folate in a patient whose B12 status is unknown.** In the absence of B12, which acts as a coenzyme, homocysteine and methylmalonic acid accumulate. Administration of folate, which also acts as a coenzyme, alleviates some features of B12 deficiency such as the megaloblastic anaemia; but without concomitant administration of B12, folate will not prevent subacute combined degeneration. The clinical shape is what makes it dangerous: the blood count improves, the patient looks treated, and the cord goes on demyelinating underneath a corrected haemoglobin. Treat a haematological response as no evidence at all about the nervous system.

Folate has a second, distinct indication, and the two must not be run together. As augmentation in major depressive disorder, a meta-analysis of nine randomised controlled trials with 1,061 participants found folate adjunctive to antidepressant therapy improved depressive symptoms in adults with major depressive disorder with a small effect size, and raised the remission rate, with remission induced in 48% of the folate group against 27% on placebo. The strategies used were folic acid 0.5 to 10 mg per day and **L-methylfolate** at 15 mg per day, over a mean study duration of 15.2 weeks. Antidepressant pharmacology and the sequencing of augmentation belong to the Mood disorders: pharmacotherapy notes; what belongs here is that this is a nutritional agent used pharmacologically and it is not risk-free, since L-methylfolate at 15 mg per day for depressive augmentation has triggered irritability and agitation in a few reported cases, one of them in a patient with bipolar disorder type 1.

There is an upper bound, and its rationale closes the loop with the masking trap: the Food and Nutrition Board at the National Academies of Sciences, Engineering, and Medicine has set an upper limit for supplemental folate in adults over 19 years, one stated reason being that folate can mask B12 deficiency. The quantity is not printed here. The figure as the source gives it carries the same order-of-magnitude unit problem already flagged for the parenteral B12 dose, and a gram-for-milligram slip overstates a safety ceiling a thousandfold, so this limit is carried as a principle and its value read off a current dietary reference intake table rather than reproduced on trust. What is examinable is the existence of a ceiling and the reason for it, which is the masking rule again in another guise. The psychological and social modes are brief but not trivial, since adherence to lifelong maintenance is a different problem from adherence to a short course.

IN INDIA

Two numbers on this page are population-bound. The rarity of frank folate deficiency in the source literature is a post-fortification finding: folate deficiency is rare in the United States because of the 1996 Food and Drug Administration mandate requiring folate supplementation of enriched grain products, completed in 1998, and the insufficiency rate quoted earlier comes from that same fortified population. Neither transfers to a population without an equivalent long-standing nationwide grain-fortification programme, and quoting either as a general fact quotes a policy outcome as a biological one. The B12 side runs the other way: a vegan or vegetarian diet is a listed risk factor and B12 is essentially found only in animal products, so where lifelong vegetarianism is common, dietary deficiency is a far more available explanation than the absorptive causes dominating Western teaching. Practically, serum B12 is cheap and widely available across Indian laboratories while methylmalonic acid is a send-out in most centres at a cost the patient meets, so the borderline-value pathway is often settled on clinical grounds and a therapeutic trial instead. Where the metabolite is unaffordable, record that rather than filing a borderline B12 as normal.

Homocysteine rises in both B12 and folate deficiency while methylmalonic acid rises in B12 deficiency alone; B12 deficiency dementia occurs without macrocytosis and without anaemia, so a normal blood count excludes nothing; and folate given without B12 corrects the anaemia while the cord degenerates.

14 · Pellagra and other vitamin deficiency syndromes

These are the diagnoses where being right still changes the outcome. A patient whose cognition, mood or conduct is deteriorating because a vitamin is missing recovers when it is replaced and not when it is not, and the window is finite. Two features make the group harder than it looks: each syndrome is named after its complete, textbook form, which is the form you will least often meet, and deficiencies travel in company, so the vitamin you identify is seldom the only one absent.

6D85.8	15 DAYS	UNDER 20 NG/ML	SMD 0.58
ICD-11 DEMENTIA DUE TO PELLAGRA	HALF-LIFE OF 25(OH)D	VITAMIN D DEFICIENCY	VITAMIN D IN UNIPOLAR DEPRESSION

14.1 Pellagra: the name, the triad and the third D that keeps moving

Pellagra takes its name from the skin, not the brain: the word is Italian for rough skin, from pelle for skin and agro for rough. The standard neurology text for psychiatrists calls it a starvation-induced disorder, which locates it among conditions of deprivation, not primary neurological disease.

MNEMONIC

Dementia, dermatitis, diarrhoea

The three Ds. An aide-memoire for which three systems to examine, not a checklist to satisfy before the diagnosis can be entertained. Skin, gut and brain are involved because niacin sits in the energy metabolism of tissues with high turnover.

The third D is the one to watch, because the sources do not print the same word. The neurology text gives dementia in its own account of the triad and, in a worked clinical answer elsewhere in the same book, dermatitis, diarrhoea and delirium; the psychiatric glossary sidesteps the choice and defines the syndrome as diarrhoea, dermatitis and mental disturbance. These are not three competing facts but one fact at three levels of resolution. That book's own neuropsychiatric shorthand puts both words side by side, giving pellagra with delirium and dementia, because niacin deficiency produces a diffuse encephalopathy that can present acutely and fluctuantly, or insidiously and persistently. Delirium as a syndrome and its workup belong to the Stroke, TBI, delirium and focal brain syndromes notes, the dementia syndrome and its investigation to the Dementias and neurocognitive disorders notes. An examiner writing dementia and one writing delirium are both quoting a real source.

14.2 The incomplete triad, and the skin that gives it away

Chronic niacin deficiency produces the classic picture through the gradual onset of the three Ds, with dermatitis on sun-exposed areas, but in most cases of **pellagrinous dementia** only one of the other Ds is present, as with the classical triad of thiamine deficiency: a general property of nutritional encephalopathies, not a quirk of one disease.

In most patients with pellagrinous dementia the triad is incomplete: only one of the other two Ds accompanies the cognitive syndrome, so a normal gut or normal skin excludes nothing.

RULE **These syndromes are diagnosed from context, not from completeness.** The diet, the alcohol history, the drug list and the socioeconomic circumstances carry more weight than the number of classical features present. Anyone who waits for the full triad before naming pellagra will miss most of the pellagra.

The skin is the best single clue when present. The rash is necklace-like: dermatitis of sun-exposed areas including **Casal's necklace** heads the clinical methods list of signs, which also includes dementia, poor appetite, difficulty sleeping and diarrhoea. Poor appetite and disturbed sleep matter for psychiatry: they are the complaints that route a malnourished patient into a psychiatric clinic with a provisional label of depression. The photosensitive distribution is the discriminator: a rash respecting the collar line, the backs of the hands and the face is describing sunlight, and sunlight plus cognitive decline plus a deprived diet is specific enough to act on.

14.3 Where it comes from: maize, tryptophan, alcohol and isoniazid

The historical account is dietary. Pellagra was endemic in the rural southeastern United States in the early 1900s and results from the absence of niacin from the diet; the population affected there subsisted on maize, which lacks niacin and also lacks its precursor, tryptophan. The second clause is the half candidates drop. A diet deficient in niacin can still hold if it supplies enough of the amino acid precursor, so a staple poor in both is far more dangerous than one poor in only one. **Tryptophan** is why niacin requirement is not a fixed quantity.

Three routes bring a modern patient to the same place.

- Deprivation and alcohol. The condition is described as typically found only in malnourished people with alcohol use disorder, and the mechanism is doubled: alongside dietary deficiency, niacin absorption is itself impaired in chronic alcohol dependence.
- Drugs. Isoniazid can also cause pellagra.
- Company. Other B vitamin deficiencies are often associated, and anaemia and hypoproteinaemia are common in pellagra; with nutritional deprivation, Wernicke-Korsakoff disease may be comorbid with it. Both of those have their own homes, in this chapter and in the Stroke, TBI, delirium and focal brain syndromes notes.

IN INDIA

The drug cause is the divergence that matters. Where anti-tuberculosis treatment is commonplace, isoniazid is not a curiosity at the end of an aetiology list but the exposure most likely to be in your patient's current prescription. The same drug is named in the clinical methods literature as the agent associated with pyridoxine deficiency, so one medication reaches into both halves of this section. Take a tuberculosis treatment history in any patient presenting with an encephalopathy, a photosensitive rash or a peripheral neuropathy. The second point is an absence: the sources used here give no Indian prevalence figure for pellagra or vitamin D deficiency, so no local rate is quoted.

14.4 The niacin attribution, and the argument that has not been settled

Almost every source treats pellagra and niacin deficiency as the same statement. The psychiatric glossary defines the disease as a deficiency of niacin, that is nicotinamide; the clinical methods table lists pellagra as the deficiency syndrome of vitamin B3, niacin, nicotinic acid; the general psychiatry text has chronic niacin deficiency causing pellagra. The international classification goes furthest, giving dementia due to pellagra its own code, the only nutritional deficiency so distinguished. When a diagnostic system carves out a code, it has committed to the aetiology.

One text dissents. The neurology reference for psychiatrists records that, despite pellagra's status as a classic illness, the role of niacin deficiency has been challenged, with deficiencies of other nutrients either co-existing with it or being more likely to be the actual cause. The same book hedges in its own definition, writing that niacin deficiency is associated with or causes pellagra, then elsewhere states flatly that the disease results from absence of niacin in the diet. The challenge is not even internally consistent within the book that raises it.

TRAP **Treating the niacin attribution as either settled beyond question or as discredited.** Both readings are available in the standard texts and both are wrong as absolute statements. The position that survives an examiner from either camp is that niacin deficiency is the established and codified account, that a serious source questions its sufficiency because these patients are rarely deficient in one nutrient alone, and that this is precisely why treatment is not niacin alone.

14.5 Managing pellagra

LOCUS. Most pellagra is treated where the patient already is: the general medical ward for the acutely encephalopathic or dehydrated, the psychiatric inpatient unit for those admitted for the mental state and found malnourished, the outpatient clinic for prophylaxis in someone at risk. What does not work is a psychiatric admission where nutrition is somebody else's problem.

FOCUS. Acutely, the target is the encephalopathy and the systemic deficit, alongside any comorbid thiamine-responsive illness. In the short and medium term it is the rash, the diarrhoea and the reversal of cognitive impairment, with the anaemia and hypoproteinaemia that accompany the disease. Long term it is the cause: an alcohol use disorder, a monotonous cereal-based diet, or a drug exposure that will reproduce the illness once replacement stops.

MODUS. The pharmacological mode is vitamin replacement and it is deliberately plural: the treatment of pellagra is niacin, and physicians usually add thiamine and other nutrients to the medical regimen: a patient malnourished enough to develop pellagra needs more than one vitamin. Preparations exist as **nicotinamide** as well as nicotinic acid, and the daily nutritional requirement of niacin, which is not a treatment figure, is given as **20 mg per day**. Without a change in diet, drinking or supervision, replacement is temporary.

On the treatment dose this chapter prints one source's figures and says so. For established pellagra the pharmacology text gives **200 to 500 mg per day** in divided doses, orally or parenterally, and for prophylaxis in people at risk 20 to 50 mg per day by mouth. No other reference consulted here states any niacin dose for pellagra: the neurology text says only that the treatment is niacin, and the general psychiatry and clinical methods texts give no figure. Treat those numbers as uncorroborated and check them against your formulary before prescribing.

PITFALL

Correcting one vitamin and considering the patient treated. The error is not a wrong diagnosis but an incomplete correction: niacin is given, the rash improves, the cognitive state improves partially, and the residual deficit is attributed to an established dementia or to alcohol-related brain damage. Since other B vitamin deficiencies frequently accompany pellagra and thiamine-responsive disease may be comorbid, a partial response is first a question about what else is missing and only later about irreversibility.

14.6 Pyridoxine: two clinical facts and one drug

This section is short because the evidence base is: the standard texts that spend pages on pellagra give pyridoxine two lines. Both are worth knowing exactly.

VITAMIN	DEFICIENCY SYNDROME	PRINCIPAL FEATURES NAMED
B3, niacin, nicotinic acid	Pellagra	Dermatitis of sun-exposed areas including Casal's necklace, dementia, poor appetite, difficulty sleeping, diarrhoea
B6, pyridoxine	Deficiency associated with isoniazid use	Poor appetite, lassitude, oxaluria, seborrhoea, neuropathy
D, ergocalciferol and cholecalciferol	Rickets and osteomalacia	Bone pain, proximal myopathy, waddling gait, growth retardation

The neuropsychiatric shorthand is the first fact: **pyridoxine deficiency** causes a neuropathy and seizures. Set beside the niacin sentence it gives a clean discrimination for a viva: niacin deficiency produces a diffuse encephalopathy with skin and gut involvement, pyridoxine deficiency a peripheral nerve and seizure threshold problem, without the rash and without a dementia.

The second fact is the drug association, and where the chapter deliberately stops. The clinical methods table names isoniazid as the cause and prints no prophylactic pyridoxine dose. The pharmacology literature consulted here carries a pyridoxine figure, but it is stated for sideroblastic abnormality rather than neuropathy prophylaxis, so it is the wrong indication as well as an unreliable read. No number is therefore given for pyridoxine, in either deficiency or prophylaxis: a plausible remembered dose in a revision text is how a wrong figure enters a resident's answer and stays there. Know the association, know that co-prescription with isoniazid is standard practice, and take the dose from your national programme guidance.

14.7 Vitamin D: the biomarker, the bands and the trap inside them

Vitamin D is the deficiency a psychiatrist is now most likely to be asked about, and it behaves differently from the B vitamins. Its named deficiency syndromes are skeletal, rickets in the growing skeleton and **osteomalacia** in the mature one, and the clinical methods table listing its features records no neuropsychiatric sign at all. The psychiatric interest comes from a separate literature about status and symptoms, not from the classical deficiency disease, and keeping those apart is most of the clarity available.

Status is measured as **serum 25-hydroxyvitamin D**, the optimal biomarker for two stated reasons: its relatively long half-life of 15 days, and the fact that it reflects endogenous production as well as vitamin D obtained from food and supplements. A short-lived marker would track this week's sunshine; a marker capturing only intake would miss the skin's contribution. The cut-points run below 20 ng/mL for deficiency, 20 to 29 ng/mL for insufficiency and above 30 ng/mL for sufficiency, with SI equivalents printed alongside.

TRAP **Quoting the SI band boundaries as though they were exact.** The conventional-unit bands tile the number line cleanly; their nanomole equivalents in the same source do not. Sufficiency is given as above 75 nmol/L while insufficiency is given as 50 to 70 nmol/L, so values between 70 and 75 nmol/L belong to no band, and the lower boundary is claimed by both insufficiency and deficiency depending on which line you read. This is one source being internally inconsistent rather than two bodies disagreeing: the ng/mL figures are primary and the nanomolar values are rounded conversions. Quote the conventional units as primary and never build an answer on a nanomolar boundary being exact.

Population data must stay in their own population. In a national survey of United States adults covering 2001 to 2010, one in three adults was considered vitamin D deficient and a further 40% met criteria for insufficiency. This chapter does not transplant those figures, which matters especially because dark pigmented skin is itself among the named risk factors. The rest of the list is directly usable in a psychiatric clinic: older age, obesity, physical inactivity, smoking, limited milk intake, limited sunlight exposure, fat malabsorption, primary hyperparathyroidism, chronic granulomatous disease, and medications including anticonvulsants, glucocorticoids and anti-HIV agents. Read it against a long-stay psychiatric population and it describes most of them.

14.8 Repletion, and what the psychiatric trials actually show

LOCUS for vitamin D is almost entirely outpatient, a clinic habit rather than a ward protocol. FOCUS moves in two phases, repletion to bring the measured level up and then indefinite maintenance, with the psychiatric symptom as a secondary target. MODUS is oral replacement, with either cholecalciferol, that is vitamin D3, or ergocalciferol, vitamin D2, being acceptable, alongside the social modes of sunlight exposure and diet. The guidance most commonly cited is the Endocrine Society's, whose 2011 recommendations are reproduced in the standard psychiatric textbook and set out below for established deficiency, not for routine supplementation of the replete.

GROUP BEING TREATED FOR VITAMIN D DEFICIENCY	REPLETION	DURATION	MAINTENANCE
Adults over 18 years	50,000 IU per week or 6,000 IU per day	Eight weeks in total	1,500 to 2,000 IU per day or 50,000 IU every 2 weeks
Children and adolescents aged 1 to 18 years	2,000 IU per day or 50,000 IU per week	At least six weeks in total	600 to 1,000 IU per day
Obese adults, malabsorption syndromes, or patients on drugs affecting vitamin D metabolism	6,000 to 10,000 IU per day	Titrated to the measured level	3,000 to 6,000 IU per day

Repletion is judged against a target rather than a symptom: the durations are estimated to achieve a level of at least 30 ng/mL, the same sufficiency threshold as before, which is why the biomarker is worth measuring twice.

GOOD TO REMEMBER

The third row of that table is a psychiatric row. The interfering medications named are anticonvulsants, glucocorticoids and other drugs that enhance activation of the steroid xenobiotic receptor, which results in destruction of 25-hydroxyvitamin D. A patient on long-term anticonvulsant treatment therefore needs the higher repletion and maintenance regimen and will drift back down on the standard adult dose. Anticonvulsants used as mood stabilisers are covered as drugs in the Mood disorders: pharmacotherapy notes; what belongs here is that their effect on vitamin D changes the dose you prescribe.

The psychiatric evidence is real but modest. In adults with unipolar depression, a meta-analysis of four randomised controlled trials with 948 participants found supplementation improved depressive symptom scores on the Hamilton Depression Rating Scale or the Beck Depression Inventory-II, with a moderate effect size of SMD 0.58, P less than .05. In attention deficit hyperactivity disorder, a separate meta-analysis of four randomised controlled trials with 256 children and adolescents aged 2 to 18 years found supplementation added to methylphenidate improved symptoms, with a small effect on total scores, SMD 0.39, and medium effects on inattention, SMD 0.67, hyperactivity, SMD 0.60, and behaviour, SMD 0.54, all P less than .01. Two meta-analyses, both of four trials, different participant numbers, different populations: keep each set of numbers attached to its own endpoint, because a merged figure is a fabricated one.

Enthusiasm is checked by pharmacology. Vitamin D is a **fat-soluble vitamin**, so excess supplementation carries a genuine risk of toxicity, and many participants in these trials were deficient or insufficient at baseline, so the benefit observed may be that of correcting a deficiency rather than of supplementing anybody. The stated responsible practice follows: check the serum 25-hydroxyvitamin D level in a patient with depression before starting supplementation, then follow evidence-based repletion and maintenance dosing.

14.9 When to test, and when to treat without testing

The last question is the one you will face on a ward round. The principle is stated plainly: it is the clinical history and examination that should provide the clues as to whether nutritional deficiency is contributing to the presentation. Testing follows suspicion; it does not generate it.

Where a deficiency is common and the consequence of missing it is severe, practice inverts. Thiamine and folate deficiency are common in patients who misuse alcohol, and although blood thiamine concentration can be measured, for patients at known risk most clinicians simply order thiamine supplementation without first ordering a laboratory evaluation. That is a rational asymmetry rather than sloppiness: the test is slow and the untreated disease is fast. Thiamine-responsive encephalopathy has its own section in this chapter, as do the cognitive and psychiatric consequences of vitamin B12 and folate deficiency; the persistent amnestic syndrome belongs to the Stroke, TBI, delirium and focal brain syndromes notes.

For the water-soluble vitamins in a deprived or alcohol-dependent patient, suspicion justifies treatment and the treatment is broad rather than targeted. For vitamin D, where the deficiency is chronic and the vitamin accumulates, you measure first and dose to the measurement. Reverse

that and you get the two characteristic errors here: a patient with an evolving nutritional encephalopathy waiting on an assay, and a patient with low mood taking a high-dose fat-soluble vitamin nobody ever measured.

The metabolic cost of treatment, diabetes and electrolytes

15 · Antipsychotic metabolic effects: weight gain, dyslipidaemia and glucose

This is where antipsychotic treatment collects its long bill. The test is not whether you know that antipsychotics cause weight gain, but whether you can separate three liabilities, attach each to the drugs and patients where it bites, and say where the evidence stops. **Both first-generation and second-generation antipsychotics** carry weight gain, dyslipidaemia, raised plasma glucose and diabetes, alongside hyperprolactinaemia, hip fracture, sexual dysfunction, extrapyramidal effects including neuroleptic malignant syndrome, anticholinergic effects, venous thromboembolism, sedation and postural hypotension. The class shorthand is that second-generation agents buy fewer extrapyramidal symptoms at the price of more metabolic harm: true as a class statement, useless as a prescribing one, since some older drugs behave like the safest of the new.

Two facts frame what follows. The burden is not evenly spread: on clozapine, nearly every exposed patient shows at least one of the triad of weight gain, insulin resistance and dyslipidaemia. And the baseline is not clean, because schizophrenia carries high rates of insulin resistance and diabetes and that was observed before antipsychotics existed. The drug amplifies an existing vulnerability rather than authoring it.

NEARLY 100%	42.7%	AS HIGH AS 61.6%	2 TO 3-FOLD
CLOZAPINE, AT LEAST ONE OF THE TRIAD	DIABETES, US CLOZAPINE DATA SET	METABOLIC SYNDROME, SAME POPULATION	DIABETES IN SCHIZOPHRENIA VERSUS POPULATION

15.1 Three liabilities, not one

The commonest error is to treat this as one process, with weight gain the engine and lipids and glucose the passengers. The cleanest counter-demonstration: olanzapine-treated and risperidone-treated patients gained similar weight, yet triglycerides rose four times as much on olanzapine, by 105 mg/dl against 32 mg/dl. Identical weight, very different lipids.

RULE **Weight, lipids and glucose are three separate liabilities and must be measured separately.** They cluster in the same high-risk agents, but antipsychotic-induced dyslipidaemia and antipsychotic-related insulin resistance can each occur without weight gain. A stable weight is reassurance about weight and nothing else.

15.2 Mechanism: impaired satiety, not a slowed metabolism

The mechanism of antipsychotic-induced weight gain, and of the two metabolic effects alongside it, is receptor-mediated and belongs here; antipsychotic action in psychosis and the principles of drug selection belong to the Schizophrenia: management, antipsychotics and adverse effects

notes, and the underlying receptor biology to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. What matters here is how a receptor profile becomes a waistline.

The honest starting position is that **the mechanisms of antipsychotic-induced weight gain** are not well understood. The factors commonly implicated are 5-HT2C antagonism, H1 antagonism, D2 antagonism, and a rise in serum leptin producing leptin desensitisation. The most robust is **histamine H1 antagonism at hypothalamic sites regulating food intake**, with a possible added contribution from **5-HT2C antagonism**, supported by animal models and early polymorphism studies, though that genetic association is inconsistent.

The most useful mechanistic fact is negative. There is no evidence of any direct metabolic effect: weight gain results from increased food intake and, in some cases, reduced energy expenditure. The H1 account is one of impaired satiety, so patients eat more and metabolic rate is not switched off. That reframes the conversation, because satiety is something dietary structure and activity can engage with.

The mechanisms of antipsychotic-related diabetes are similarly unclear, and may include 5-HT2A and 5-HT2C antagonism, raised plasma lipids, weight gain itself and leptin resistance. Two agents differ in kind: olanzapine and clozapine appear to directly induce insulin resistance, which explains why impaired glucose tolerance appears on them in patients neither obese nor family-history positive.

15.3 Magnitude and time course of weight gain

Weight gain occurs primarily in the first few months but continues for many months or years afterwards, and in those who gain most the rate is maintained for at least two years. It is a long curve with a steep beginning, and the figures worth carrying are drug-bound and population-bound.

In a ten-year study of first-episode schizophrenia on mixed antipsychotics, mean weight gain was 15 kg, of which 9 kg came in the first year. That figure must never be transplanted onto a single drug or a chronic population. For clozapine, **60 to 75% of patients gain at least 4.5 kg during the first year**, and gain is often profound, with **4.5 kg in the first 10 weeks**. Naturalistic American data give a mean increase of 13.5 kg after 10 years on clozapine, of which that same early 4.5 kg came in the first 10 weeks. Two independent sources agree on it, which is why it is worth memorising.

Information on individual first-generation agents other than chlorpromazine and haloperidol is scarce, but one comprehensive analysis found first-generation drugs excluding haloperidol carried moderate risk, with 20 to 30% of people gaining more than 7% of original body weight in the medium term. Two things travel with that: more than 7% of original body weight is the conventional definition of clinically significant weight gain, and the population excludes haloperidol, which matters for the tier table.

GOOD TO REMEMBER

The steepest part of the curve is the part you are present for. Dietary counselling is essential, and advice may be more effective when it comes before weight gain starts, which is the argument for placing it at initiation.

15.4 Who gains, and why the group mean misleads

Almost all antipsychotics have been associated with weight gain and the mean varies substantially between them, but variation between individuals on the same drug is greater still, some losing weight and some gaining a great deal. The source supplying the ranking states plainly that a drug's reported mean may not usefully predict what an individual will gain. Some predictors are consistent. Gain may be more pronounced in antipsychotic-naive patients and early in treating a psychotic illness, and women may be at greater risk than men.

- Weight gain: younger age, female gender, nonwhite race or ethnicity, family history.
- Insulin resistance: a diagnosis of schizophrenia itself, nonwhite race or ethnicity, family history.
- During treatment: rapid weight gain and a rise in plasma triglycerides both predict later diabetes.

The third turns two routine measurements into an early-warning system before any glucose abnormality declares itself. One intuitive lever does not work: within the dose range commonly used for schizophrenia spectrum disorders there is no evidence of a dose relationship for metabolic disorders, so dose reduction is not a strategy to treat them. That is stated for clozapine and is the general rule; the quetiapine finding below is a documented exception.

PITFALL

The reflex response to weight gain on clozapine is to shave the dose. It buys nothing metabolically and risks what clozapine was prescribed to do. The specific interventions belong with the management of antipsychotic metabolic disturbance rather than here.

15.5 The comparative ranking, and the discrepancy inside it

The comparative metabolic risk ranking is best held as ordinal tiers, not a league table of kilograms. The standard rendering clusters antipsychotics into three groups derived from meta-analyses.

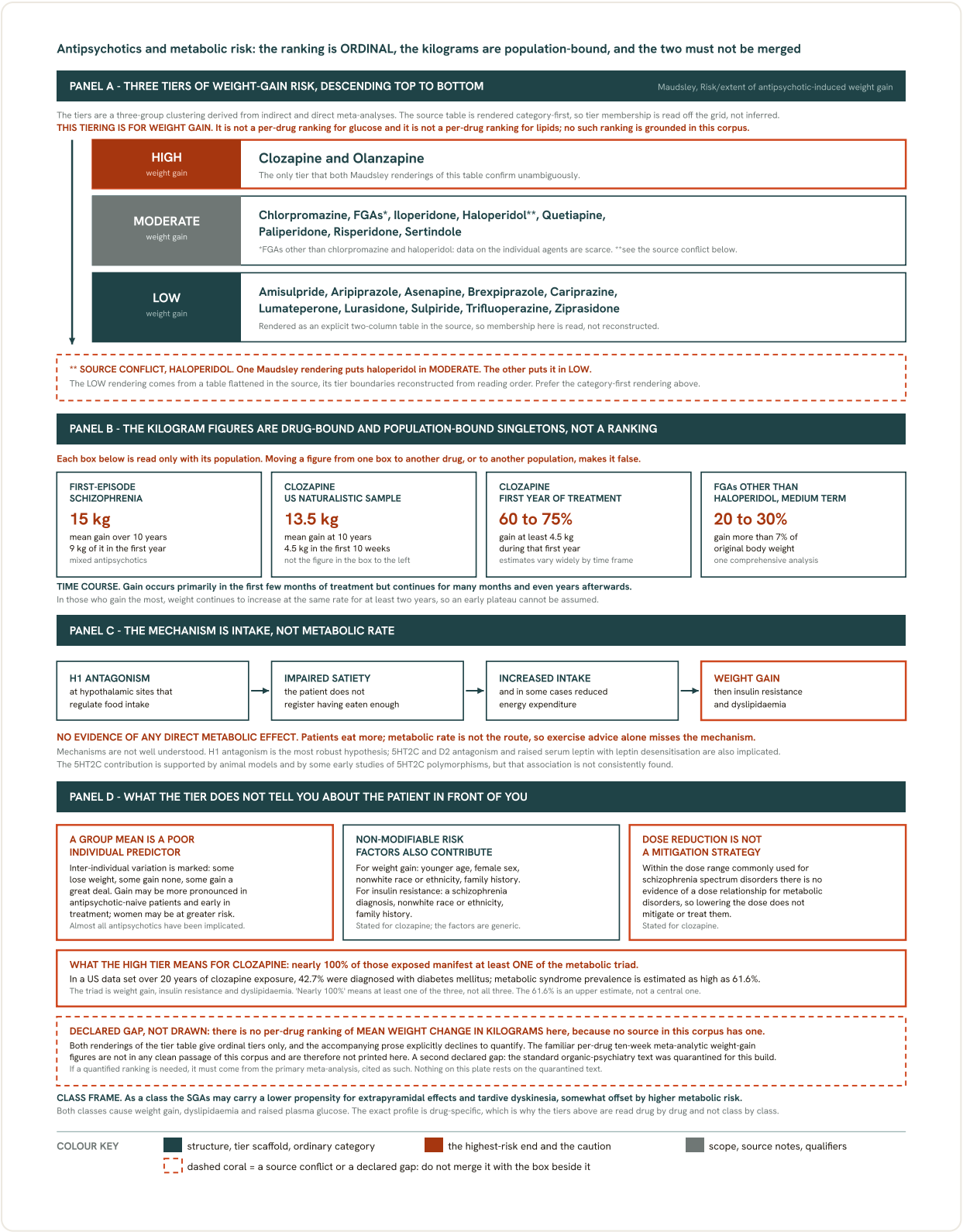

Fig 33.6 Comparative metabolic risk of antipsychotics: an ordinal three-tier ranking for weight gain, with the grounded kilogram figures kept as population-bound singletons. The teaching point is the shape of the evidence, not a league table. The corpus supports High, Moderate and Low tiers for weight gain and nothing finer, and the two available renderings of the same tier table disagree about haloperidol. Every kilogram and every percentage on the plate belongs to a named drug in a named population and does not travel. The mechanism is impaired satiety and increased intake, not a direct effect on metabolic rate, and dose reduction is not a mitigation. (The Maudsley Prescribing Guidelines and Maudsley 15th edition; Stahl's The Clozapine Handbook.)

TIER	AGENTS	READING
High risk or extent of weight gain	Clozapine and olanzapine.	Stable across both renderings and across the lipid and glucose evidence.
Moderate	Chlorpromazine, first-generation antipsychotics as a group, iloperidone, haloperidol, quetiapine, paliperidone, risperidone, sertindole.	The first-generation entry carries the footnote excluding haloperidol.
Low	Amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, lumateperone, lurasidone, sulpiride, trifluoperazine, ziprasidone.	Sulpiride and trifluoperazine sit here: the generation label does not predict metabolic risk.

The accompanying figure sets the same ordering out across weight, glucose and lipids. Read the tiers as tiers: no source here ranks antipsychotics by mean weight change in kilograms, and the source prose explicitly declines to quantify. A per-drug kilogram league table asserts what the evidence does not support.

MNEMONIC

Same two drugs, all three lists

Clozapine and olanzapine head the weight-gain tier, head the lipid ranking, and carry the strongest links to impaired glucose tolerance, diabetes and ketoacidosis. The top of all three lists is the same pair.

Now the part that separates a good answer from a safe one. Two renderings of the same three-tier table place haloperidol differently. The fifteenth edition of the Maudsley guidance puts it in the moderate tier, as above; the other Maudsley rendering puts haloperidol in the low tier, with the aripiprazole and ziprasidone group. This is unresolved: it may be an editorial revision, or an artefact of the second table's layout, whose tier boundaries must be reconstructed from a flattened run of drug names, not read off a grid. Consistent across both is that the general first-generation weight-gain statement excludes haloperidol.

TRAP **Being asked to place haloperidol in a weight-gain tier.** Candidates answer confidently in one direction and are marked against the other, because two renderings disagree and neither can be dismissed. Answer what is certain in both: clozapine and olanzapine are the high-risk pair, and haloperidol is not in the high-risk tier. Then name the discrepancy rather than resolving it by assertion.

15.6 Dyslipidaemia: triglycerides are the headline

Among older drugs the phenothiazines raise triglycerides and low-density lipoprotein cholesterol and lower high-density lipoprotein cholesterol, though the magnitude is poorly quantified, while haloperidol appears to have minimal effect on lipid profiles. Cholesterol can rise, but the most profound effect of this class is on triglycerides.

The lipid ranking parallels the weight ranking without duplicating it. Clozapine and olanzapine have the greatest propensity to raise lipids; quetiapine and risperidone are moderate; aripiprazole, lurasidone and ziprasidone have minimal effect and may modestly reverse dyslipidaemia from a previous antipsychotic; cariprazine and brexpiprazole also appear limited. Haloperidol therefore sits at the minimal end for lipids and in the moderate weight tier. That axis-dependence is what a viva turns on.

Olanzapine raises triglyceride levels by **40% over the short term at 12 weeks and the medium term at 16 months**, and levels may keep rising for up to a year. Up to two-thirds of olanzapine-treated patients have raised triglycerides and just under one in ten may develop severe hypertriglyceridaemia. A United Kingdom case-control study found olanzapine-treated patients five times more likely to develop hyperlipidaemia than those with no antipsychotic exposure and three times more likely than those on first-generation drugs; those multipliers have different comparators and are not interchangeable. Risperidone showed no increase against either. Clozapine gives the same picture over a longer horizon, with mean triglycerides doubling and cholesterol rising by at least 10% after 5 years. Both drugs warrant particular care in patients already obese, diabetic or hyperlipidaemic.

The threshold that converts a laboratory abnormality into acute medical risk is **severe hypertriglyceridaemia**, a fasting level above **5 mmol/L**, which is a risk factor for pancreatitis. The sample must be fasting, and this threshold sits far above the much lower triglyceride cut-off used as a metabolic syndrome criterion. Confusing the two produces false alarm or false reassurance.

15.7 Glucose: insulin resistance, diabetes and ketoacidosis

Diabetes is two to three times more prevalent in schizophrenia than population norms, and the observation predates antipsychotics. Drug-attributable risk sits on top of illness-attributable risk, and the two cannot be separated at the bedside.

Clozapine is strongly linked to hyperglycaemia, **impaired glucose tolerance and diabetic ketoacidosis**, with a risk apparently higher than with other second-generation or first-generation drugs, especially in younger patients, though not consistently. As many as a third of patients might develop diabetes after 5 years of clozapine treatment. Timing is wide: many cases in the first six months, some within a month, some only after years. Death from ketoacidosis has been reported, and clozapine-associated diabetes is not necessarily linked to obesity or family history, though both raise risk. Olanzapine mirrors this, and is probably more diabetogenic than risperidone.

Quetiapine and risperidone have both been linked to new-onset diabetes and ketoacidosis, with far fewer reports. Quetiapine appears more likely than first-generation drugs to be associated with diabetes, and two studies found it equal to olanzapine. Here is the one documented dose relationship in this territory: in patients taking quetiapine for a psychotic illness, glycaemic risk may be dose-related, with **400 mg or more per day** clearly linked to changes in glycosylated haemoglobin. That is a metabolic-risk threshold, not a dosing recommendation.

At the favourable end, amisulpride appears not to elevate plasma glucose or be associated with diabetes, and neither aripiprazole nor ziprasidone alters glucose homeostasis, with a large case-control study confirming no increased diabetes risk for amisulpride or aripiprazole. Those three are recommended for patients predisposed to diabetes, or as an alternative to a known diabetogenic drug; lurasidone and asenapine appear to have no effect, and initial data suggest the same for brexpiprazole and cariprazine. One caveat: ketoacidosis has been reported with aripiprazole, so low risk is not no risk. Because between-drug differences are small and inconsistently shown, they may be unimportant in practice: risk is probably increased for everyone with schizophrenia receiving any antipsychotic.

TRAP **Applying the general-population age gradient for diabetes.** Candidates reason that risk climbs with age and name the elderly patient. It runs the other way here. Risk is increased to a much greater extent in younger adults than in the elderly, in whom antipsychotics may show no increased risk at all, and first-episode patients are particularly prone across a variety of agents.

15.8 Detecting it: which test, which threshold, what it means

LOCUS determines what is realistically obtainable. In an outpatient clinic a fasting sample can be arranged for a return visit; on an acute ward or with any disorganised patient, fasting tests are often unobtainable, and insisting means obtaining nothing. In every locus the pre-treatment measurement has the most leverage, separating an abnormality the drug produced from one the patient already had.

FOCUS shifts with phase. Before treatment the target is undiagnosed disease: although ketoacidosis shortly after starting clozapine was an early concern, later studies showed these patients had untreated diabetes, with a mean glycosylated haemoglobin of 13.3% at admission for ketoacidosis. That is a mean at presentation, not a threshold or target. Acutely the focus is symptomatic hyperglycaemia and ketoacidosis; over the short and medium term the rate of weight change and the triglyceride trajectory; long term the accumulated cardiovascular risk.

MODUS is the choice of test, governed by the Maudsley prescribing guidance on antipsychotic monitoring, the American Psychiatric Association practice guideline, and the American Diabetes Association criteria that both reproduce. The oral glucose tolerance test is the most sensitive method and the ideal; fasting plasma glucose is less sensitive but recommended, and any abnormal fasting value should provoke an oral glucose tolerance test. Where fasting is impractical, random plasma glucose or **glycosylated haemoglobin** may be used. Patients should report fatigue, candida infection, thirst and polyuria. The cadence is set out where this chapter deals with metabolic monitoring protocols.

The thresholds are the general diabetes ones. Diabetes is diagnosed by a fasting plasma glucose of at least 126 mg/dl or 7.0 mmol/l, with fasting defined as no caloric intake for at least 8 hours; or a two-hour value of at least 200 mg/dl during a 75 gram oral glucose tolerance test; or a random plasma glucose of at least 200 mg/dl with classic hyperglycaemic symptoms or crisis; or a glycosylated haemoglobin of at least 6.5%, confirmed on repeat testing where hyperglycaemia is

not unequivocal. The American Psychiatric Association states it as higher than 125 mg/dL: the same cut-off expressed differently, not a competing standard.

Interpreting glycosylated haemoglobin means holding its window in mind. It reflects mean blood glucose over the preceding 8 to 12 weeks; below 5.7% is normal, 5.7 to 6.4% indicates increased risk of developing diabetes, 6.5% or above indicates diabetes mellitus, and 7% or less is a common treatment target in established diabetes. That lookback is why the test cannot exclude recent antipsychotic-induced hyperglycaemia: a patient three weeks into olanzapine with a normal result has been told about the two months before the drug started. Metabolic syndrome, meanwhile, is measured against jurisdiction-dependent criteria. The International Diabetes Federation definition uses **ethnicity-specific waist circumference thresholds** whose Asian values apply to Asian-Indian patients, while the definition used for the United States and Canada sets a considerably higher waist threshold. Both require at least three of five risk factors.

IN INDIA

Two divergences bite. Glycosylated haemoglobin is not a universal substitute here: where a haemoglobinopathy or any cause of increased red cell turnover is present, including second-trimester and third-trimester pregnancy, haemodialysis, recent blood loss, transfusion and erythropoietin therapy, fasting blood glucose should be used rather than glycosylated haemoglobin. Haemoglobinopathies are not rare here, so the convenient test is unreliable in exactly the patients from whom a fasting sample is hardest to obtain. Second, Indian consultation-liaison guidance reaches the international conclusion independently: olanzapine and clozapine carry the maximal risk of precipitating metabolic syndrome and should be used with proper clinical prudence in conditions such as diabetes, stroke and heart disease, while aripiprazole may be used as a first-line agent in cardiac disease given its safer metabolic and cardiac profile.

Taken whole, the shape is simple: the same pair at the top of every axis, a broad unremarkable middle, a low-risk group of both newer and older agents, and one drug whose position is contested. Choosing between them belongs to the Schizophrenia: management, antipsychotics and adverse effects notes; this chapter asks only that you know what you are trading away.

Clozapine and olanzapine top the weight, lipid and glucose rankings alike; the three effects dissociate, so weight, a fasting lipid panel and a glucose measure are three separate obligations, and dose reduction is a remedy for none of them.

16 · Metabolic monitoring protocols and parameters for patients on antipsychotics

This is the part of antipsychotic prescribing every guideline calls mandatory and almost nobody does properly. The question always has three parts: which parameters you record, at what intervals you repeat them, and what you do with a value outside the reference range. The first is nearly uncontested and the third is where marks are won, because a schedule generating numbers nobody acts on is an audit exercise rather than care. The second is where candidates lose marks, because the major guidelines give different intervals for the same test in the same patient.

Four bodies of guidance govern this territory and each is internally coherent. The Maudsley Prescribing Guidelines carry a parameter-by-parameter table with drug-specific intensification and an action column. NICE guidance, reproduced in that chapter, specifies a baseline panel. The American Psychiatric Association practice guideline gives a separate schedule and is candid that there are no absolute criteria for frequency, so decisions must follow clinical circumstance. Stahl's The Clozapine Handbook gives a clozapine-specific routine synthesised from published recommendations rather than issued by one body. Kaplan and Sadock's Comprehensive Textbook of Psychiatry reproduces the older multi-society consensus table and gives its own prose recommendations, and the two disagree. Hold them as four positions, not one consensus.

8% TO UNDER 30% PATIENTS GETTING BASELINE GLUCOSE AND LIPID CHECKS	**8.8%** GETTING ANY FOLLOW-UP ASSESSMENT	**23.0 kg/m2** OVERWEIGHT THRESHOLD, ASIAN CUTPOINTS	**1 BMI UNIT** RISE THAT SHOULD TRIGGER INTERVENTION

16.1 The baseline panel: what is recorded before the first dose

Everything downstream depends on a pre-treatment measurement, because without one you cannot separate an abnormality the drug produced from one the patient brought with them. A raised fasting glucose before the first tablet is a comorbidity to treat; the same value four months in is a reason to reconsider the drug. NICE sets out the **baseline investigations** to be undertaken and recorded before starting.

- Weight.
- Waist circumference.
- Pulse and blood pressure.
- Fasting blood glucose, HbA1c, a blood lipid profile and prolactin.
- Assessment of movement disorders.
- Assessment of nutritional status, diet and level of physical activity.

Note that the panel asks for both a fasting glucose and a glycated haemoglobin in everyone, and for a prolactin level in everyone. An electrocardiogram is added selectively, where the summary of product characteristics specifies it, where examination has identified a specific cardiovascular risk such as a diagnosis of high blood pressure, where there is a personal history of cardiovascular disease, or where the person is being admitted as an inpatient. The American baseline panel is narrower and differently shaped: body weight, height and BMI; screening for diabetes risk factors with a fasting blood glucose; a lipid panel; a determination of whether metabolic syndrome criteria are met; pulse and blood pressure; and screening for symptoms of hyperprolactinaemia, with a prolactin level only if the clinical history indicates one. The criteria that determination uses are set out where this chapter deals with metabolic syndrome, obesity and mortality in serious mental illness.

MNEMONIC

Weight, Waist, Pressure, Bloods, Movements, Lifestyle

The six headings of the baseline panel in the order they are recorded. Five of the six need no laboratory.

16.2 The architecture of follow-up, and where the sources part company

Every schedule shares one skeleton: a baseline, intensified early surveillance, a consolidating check inside the first six months, then a maintenance interval. What differs is the length of the intensified period, the timing of the consolidating check and, most consequentially, the maintenance floor. The accompanying figure lays that skeleton out.

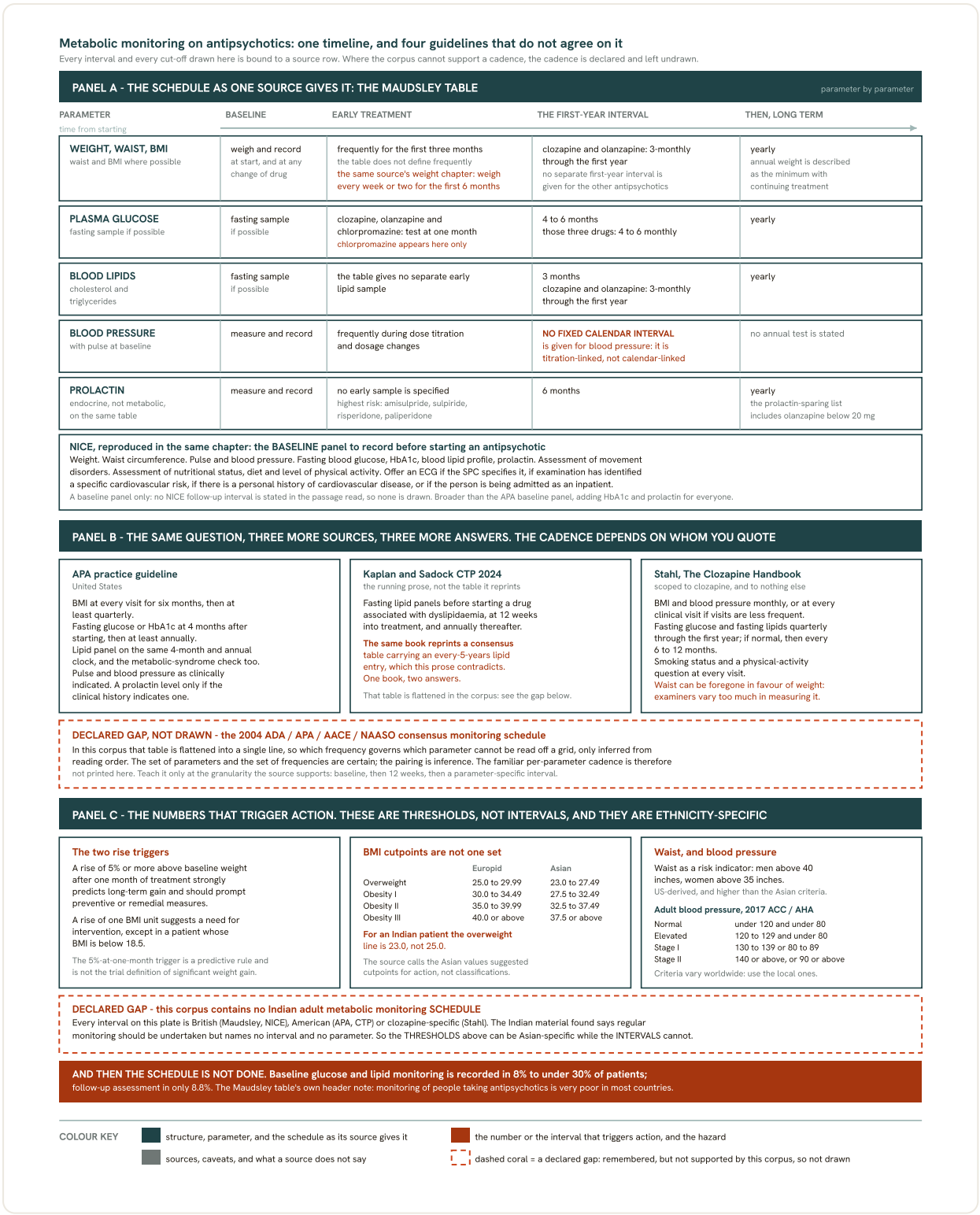

Fig 33.7 Metabolic monitoring on antipsychotics: one timeline, and four guidelines that do not agree on it. The Maudsley table is the only complete parameter-by-parameter schedule in this corpus, and its blood-pressure row is titration-linked rather than calendar-linked, so there is no annual blood-pressure interval to quote. Chlorpromazine joins clozapine and olanzapine in the special-precaution list for glucose and for glucose only. The APA guideline, the CTP prose and the clozapine-specific Stahl schedule each answer the same question differently, so the cadence you quote depends on whom you quote. The anthropometric thresholds can be Asian-specific, but every interval drawn here is British or American: no Indian adult monitoring schedule is present in this corpus, and the flattened 2004 consensus table is declared and left undrawn rather than reconstructed from memory. (The Maudsley Prescribing Guidelines, and NICE as reproduced there; the American Psychiatric Association practice guideline; Kaplan and Sadock's Comprehensive Textbook of Psychiatry 2024; Stahl, The Clozapine Handbook.)

PARAMETER	THE MAUDSLEY PRESCRIBING GUIDELINES	APA PRACTICE GUIDELINE	STAHL'S THE CLOZAPINE HANDBOOK (CLOZAPINE)
Weight and BMI	Baseline, frequently for three months, then yearly; clozapine and olanzapine, 3-monthly for the first year, then yearly	BMI every visit for 6 months, then at least quarterly	Monthly, or every clinical visit if visits are less frequent
Blood pressure	Baseline, then frequently during titration and dose changes; no fixed calendar interval	Pulse, blood pressure and temperature as clinically indicated	Monthly, or every clinical visit if less frequent
Fasting glucose	Baseline, at 4 to 6 months, then yearly; clozapine, olanzapine and chlorpromazine at baseline, one month, then 4 to 6 monthly	Fasting glucose or HbA1c at 4 months, then at least annually	Quarterly in the first year, then every 6 to 12 months if normal
Fasting lipids	Baseline, at 3 months, then yearly; clozapine and olanzapine 3-monthly for the first year, then yearly	Lipid panel at 4 months, then at least annually	Quarterly in the first year, then every 6 to 12 months if normal
Prolactin	Baseline, at 6 months, then yearly	Symptom screening each visit until stable, then yearly on a prolactin-raising drug; a level only if the history indicates one	Not among this routine table's parameters

An older multi-society consensus sits behind much of this. The **2004 consensus development conference on antipsychotic drugs, obesity and diabetes**, convened by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists and the North American Association for the Study of Obesity, produced the table most later schedules descend from: personal and family history, weight and BMI, waist circumference, blood pressure, fasting plasma glucose and fasting lipid profile, on a baseline and 12-week frame. Reproduce it only at the granularity you can defend: in the rendering available here the pairing of interval to parameter is reading order rather than a grid, and the consensus called these routine recommendations that specific situations may warrant intensifying.

16.3 Weight: the parameter that moves first and costs nothing

Body weight is the most informative single measurement here because it changes earliest, needs no laboratory and predicts the rest. The minimum standard is that every patient starting or changing antipsychotic medication is weighed and the weight clearly recorded, ideally with BMI and waist circumference. The intensity that matters is early: weighing every week or two for at least the first six months, more often than any parameter table above asks for.

That frequency exists to catch one signal. **Rapid weight gain in early treatment**, taken as an increase of **at least 5% above baseline after a month of treatment**, strongly predicts long-term weight gain and should prompt consideration of preventative or remedial measures. It converts a month of observation into a prediction about years, long before any laboratory value moves. With continuing treatment, annual weighing is the stated minimum, and that floor is where guidelines diverge.

The second trigger is expressed in BMI. A BMI of 25 to 29.9 is overweight and 30 or above is obese, and, except where BMI is below 18.5, a rise of **1 unit** should prompt intervention: closer weight monitoring, a weight management programme, an adjunctive treatment to reduce weight, or a change of antipsychotic. The low-BMI exemption is dropped more often than remembered, and it matters: an underweight patient gaining a unit of BMI is doing something desirable. What to do once the trigger fires belongs where this chapter deals with managing antipsychotic metabolic disturbance and hyperprolactinaemia; drug selection belongs to the Schizophrenia: management, antipsychotics and adverse effects notes.

TRAP **Confusing the early-prediction percentage with the trial definition of clinically significant weight gain.** The figure triggering action at one month is a predictive threshold, set low so it fires early. The percentage of baseline weight used in trials to define clinically significant gain is a different and higher figure, taught with the antipsychotic metabolic effects material. Two percentages, two jobs; quote the wrong one and the answer changes from surveillance to a switching decision.

16.4 Anthropometric thresholds, and why the Indian ones are different

Waist circumference as a risk indicator is where a Western protocol becomes actively misleading in an Indian clinic. The general health-risk figures in the standard textbook are that men with a waist larger than 40 inches and women with a waist larger than 35 inches are at increased health risk. Those are American-derived. The International Diabetes Federation criteria, ethnicity-specific and with materially lower Asian values, are set out where this chapter deals with metabolic syndrome, obesity and mortality in serious mental illness. The same problem recurs with BMI.

CATEGORY	EUROPID INDIVIDUALS	ASIAN INDIVIDUALS
Overweight	25.0 to 29.99 kg/m2	23.0 to 27.49 kg/m2
Class I obesity	30.0 to 34.49 kg/m2	27.5 to 32.49 kg/m2
Class II obesity	35.0 to 39.99 kg/m2	32.5 to 37.49 kg/m2
Class III obesity	40.0 kg/m2 or above	37.5 kg/m2 or above

These are offered as **suggested cutpoints for action** rather than as a reclassification of obesity, a hedge worth reproducing. A methodological dissent follows: the clozapine source recommends foregoing waist circumference for the more accurate weight, given significant variation between examiners, whereas the Maudsley table and NICE both keep monitoring waist circumference in the protocol.

IN INDIA

The thresholds are Indian, the intervals are not. Ethnicity-specific cutpoints apply directly here, with overweight beginning at a BMI of 23.0 kg/m2 rather than 25.0, so a patient carrying what a Western chart calls a normal BMI can already be in the band where action is suggested. Blood pressure criteria carry the same warning: the source cautions that they are the American criteria as modified in 2017, that criteria vary worldwide, and that clinicians should know those used locally. What no source here supplies is an Indian adult schedule for antipsychotic metabolic monitoring; Indian consultation-liaison guidance says regular monitoring should be undertaken but specifies neither parameters nor intervals. Take thresholds from the ethnicity-specific tables and timing from Western guidance, and say so rather than imply a domestic schedule.

16.5 Glucose: the interval nobody agrees on

Baseline and follow-up fasting glucose appears in every schedule above, and the parameter is a fasting plasma glucose where a fasting sample can be had; an abnormal value draws a graded response: lifestyle advice, a fasting sample or a non-fasting sample with a glycated haemoglobin, and referral to the general practitioner or a specialist. Glucose carries the most explicit drug-specific intensification. Clozapine, olanzapine and chlorpromazine attract a check at **one month** that other antipsychotics do not; note which drug joins the usual pair, since chlorpromazine is on the special-precaution list for glucose but not for lipids or weight.

The routine interval has three answers. The Maudsley table rechecks at four to six months and then yearly. The American guideline rechecks a fasting glucose or a glycated haemoglobin at four months and then at least annually, with no drug-specific intensification. The clozapine handbook tests quarterly through the first year and then every six to twelve months if normal, adding that monthly or bimonthly fasting glucose should be considered in the first six months where multiple diabetes risk factors are present, and adding a glycated haemoglobin where fasting values are hard to obtain. Monitoring for **impaired fasting glucose** is recommended whatever the drug, because prevalence in this population is high enough that nobody is exempt.

TRAP **Answering "the" recheck interval as though one exists.** Four sources give four lipid schedules and three give three for glucose, and the Maudsley guidance concedes in its own prose that there is no clear consensus on diabetes monitoring for antipsychotic-treated patients and that formal guidelines vary considerably. The safe answer names the source with the interval, notes the divergence, then gives the item most often missed: the one-month glucose check for clozapine, olanzapine and chlorpromazine.

16.6 Lipids: four schedules and a source that contradicts itself

A fasting sample is preferred where obtainable, and cholesterol and triglycerides are the reported values. The action column is more interventionist than for glucose: lifestyle advice, and consideration of both a change of antipsychotic and a statin. Some agents, aripiprazole and lurasidone among them, are not clearly associated with dyslipidaemia, yet everyone is monitored, because prevalence in this population is high. Population risk rather than drug risk sets the monitoring floor across all three parameter tables.

The intervals are the most divergent set in the topic. The Maudsley table rechecks at 3 months, then yearly, with clozapine and olanzapine 3-monthly through the first year. The American guideline rechecks at four months and then at least annually. Kaplan and Sadock's prose evaluates fasting lipid panels before starting a medication associated with dyslipidaemia, at 12 weeks into treatment, and annually thereafter. The clozapine handbook runs quarterly through the first year and then six to twelve monthly. Three months, four months and twelve weeks make no clinical difference and are examinable separately.

PITFALL

The outlier deserves naming rather than quiet omission. The reproduction of the 2004 consensus table sets the fasting lipid profile at baseline, 12 weeks and then every five years, a maintenance interval the same textbook's own prose contradicts by specifying annually. Quoting a five-yearly lipid check as current practice quotes a position later guidance moved away from. Present it as history, not protocol.

16.7 Blood pressure and prolactin: the two parameters that are not metabolic

Two parameters on the monitoring sheet answer to a different logic. Blood pressure is not calendar-linked in the Maudsley scheme at all: baseline, then frequently during titration and dose changes, because the risk it tracks is haemodynamic and dose-driven rather than cumulative. Clozapine, chlorpromazine and quetiapine are most likely to produce postural hypotension, while amisulpride, aripiprazole, brexpiprazole, cariprazine, lurasidone, trifluoperazine and sulpiride are listed as not requiring the same precaution. Slow titration where severe hypotension, or hypertension on clozapine, is seen; consider switching to another antipsychotic where postural hypotension is symptomatic; treat hypertension along standard guideline lines.

Staging the reading matters because the thresholds moved. Against the **2017 American College of Cardiology and American Heart Association criteria**, normal is a systolic below 120 mmHg and a diastolic below 80 mmHg; elevated is a systolic of 120 to 129 mmHg with a diastolic below 80 mmHg; stage I hypertension is a systolic of 130 to 139 mmHg or a diastolic of 80 to 89 mmHg; and stage II is a systolic of 140 mmHg or more or a diastolic of 90 mmHg or more. Note the connectives: normal and elevated require both criteria, the hypertensive stages either.

Prolactin is measured at baseline, at six months and then yearly, and the drugs attracting attention are amisulpride, sulpiride, risperidone and paliperidone. Several usually do not raise it, including asenapine, aripiprazole, brexpiprazole, cariprazine, clozapine, lurasidone, quetiapine, ziprasidone and, with a dose qualification easy to lose, olanzapine at **less than 20 mg**. Where hyperprolactinaemia is confirmed and symptomatic the response is to switch, and **bone mineral density testing such as DEXA scanning** should be considered where levels are chronically raised. Management belongs where this chapter deals with managing antipsychotic metabolic disturbance and hyperprolactinaemia.

RULE **Every parameter carries an action, and the action is what makes it monitoring rather than measurement.** Each row of the standard tables pairs a test with a response: lifestyle advice, a confirmatory test, a drug change, a pharmacological intervention, or a referral. If you cannot say what you would do with an abnormal value before ordering it, you are collecting data, not monitoring.

16.8 Making the protocol actually happen

LOCUS decides what is obtainable. On an inpatient ward the fasting sample, weight and blood pressure are all easy and the baseline panel should be completed before the first dose; admission itself triggers a baseline electrocardiogram. In the outpatient clinic the fasting sample is the constraint, which is why the alternatives are written into the guidance: a non-fasting sample with a glycated haemoglobin. In shared care, abnormal values are referred onward, making the referral pathway part of the protocol rather than an afterthought.

FOCUS shifts by phase. Before the first dose the target is undiagnosed existing disease and a clean set of reference values. Through the first weeks it is the rate of change in weight, the only signal moving fast enough to inform this early. Between three and six months it moves to the laboratory parameters as the consolidating checks fall due. In maintenance it is accumulating cardiovascular burden, and here the sources disagree most sharply: annual, at least quarterly, or monthly for clozapine.

MODUS is the set of instruments, and most are not tests. Scales, a tape measure and a sphygmomanometer cover four parameters. Two further items belong on the clozapine routine sheet and are useful for everyone: smoking status, asked and quantified at every visit, with cessation programmes and medication offered quarterly once the patient is psychiatrically stable, and a **physical activity vital sign**, asked and recorded at every monthly visit. Framing activity as a vital sign rather than as advice is the point.

Build the metabolic monitoring protocol into the structure of the clinic rather than into individual intention, because intention demonstrably fails. Screening for metabolic risk occurs at very low rates in schizophrenia even where the prescribed antipsychotic is one associated with glucose and lipid disturbance, and despite recommendations from the American Psychiatric Association, the American Diabetes Association and other groups, and despite regulatory warnings. The Maudsley table prefaces itself in plainer words: monitoring of people taking antipsychotics is very poor in most countries.

GOOD TO REMEMBER

Put the parameters on the prescription sheet, so the review that renews the drug cannot be completed without them.

Baseline everything before the first dose, weigh every week or two through the early months and act on a 5% rise at one month or a 1-unit rise in BMI, recheck glucose and lipids between three and six months and then at your guideline's maintenance floor, and remember the extra one-month glucose check for clozapine, olanzapine and chlorpromazine.

17 · Managing antipsychotic metabolic disturbance and hyperprolactinaemia

Knowing that antipsychotics wreck metabolism and raise prolactin earns nothing on its own. The marks are for the sequence: what you try first, what you switch to, what you refuse to add, and when a metabolic complication stops the drug. Both problems are iatrogenic, and both are found by a measurement rather than reported by the patient.

Detection aside, drug selection belongs to the Schizophrenia: management, antipsychotics and adverse effects notes; metabolic syndrome criteria to where this chapter deals with metabolic syndrome, obesity and mortality in serious mental illness; the measurement schedule to where it deals with metabolic monitoring protocols; the reproductive-endocrine view of a raised prolactin to where it deals with reproductive hormones and mood.

500-2000 MG/DAY METFORMIN, ANTIPSYCHOTIC WEIGHT GAIN	**2.5-3 G/DAY** METFORMIN, PROLACTIN LOWERING	**3 MG/DAY** LIRAGLUTIDE, WEIGHT LOSS INDICATION	**UNDER 25** AVOID HIGH-PROLACTIN DRUGS, PRE-PEAK BONE MASS

17.1 The order of moves for a patient who has gained weight

LOCUS. Almost all outpatient: what works is what a patient sustains between appointments. Admission supervises a structured diet and activity programme and gives a switch daily observation. Emergency presentation belongs to the acute metabolic decompensations, not to weight.

FOCUS is phase-dependent: acutely, nothing to treat but the recognition; short term, the rate of gain, steepest early; medium term, reversal of accrued gain with its lipid and glucose consequences; long term, cardiovascular risk and willingness to stay on an effective antipsychotic at all.

MODUS. The Maudsley prescribing guidance sets the sequence, the American Psychiatric Association practice guideline agreeing in spirit. **Behavioural lifestyle programmes** improving diet and physical activity come first, no token gesture: meta-analyses show a robust effect for prevention and treatment alike, and early intervention prevents gain rather than chasing it. Alongside or instead, switching antipsychotic to reduce metabolic risk is the other first-line option, with fairly strong support for aripiprazole, ziprasidone or lurasidone for reversing gain already accrued, though it risks relapse and discontinuation. **Adjunctive aripiprazole** is the related option, weight loss observed when added to clozapine or olanzapine. The effect of both is modest and many patients remain overweight.

Pharmacological treatment sits after those two, only where behavioural strategies or a switch have failed, or where obesity already poses an immediate physical risk. **Metformin** is then probably the drug of choice for prevention and treatment alike, though glucagon-like peptide-1 agonists may ultimately prove better. Bariatric surgery may have a place in the rare severe case where all else has failed, its efficacy for drug-induced gain unknown.

MNEMONIC

Lifestyle, Switch, Metformin, then the rest

The order the Maudsley guidance puts it in, the rest being thinner evidence. Clozapine is the documented exception to the ordering, not to the content.

17.2 Metformin: the exception that reverses the order

Metformin for antipsychotic-induced weight gain has the largest evidence base of any agent here. In non-diabetic patients it reduces and reverses the gain at 500 to 2000 mg per day, with benefit on other metabolic parameters, the evidence mainly for olanzapine-induced gain. Individual studies are not unanimous, but meta-analyses show a clear effect, with a positive randomised trial and extension study in children and adolescents with autism spectrum disorder. Two editions of the same guidance give the identical 500 to 2000 mg per day range for antipsychotic-induced weight gain; the second adds that a Cochrane review found only low-certainty evidence that metformin prevents gain in schizophrenia, and that a later cohort study found it did prevent gain with clozapine. It suits weight gain coexisting with diabetes or polycystic ovary syndrome.

Against that ordering stands clozapine-specific guidance. Unless renal function forbids it, every patient starting clozapine should commence metformin concurrently: gain with clozapine is pervasive and starts early, and metformin brings benefits beyond weight, including triglyceride reduction and delayed progression to type 2 diabetes in prediabetic patients. Prophylaxis at initiation, not rescue after failure.

TRAP **Being asked when metformin for antipsychotic-induced weight gain should be started, and answering with one rule.** Two clean sources sit in opposite positions: the Maudsley guidance puts drug treatment last, after behavioural strategies and switching have failed; the clozapine-specific guidance starts metformin on the same day as clozapine, for everyone. State the partial reconciliation rather than assuming it: the prophylactic stance is explicitly clozapine-specific, and switching is largely unavailable on clozapine anyway. Present neither as the universal rule.

17.3 Starting and titrating metformin without losing the patient

For clozapine-associated weight gain and metabolic adverse effects, begin at 500 mg orally each morning, since higher initial doses cause diarrhoea and nausea; extended-release forms may help further. Titrate over three weeks: 500 mg each morning in the first week, then 500 mg twice daily or 1000 mg of the extended-release preparation each morning in the second, then 1000 mg twice daily or 2000 mg extended-release each morning from the third week if tolerated. If 2000 mg per day is not tolerated, fall back to 1500 mg per day, as 750 mg twice daily or 1500 mg extended-release each morning.

Renal function governs eligibility. Metformin for antipsychotic-induced weight gain is safe at an estimated glomerular filtration rate of 30 ml/min or above, with use reviewed below 45 ml/min. The ladder: yearly eGFR while it is 60 ml/min or above; every 3 to 6 months once below 60; below 45, halve the metformin dose and check eGFR every 3 months; stop metformin altogether below **30 ml/min**. Check vitamin B12 yearly: deficiency is commoner on metformin, and its cognitive and affective consequences are readily misread as illness rather than as iatrogenic and correctable.

GOOD TO REMEMBER

Metformin is usually abandoned for one of two reasons: a gastrointestinal start that was too fast, or a renal result nobody looked at. Both are procedural. Write the titration on the prescription, default to extended-release where cost allows, and put eGFR and vitamin B12 on the annual bloods.

17.4 The rest of the pharmacological menu

Four other agents are positively recommended, each with a narrower indication than candidates assume. **Adjunctive aripiprazole** for antipsychotic-induced weight gain is given at 5 to 15 mg per day, randomised trials showing benefit on weight and possibly other metabolic parameters. The scope is strict: weight gain on clozapine or olanzapine only, explicitly not other antipsychotics. It appears safe and unlikely to worsen psychosis. Clozapine-specific guidance restricts it to clozapine monotherapy, and stops it for adverse effects or if no benefit has appeared by 12 to 16 weeks.

Liraglutide, a glucagon-like peptide-1 agonist approved for type 2 diabetes and later as an anti-obesity agent, is given for weight loss at 3 mg per day by subcutaneous injection, higher than the diabetes dose of 1.8 mg or less per day; the two must not be collapsed. Data in drug-induced gain are limited, but one randomised trial showed significant weight loss in overweight prediabetic patients stable on olanzapine or clozapine. It is well tolerated apart from gastrointestinal disturbance, and is recommended in prediabetic or diabetic patients and for clozapine-induced gain.

Orlistat, at 120 mg three times daily before or after food for medication-induced weight gain, works reliably in obesity with calorie restriction; data in drug-induced gain are few. Two qualifications are easily lost: in clozapine-induced or olanzapine-induced gain the effect appeared only in men, and without calorie restriction the effect in psychiatric patients is very limited. Failure to keep to a low-fat diet produces fatty diarrhoea and possible malabsorption of oral medication, here perhaps the antipsychotic itself. It remains a good choice for clozapine-induced gain, reducing weight and constipation alike. **Topiramate**, at up to 300 mg daily in the same indication, reliably reduces weight even when the gain is medication-induced, with a greater effect for prevention than treatment. Its problem is neuropsychiatric: sedation, confusion and cognitive impairment.

17.5 What the evidence does not support

An examiner can as easily ask what you would not prescribe. The agents below were assessed for antipsychotic-induced weight gain and are not recommended; the figures are doses studied, never recommendations, and several still appear on ward rounds on a plausible mechanism.

AGENT	DOSE STUDIED IN ANTIPSYCHOTIC-INDUCED WEIGHT GAIN	VERDICT
Amantadine	100-300 mg/day	Too limited to recommend
Alpha-lipoic acid	1200 mg/day	Not recommended
Betahistine	48 mg/day	Limited data; not recommended
Bupropion	no dose recorded	Few data in drug-induced gain; not recommended
Bupropion with naltrexone	no dose recorded	No data in drug-induced gain; not recommended, but not ruled out
Fluvoxamine	50 mg/day	Too limited to recommend, and markedly raises clozapine levels: extreme caution
Melatonin	up to 5 mg at night	Effect, if any, is small
Modafinil	up to 300 mg/day	Not recommended
Naltrexone	25-50 mg/day	Two small pilot randomised trials only
Zonisamide	100-600 mg/day	Not recommended

Agents recommended in earlier editions, including the histamine H2 antagonists, have been removed, though the older textbook a candidate revised from may still carry them.

17.6 Lipids, glucose, and when a metabolic problem stops the drug

Patients with raised cholesterol may benefit from dietary advice, lifestyle change and statins, which seem to be effective in this patient group though interactions are possible. Evidence supports treating cholesterol as low as **4 mmol/l** in high-risk patients, the highest level the National Institute for Health and Care Excellence recommends for secondary prevention of cardiovascular events; no target is set for primary prevention, though recent advice promotes statins wherever ten-year cardiovascular risk exceeds 10%. Separately, coronary heart disease and stroke risk fall by a third if cholesterol is reduced to as low as 3.5 mmol/L. Where triglycerides alone are raised, a low-saturated-fat diet, fish oil and fibrates work without proven mortality benefit, and such patients need screening for impaired glucose tolerance and diabetes. For moderate to severe hyperlipidaemia, switch first to a less offending agent; D2 partial agonists such as aripiprazole are treatments of choice after previous antipsychotic-induced dyslipidaemia.

The glucose lane follows the same logic. Switching to an antipsychotic of lower cardiometabolic risk often reverses changes in glucose tolerance, most compellingly to aripiprazole and also

ziprasidone; for prediabetes or diabetes on clozapine, olanzapine or quetiapine, switch to aripiprazole, brexpiprazole, cariprazine, lurasidone or ziprasidone. Lifestyle intervention prevents diabetes and belongs to everyone with schizophrenia, not only those whose glucose has drifted.

Then comes the question the lane is really testing. Metabolic adverse effects are almost never grounds for stopping clozapine. Weight gain, hypertension, dyslipidaemia and metabolic syndrome are each so classed. The exceptions are emergencies: out-of-control diabetes, diabetic ketoacidosis or a hyperosmolar hyperglycaemic state, during which temporary cessation may help. Developing diabetes is not itself a reason to stop, and no evidence supports dose reduction for glycaemic control. The reflex to shave the dose costs the patient the only drug that worked and buys nothing.

17.7 Hyperprolactinaemia: mechanism, and which drugs actually do it

Dopamine inhibits prolactin release, so dopamine antagonists raise plasma prolactin, probably dose-relatedly. For most antipsychotics the D2 occupancy at which prolactin starts to rise sits very close to that needed for efficacy, leaving little window to exploit. Hence the effect is called probably unavoidable in practice with first-generation drugs, whose main drawbacks are acute extrapyramidal symptoms, hyperprolactinaemia and tardive dyskinesia.

The correction that carries marks: hyperprolactinaemia is usually worse with risperidone, paliperidone and amisulpride than with typical drugs. The generation label predicts nothing; the three-tier ranking makes this explicit. **Prolactin-sparing**, increase very rare: aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lumateperone, pimavanserin, quetiapine. **Low-risk prolactin-elevating**, minor changes: lurasidone, olanzapine, ziprasidone. **High-risk prolactin-elevating**, major changes: amisulpride, paliperidone, risperidone, sulpiride and the first-generation antipsychotics. Clozapine and olanzapine head the metabolic lists yet sit in the sparing and low-risk prolactin groups: metabolically brutal may mean endocrinologically gentle, and the reverse.

High-risk prolactin-elevating drugs should be avoided where possible in four groups.

- Patients under 25 years of age, before peak bone mass is reached.
- Patients with osteoporosis.
- Patients with a history of hormone-dependent breast cancer.
- Young women.

The first bears directly on first-episode psychosis, where the typical patient is younger than the threshold and risperidone is a common first choice. The rationale is skeletal, not cosmetic: prolactin-driven hypogonadism during bone accrual costs peak bone mass never fully recovered.

17.8 What the number means, and the three normal ranges

Hyperprolactinaemia is often superficially asymptomatic, and some evidence suggests it does not affect subjective quality of life. The silence misleads. The consequences of hyperprolactinaemia accrue whether or not the patient reports anything, because persistent elevation suppresses the

hypothalamic-pituitary-gonadal axis: sexual dysfunction, menstrual disturbance, breast growth and galactorrhoea, occasionally delusions of pregnancy, and long term reduced bone mineral density and a possible increase in breast cancer risk. That last is hedged in the source and must stay hedged. In premenopausal women, above 100 ng/mL brings infertility and amenorrhoea, hot flushes and vaginal dryness; 50 to 100 ng/mL may cause amenorrhoea or oligomenorrhoea; 20 to 50 ng/mL may cause infertility even with a normal cycle, though most have no galactorrhoea. In men, reduced libido, erectile dysfunction, fatigue, gynaecomastia and infertility, with galactorrhoea only rarely; chronic elevation costs body hair, muscle mass and bone.

Before attributing any of it to the antipsychotic, clear the differential: prolactin also rises with stress, pregnancy and lactation, seizures, renal impairment and other medical conditions including prolactinoma. Venepuncture in a distressed patient is itself a cause.

PITFALL

The raised prolactin is read off the report and blamed on the drug, and a pregnancy that would have changed everything is missed, or a prolactinoma grows behind a pharmacological alibi. Exclude pregnancy, recent seizure, renal impairment and acute stress at sampling first. The corollary error: an elevation on a prolactin-sparing agent dismissed as expected, when nothing about that drug predicts it.

Three sources give three different definitions of normal, and the disagreement is substantive rather than rounding.

SOURCE	NORMAL RANGE	WHAT THE NUMBER TRIGGERS
Maudsley 15th edition	Sex-specific: women 0-25 ng/ml, about 0-530 mIU/L; men 0-20 ng/ml, about 0-424 mIU/L	Elevated is 25-118 ng/ml (530-2500 mIU/L): assess prolactin-related adverse effects systematically and discuss the consequences of prolonged elevation. Highly elevated is above **118 ng/ml, above 2500 mIU/L**: refer to rule out prolactinoma.
Kaplan and Sadock's Comprehensive Textbook of Psychiatry	Not sex-specific: 5 to 20 ng/mL, a lower bound the Maudsley range lacks	Contextual: imaging is not usually performed if the patient is on an antipsychotic known to cause hyperprolactinaemia and the magnitude fits a drug cause
Indian consultation-liaison guidance	Not sex-specific; defined as more than 20 ng/ml	Prompts the search for a contributing drug
Dulcan's Textbook of Child and Adolescent Psychiatry	Not stated	Above 200 ng/mL, or persistent elevation despite a change to a prolactin-sparing drug, image the sella turcica for pituitary adenoma or parasellar tumour; if normal, replace sex steroids to prevent osteoporosis

A woman whose prolactin sits just above the American textbook's upper bound but below the Maudsley ceiling for women is normal by the Maudsley range, above range by that textbook, and hyperprolactinaemic by the Indian definition. Only one sets a different ceiling for women than men, and that sex-specificity is itself the disagreement worth teaching. The imaging thresholds diverge almost twofold, and the child and adolescent figure comes from a different population in a truncated sentence, so neither dismisses the other. Monitoring is contested the same way. The Maudsley fifteenth edition measures plasma prolactin at baseline in every patient, with symptom enquiry at 3 months and a level obtained then only if hyperprolactinaemia is suspected or the patient is on a prolactin-elevating antipsychotic. The same publisher's other edition sets a different routine interval; the American Psychiatric Association guideline obtains a level only where clinical history indicates it; the National Institute for Health and Care Excellence puts prolactin in its universal baseline panel. The cadence belongs where this chapter deals with metabolic monitoring protocols; what belongs here is that a routine baseline level is not universally agreed to be necessary.

17.9 Treating it: what to change, what to add

LOCUS is again the outpatient clinic, switching and adding both carrying a psychiatric risk managed across weeks with the patient at home. **FOCUS** divides cleanly: acutely, whichever symptom brought it to attention, usually sexual dysfunction or amenorrhoea; long term, bone. **MODUS** for antipsychotic-induced hyperprolactinaemia follows the Maudsley guidance, the Indian consultation-liaison position converging on the same manoeuvres.

RULE **Treatment of hyperprolactinaemia depends more on symptoms and long-term risk than on the reported plasma prolactin level.** This is why the guidance stating it offers no action threshold, and it is the safest framing when sources disagree about where normal ends. A markedly raised but asymptomatic level in a patient with no bone risk factors may reasonably be observed after a shared discussion of the consequences of hyperprolactinaemia; a modestly raised level in a young woman with amenorrhoea demands action.

Switching to an antipsychotic of lower prolactin liability is usually the first choice once treatment is judged necessary, though it risks destabilising the illness. Adding aripiprazole is the alternative. Bone-protective measures run in parallel and cost little: stopping smoking, weight-bearing exercise, adequate calcium and vitamin D3. Where a patient must stay on a prolactin-elevating agent and cannot tolerate aripiprazole, **dopamine agonists** work; amantadine, cabergoline and bromocriptine have all been used, each with at least a theoretical potential to worsen psychosis, unreported in trials.

The dose figures for antipsychotic-induced hyperprolactinaemia are where the guidance comes apart. In the management prose, aripiprazole lowers prolactin dose-dependently: 3 mg per day is effective and 6 mg per day more so, **6 mg per day** appearing sufficient. The summary box in the same guidance instead gives aripiprazole 5 mg a day as first choice, with second choices in no particular order: the dopamine agonists cabergoline, bromocriptine and amantadine; Peony Glycyrrhiza Decoction; and metformin 2.5 to 3 g a day. A footnote qualifies the first choice: aripiprazole may not normalise prolactin in amisulpride-induced hyperprolactinaemia. That metformin figure derives from a study of diabetic women on antipsychotics, a narrow population. In the paediatric literature aripiprazole 5 to 15 mg per day is a prolactin-lowering partial dopamine agonist option in children and adolescents, effective without worsening psychosis.

TRAP **Quoting one aripiprazole dose, or one metformin dose, without its indication.** The 3 mg per day and 6 mg per day of the prose and the 5 mg a day of the summary box are read in clean passages; neither is a rendering artefact, and all sit far below antipsychotic doses. All differ again from the 5 to 15 mg per day of adjunctive aripiprazole for weight gain, and that range is not unique to weight gain either: the paediatric prolactin-lowering dose is 5 to 15 mg per day as well, so the number alone settles nothing and the indication and the age group have to be carried with it. Metformin is worse: 500 to 2000 mg per day for weight gain against 2.5 to 3 g per day for prolactin lowering. Name the indication first and the number second, and flag the discrepancy rather than smoothing it away.

IN INDIA

Indian consultation-liaison guidance takes a lower and simpler line, defining hyperprolactinaemia as a serum prolactin above 20 ng/ml, with no separate ceiling for women. Its ranking diverges at the low end: phenothiazines, butyrophenones, risperidone and amisulpride carry the greatest risk; olanzapine and quetiapine modest risk; ziprasidone and aripiprazole low risk, whereas the Maudsley table classes quetiapine as prolactin-sparing; both agree at the high-risk end. It adds that potency of D2 blockade, increasing age and female sex all raise risk, that antidepressants, opioids, antiemetics and antihypertensives are major contributors, and that the strategies are dose reduction, changing agent, a partial D2 agonist such as aripiprazole, or a dopamine agonist, naming bromocriptine. Which of the dopamine agonists is the more available or the cheaper in Indian practice is not addressed by any source drawn on here, so no preference between bromocriptine and cabergoline is stated.

In both lanes the first move is to change the antipsychotic, not add a drug; and if a drug is added, name the indication before the number: metformin at 500 to 2000 mg per day for weight gain but 2.5 to 3 g per day for prolactin, aripiprazole at 5 to 15 mg per day for weight gain, single-figure doses for prolactin in adults, and 5 to 15 mg per day for prolactin again in children and adolescents, so one range serves two indications and only the indication and the age group tell them apart.

18 · Diabetes, depression and hypoglycaemia

Two questions live inside this topic and they are examined differently. The first is epidemiological and prognostic: the bidirectional relationship of diabetes and depression keeps the two travelling together, and the comorbid patient dies earlier than either illness alone predicts. The second is acute and physiological: hypoglycaemia mimics panic before it is recognisably neurological.

The halves connect through treatment, which is where the psychiatrist's leverage lies.

12%	10 TO 15%	50%	70 mg/dL
MAJOR DEPRESSION, POOLED ACROSS 39 STUDIES	DEPRESSIVE DISORDER IN DIABETES, ROUGHLY TWICE THE AVERAGE POPULATION	INCREASED MORTALITY WITH COMORBID DEPRESSION	GLUCOSE AT WHICH THE FIRST PHYSIOLOGICAL RESPONSE BEGINS

18.1 The bidirectional relationship of diabetes and depression, unequally evidenced

Type 2 diabetes and major depression stand in a **bidirectional relationship** in disease incidence, but the arms are not evidenced to the same standard. Studies consistently report an increased risk of major depression in type 2 diabetes, with diabetes doubling the odds of comorbid depression and raising the likelihood of an antidepressant being prescribed, though estimates vary with population, measures and criteria. The depression-to-diabetes arm, an increased risk of insulin resistance and of type 2 diabetes, is asserted flatly, without an effect size, so the honest viva formulation of the bidirectional relationship of diabetes and depression is asymmetric; a remembered relative risk for it fills a blank the sources leave open. Major depression also

contributes significantly to hospital admission and to death in type 2 diabetes, and selective serotonin reuptake inhibition has been reported to improve insulin sensitivity.

The loop is sustained clinically, not molecularly. Depression has a negative impact on metabolic control, and poor metabolic control may in turn worsen depression: a feedback loop the psychiatrist can enter, because the entry point is the depression.

18.2 How common, and in which population

Prevalence figures mean nothing without their denominators. Reported rates of comorbid depressive symptoms in diabetic patients range from 9 to 60%, a spread the source attributes explicitly to differences in study design and screening method rather than real variation between populations. A mid-point would manufacture a number the literature declines to give. Three better-specified estimates:

SOURCE AND POPULATION	FIGURE	WHAT IT IS BOUND TO
Multiple studies, people with diabetes (predominantly Western, higher-income samples)	10 to 15% prevalence of depressive disorders, roughly twice that of the average population	Band and doubling travel together; the band alone loses the claim.
Meta-analysis pooling 39 studies of patients with diabetes	**12%** prevalence of major depression	A twofold increased prevalence against controls was shown in the controlled subset only.
United States health maintenance organisation cohort, approximately 4,800 adult patients with predominantly type 2 diabetes (96%)	12% met criteria for major depression and 8.5% for minor depression	A single insured cohort; the profile below travels no further.

Depression here also shades below the diagnostic threshold: perhaps as many as 25% of people with diabetes experience **subsyndromal depressive symptoms**. They are missed by categorical instruments and are the group in whom self-management quietly deteriorates.

The same cohort supplies a phenotype. Compared with diabetes alone, those with both conditions were younger, more often female, less educated, carried significantly higher medical comorbidity and more diabetes complications, had a longer duration of diabetes, higher glycosylated haemoglobin and body mass index values, and were more often smokers. They had also developed diabetes an average of 5 years earlier. Note what **minor depression** is doing: at 8.5% it is not a rounding error, and it reappears below as an independent contributor to mortality.

IN INDIA

Nearly all the data above are Western and higher-income, and the little evidence from elsewhere suggests the burden here is not smaller. A review from South Asia found the prevalence of type 2 diabetes with elevated depressive symptoms ranged from 11.6% to 67.5%; a meta-analysis from Iran estimated depression in 54% of patients with diabetes; a Saudi study of children with type 1 diabetes reported 27%. Indian investigators found a similarly high rate, with depression associated with younger age, female sex, low socioeconomic status and poor self-management. Two cautions. The standard reference states the Indian finding qualitatively and attaches no figure, so there is no Indian prevalence number to quote. And that risk profile is the patient least likely to return in a fee-for-service setting: screen at the diabetes contact, not on referral.

18.3 Not an episode but a course

Depression here tends to be chronic or recurrent, not self-limiting. In the same insured cohort, 63% of patients with diabetes and major depression had two years or longer of significant depressive symptoms. A separate study, and this is a different population that must not be merged with the first, found that 79% of patients with diabetes and major depression relapsed over a five-year follow-up, with a mean of four episodes per patient.

The first says most comorbid depression met at a clinic visit is a long-standing state, not a fresh episode, which reframes the patient described as unmotivated. The second says remission is not the endpoint. Both point at one decision: maintenance and structured review, not an acute intervention discharged on response.

18.4 What the comorbidity costs

Comorbid depression tracks hard endpoints. A meta-analysis of 22 studies involving more than a million participants found depression associated with increased risk of both macrovascular complications, hazard ratio 1.38 (95% CI 1.30 to 1.47), and microvascular complications, hazard ratio 1.33 (95% CI 1.25 to 1.41), and found the relationship bidirectional at the complication level, in that diabetes complications themselves increased the risk of depression. This is the better-quantified statement of the bidirectional relationship of diabetes and depression, with effect sizes on both arms.

Mortality is where the numbers get garbled: four comparisons in one passage, each with its own denominator.

- A systematic review of 10 longitudinal studies: comorbid depression carried a **50% increased mortality risk**.
- An older-adult study: depression or diabetes each raised mortality by almost one-third, while respondents with both had a fourfold increase compared with those who had neither.
- The Pathways Epidemiology Study, adjusted for age, gender and socioeconomic factors: comorbid major depression carried a twofold increase in mortality over three years against non-depressed patients; minor depression raised mortality risk by 67%.

- The same cohort, further adjusted for diabetes and medical disease severity and for adverse health behaviours including smoking, obesity, sedentary lifestyle and glycosylated haemoglobin: major and minor depression remained associated with an approximately 50% increase in mortality.

The fourth line is the one to carry. If depression killed only through smoking, inactivity and neglected glucose, adjusting for those behaviours should abolish the excess. Roughly half survives, which is why comorbid depression is an independent prognostic factor rather than a marker of poor self-care. The prescribing literature converges on the same magnitude, a 50% increased risk of mortality alongside a high burden of cardiovascular risk factors.

18.5 Shared mechanisms, held loosely

The closeness of the association invites a common-cause explanation, and several are on offer. The commonest is psychological: chronic disease burden predisposes to depression, or depression erodes motivation and worsens self-management. Shared biology is proposed alongside it. Hyperglycaemia can affect mood states, and high plasma glucose in the brain can increase oxidative stress, producing neuronal damage and, on this account, depression. The microvascular changes of diabetes are identifiable in the brain and may predispose to depression independently. Type 2 diabetes is associated with **low-grade systemic inflammation**, proposed as the substrate of the depression seen in diabetes, and others have suggested calcium and cyclic AMP signalling as the cellular mechanism.

The source supplies the essential qualifier itself: most of this work is cross-sectional and limited to correlation, and longitudinal research is needed before any of it can be called established. Write them as candidate mechanisms; an answer asserting inflammation as the mechanism has overstated the evidence.

18.6 Making the diagnosis of diabetes: two thresholds that do not agree

The screening decision often falls to the psychiatrist. Three clinical measures may be used: a fasting plasma glucose of 126 mg/dL or above; a non-fasting plasma glucose of 200 mg/dL or above in a person with symptoms of diabetes; or an abnormal oral glucose tolerance test with a two-hour value of 200 mg/dL or above. Alongside these, **glycosylated haemoglobin** has become a standard method both of diagnosis and of monitoring over time, reflecting glycaemic control over the preceding 2 to 3 months.

The guideline written for patients on antipsychotic medication states the same rules with different edges: a fasting blood glucose higher than 125 mg/dL, with fasting defined as no caloric intake for at least 8 hours, or alternatively a glycosylated haemoglobin of 6.5% or greater; an oral glucose tolerance test or a random blood glucose of at least 200 mg/dL in conjunction with a hyperglycaemic crisis or classic hyperglycaemic symptoms are also acceptable. Crucially, it adds that results should be confirmed by repeat testing unless unequivocal hyperglycaemia is present.

TRAP **There is no single harmonised glycosylated haemoglobin rule, and a question written around a value exactly on the threshold is testing whether you know that.** The comprehensive textbook states that two values over 6.5% are diagnostic: two measurements, strict inequality. The practice guideline, citing the American Diabetes Association, states that a single value of 6.5% or greater can be used: one measurement, inclusive threshold, with confirmation by repeat testing unless hyperglycaemia is unequivocal. A reading exactly on the threshold satisfies the second and fails the first. The fasting criterion repeats the pattern, 126 mg/dL or above against higher than 125 mg/dL: identical for whole numbers, differently expressed. Do not resolve this by picking a value; the point is that confirmation is required.

One further rule marks the limit of the convenient test. In haemoglobinopathies, or conditions associated with increased red blood cell turnover, fasting blood glucose should be used rather than glycosylated haemoglobin; the conditions named are second-trimester or third-trimester pregnancy, haemodialysis, recent blood loss, transfusion and erythropoietin therapy. These criteria belong with the account of metabolic syndrome, obesity and mortality in serious mental illness; the screening schedule, with the metabolic monitoring protocols.

18.7 Disordered eating and insulin omission in type 1 diabetes

This small topic punches above its weight, and belongs to type 1 diabetes. A meta-analysis reports eating disorders in 8.2% of patients with type 1 diabetes compared with 2.8% of controls. What makes the population distinctive is **insulin omission**, a purging method available only to a patient who injects insulin, found in **up to 40% of type 1 diabetic patients**. Insulin is withheld to lose weight; risk factors are female sex and higher body mass index. Consider an eating disorder in any patient with poor glycaemic control or multiple episodes of diabetic ketoacidosis. Neither figure carries across to type 2 diabetes, where the behaviour has no equivalent mechanism.

PITFALL

Recurrent ketoacidosis in a young woman with type 1 diabetes is routinely written up as non-adherence, and the note recommends education. Non-adherence and deliberate insulin omission look identical on a discharge summary and are entirely different problems: one needs teaching, the other an eating disorder assessment. The discriminating questions are about weight, shape and the function the omission serves, and nobody asks unless the possibility is raised.

18.8 Hypoglycaemia: the cascade, the thresholds and the symptom sequence

In the absence of prolonged fasting, healthy people almost never have blood glucose below 3.5 mM. As glucose falls, defence is mounted in stages. The pharmacological account places **reduction of endogenous insulin secretion** first, occurring at a plasma glucose of **about 70 mg/dL (3.9 mM)**; thereafter the **counter-regulatory hormones** are released, named as glucagon, epinephrine, norepinephrine, growth hormone and cortisol. Symptoms typically become manifest at 60 to 70 mg/dL (3.3 to 3.9 mM).

TRAP **Two standard texts order the physiology differently, and an answer built on the wrong ordering is wrong even with the right number.** The pharmacology text puts falling endogenous insulin secretion first and hormone release second, naming five counter-regulatory hormones. The clinical methods text opens with hormone release, stating that physiological responses begin at a plasma glucose of around 3.8 mmol/L with the release of counter-regulatory hormones such as glucagon or adrenaline, and names two. The thresholds are the same, around 3.8 mmol/L against about 3.9 mM; the disagreement is what happens first. State that both accounts exist, and prefer the fuller list when asked to enumerate.

The sequence is ordered by glucose level, not severity of distress: autonomic symptoms come first, generated at a higher glucose than neuroglycopenic ones.

STAGE	FEATURES	WHY THE ORDER MATTERS
Autonomic, at higher glucose	Sweating, hunger, paraesthesiae, palpitations, tremor and anxiety, with agitation and blurred vision described alongside them	The phenomenology of a panic attack, hence the anxiety differential. Most patients recognise these symptoms and treat themselves rapidly.
Neuroglycopenic, at lower glucose	Difficulty concentrating, confusion, weakness, drowsiness, a feeling of warmth, dizziness, blurred vision and loss of consciousness; impaired intellectual activity and diminished psychomotor skills	Cerebral glucose is now low. The patient can no longer reliably self-rescue; the presentation is cognitive.
Severe	Seizure and coma; severe agitation, confusion, coma and epileptiform seizures	Hypoglycaemia can present as an acute behavioural disturbance, not a faint.

One qualification undoes that reassurance. **Loss of awareness of hypoglycaemia** is sometimes a problem in diabetic patients with autonomic neuropathy, and in insulin-treated diabetes leads to unexpected hypoglycaemia: the warning tier is absent, and the patient reaches the neuroglycopenic stage without having felt the autonomic one. Those at risk should be warned against driving motor vehicles and taught the early symptoms of this potentially serious complication. The standard texts give no glucose value at which neuroglycopenic symptoms begin, and none should be invented.

18.9 Hypoglycaemia and psychiatric presentations: the differential, and managing the pair

The link between hypoglycaemia and psychiatric presentations earns its place twice over: as a mimic and as a hazard. As a mimic, it appears in the standard list of medical conditions associated with anxiety, in the metabolic group alongside hyperkalaemia, hyperthermia, hyponatraemia and vitamin deficiencies; hyponatraemia belongs to the account of SIADH and hyponatraemia. The discriminating feature is temporal: phaeochromocytoma and hypoglycaemia usually produce **episodic symptoms** and so are likelier to mimic a phobic or panic disorder, though both belong in the differential of generalised anxiety disorder, with examination and laboratory tests where there is doubt.

MNEMONIC

Treatment, Tumour, Taken

The commonest scenarios producing hypoglycaemia. **Treatment**: treatment of diabetes with insulin or with oral agents that promote insulin secretion. **Tumour**: inappropriate endogenous insulin from a pancreatic islet tumour, or insulin-like growth factors from non-islet tumours such as hepatomas or sarcomas. **Taken**: purposeful or inadvertent use of a glucose-lowering agent by a person without diabetes, the factitious route and the psychiatrically important one. The first and third can occur in either the fasting or the fed state, whereas hypoglycaemia from a neoplasm occurs in the fasting state. Within treated diabetes it may follow an inappropriately large insulin dose, a mismatch between peak insulin delivery and food intake, or added factors that increase insulin sensitivity, such as adrenal or pituitary insufficiency, or that increase insulin-independent glucose uptake, such as exercise.

As a hazard, it complicates glucose-lowering treatment, particularly insulin, and leaves a cognitive trace: severe hypoglycaemic episodes, meaning those associated with emergency department attendance or hospitalisation, have increased the risk of dementia in patients with diabetes. The association is bound to episodes of that severity and carries no effect size. The dementia syndrome and its workup belong to the Dementias and neurocognitive disorders notes.

RULE **Every patient presenting with coma or a reduced conscious level must have their blood glucose checked immediately.** Patients with diabetes can present with acute metabolic decompensation, leading to diabetic ketoacidosis, hyperosmolar hyperglycaemic syndrome or, in treated patients, hypoglycaemia. There is no exemption for a patient who already holds a psychiatric diagnosis. The wider assessment of the acutely confused patient belongs to the Stroke, TBI, delirium and focal brain syndromes notes; the capillary glucose comes first, and is not delegated.

LOCUS. Mostly outpatient and shared with a physician or diabetologist, the psychiatrist contributing recognition, sequencing and monitoring rather than glycaemic prescribing. The emergency locus is the rule above; inpatient care belongs to the patient whose depression has made self-management unsafe, or whose recurrent ketoacidosis needs both medical stabilisation and an eating disorder assessment. The authorities are The Maudsley Prescribing Guidelines for antidepressant selection, the American Psychiatric Association practice guideline for screening thresholds, and Kaplan and Sadock's Comprehensive Textbook of Psychiatry for epidemiology, prognosis and the eating disorder overlap.

FOCUS changes with phase. The acute target is glucose itself and the safety of a patient confused or agitated from it. The short-term target is the depressive episode on its own merits, with glycaemic control watched as it moves. The mid-term target is the recurrence risk above, making structured review the default. The long-term targets are the complication and mortality trajectories and the cognitive cost of severe hypoglycaemia.

MODUS. Every patient diagnosed with depression should be screened for diabetes. In those who are diabetic, selective serotonin reuptake inhibitors are used first line, with data supporting

sertraline, escitalopram and fluoxetine; serotonin and noradrenaline reuptake inhibitors are also likely to be safe but have fewer supporting data; agomelatine seems promising on limited data; and tricyclic antidepressants and monoamine oxidase inhibitors should be avoided where possible because of their effects on weight and glucose homeostasis. That last caution has a sharp edge here, because **irreversible monoamine oxidase inhibitors** have a tendency to cause extreme hypoglycaemic episodes as well as weight gain, an effect explicitly not attributed to moclobemide. Psychological and social modes carry the self-management burden the epidemiology keeps pointing at; the pharmacology of the antidepressants belongs to the Mood disorders: pharmacotherapy notes.

GOOD TO REMEMBER

The monitoring instruction is more specific than general vigilance. Blood glucose and glycosylated haemoglobin should be monitored carefully when antidepressant treatment is started, when the dose is changed, and after it is discontinued. Discontinuation is the forgotten one: the glucose effect outlasts the prescription.

Depression in diabetes is common, chronic, recurrent and independently lethal, carrying an approximately 50% increase in mortality that survives adjustment for health behaviours; and in any patient with reduced consciousness, seizure or acute behavioural disturbance, capillary glucose is measured immediately and before the presentation is called psychiatric.

19 · Metabolic syndrome, obesity and mortality in serious mental illness

This is where psychiatry stops being a specialty of the mind alone. Patients with schizophrenia and related psychoses do not, in the main, die of psychosis. They die of the cardiovascular and metabolic diseases that kill everyone else, only earlier and after less vigorous medical attention. Metabolic syndrome names the cluster that antipsychotic treatment aggravates, and it is the physiology of that premature death.

34% METABOLIC SYNDROME, US ADULTS, GENERAL POPULATION	**40 TO OVER 50%** METABOLIC SYNDROME IN SCHIZOPHRENIA	**TWICE** OBESITY PREVALENCE IN SCHIZOPHRENIA VERSUS GENERAL POPULATION	**10 TO 25 YEARS** LIFE-EXPECTANCY REDUCTION IN SERIOUS MENTAL DISORDER

19.1 The construct, and the bodies that own the definition

Metabolic syndrome, or syndrome X, was delineated by **Gerald Reaven** and remains contested in its detail. It is not a disease in the way diabetes is but a way of noticing that these abnormalities travel together and jointly predict outcomes no single component predicts as well alone.

Companion to Psychiatric Studies counts four major features: increased abdominal or visceral adiposity seen as raised waist circumference, atherogenic dyslipidaemia, hypertension, and impaired fasting glucose or overt diabetes. Four and not five because **atherogenic dyslipidaemia** bundles low high-density lipoprotein and raised triglycerides into one: presentation, not content.

Kaplan and Sadock trace the most widely accepted definition to the third adult treatment panel (ATP III) of the National Cholesterol Education Program, then record two modifications: the adapted panel (ATP III-A) proposed by the American Heart Association decreased the cutoff for fasting glucose, and the International Diabetes Federation stressed waist circumference by modifying the parameters to a lower cutoff. Companion agrees: the American Heart Association set requires a slightly lower fasting glucose, and the International Diabetic Association criteria, the most pragmatic if the least rigorous, are based solely on waist circumference.

19.2 The operational criteria, and the two structures that disagree

The citable set is the harmonised definition in the American Psychiatric Association practice guideline, attributed to Alberti et al. 2009: **at least three of five** risk factors, none mandatory. Two features are load-bearing and routinely dropped. First, the waist threshold is the source's own declared United States and Canada value, not a universal one. Second, each non-waist criterion is met by the number or by drug treatment for that abnormality: a fibrate, nicotinic acid or high-dose omega-3 fatty acids for the lipid criteria, an antihypertensive in a patient with a history of hypertension, or a glucose-lowering drug, so a patient controlled on medication can satisfy three criteria with every printed laboratory value normal.

A structurally different set circulates. Appendix 2 of the Maudsley Guidelines on Advanced Prescribing in Psychosis makes waist obligatory and requires only two of the remaining four, naming no issuing body.

FEATURE	HARMONISED SET (AMERICAN PSYCHIATRIC ASSOCIATION PRACTICE GUIDELINE)	WAIST-MANDATORY SET (MAUDSLEY GUIDELINES ON ADVANCED PRESCRIBING IN PSYCHOSIS, APPENDIX 2)
Structure	Any three of five, nothing mandatory	Waist obligatory plus any two of four
Waist, men	Above 102 cm (40.2 inches), a declared United States and Canada value	94 cm (37 inches) or more
Waist, women	Above 88 cm (34.6 inches)	80 cm (31.5 inches) or more
Triglycerides	150 mg/dL or more	1.7 mmol/L or more
High-density lipoprotein	Below 40 mg/dL men, below 50 mg/dL women	Below 1.03 mmol/L men, below 1.29 mmol/L women
Blood pressure	Systolic 130 mmHg or more, diastolic 85 mmHg or more, or both	130/85 mmHg or more
Fasting glucose	100 mg/dL or more	Above 5.5 mmol/L

MNEMONIC

Wide, Thick, Low, High, Sweet

In the harmonised set's own order: **Wide** waist, **Thick** blood (triglycerides), **Low** high-density lipoprotein, **High** blood pressure, **Sweet** blood (fasting glucose). Any three make the syndrome, and for the last four a drug treating the abnormality counts as the abnormality.

TRAP **Treating "the metabolic syndrome criteria" as one thing.** The disagreement is structural before it is numerical. Raised triglycerides, low high-density lipoprotein and raised blood pressure with a normal waist *is* the syndrome by the any three of five rule and *is not* by the waist-obligatory rule. Name the criteria set before applying it.

The units do not convert: the harmonised threshold for elevated fasting glucose, 100 mg/dL or more, appears in the Maudsley appendix as a strict inequality in different units, and converting between them would be the chapter's arithmetic, not a source's threshold. It is also the threshold that *moved*: both sources naming the American Heart Association adaptation as the one that lowered it give no value it was lowered from, so the original ATP III cutoff is not recoverable here. Tasman Psychiatry states the same rule in imperial units, abdominal obesity as a waist of 35 inches or more for women or 40 inches or more for men.

19.3 The definition you apply decides the prevalence you find

Kaplan and Sadock put general-population prevalence at approximately 34% of United States adults, similar to other developed countries, up from 25% in 1988, concentrated in non-Hispanic black females, and also associated with lower education and older age. Most relevant studies put prevalence in schizophrenia at about 40% to over 50%, with no criteria set named for that range. That range then circulates as the prevalence of metabolic syndrome in severe mental illness, a label wider than the schizophrenia samples it was measured in; the widening is the reader's and not the source's.

The CATIE baseline sample shows why. In the same patients, National Cholesterol Education Program criteria gave 40.9% and American Heart Association criteria gave 42.7% (McEvoy et al 2005). Change the instrument again and the spread widens: using waist circumference alone, prevalence in females was double that in males, 73.4% against 36.6%, and even accounting for body mass index, males were 85% more likely to have metabolic syndrome while the comparable figure in females was 137%.

RULE **A prevalence of metabolic syndrome quoted without its criteria set and its population is uninterpretable.** Two criteria sets applied to the same patients differ by under two percentage points, 40.9% against 42.7%. The wide spread comes from elsewhere: using waist circumference alone, that same cohort runs 36.6% in males against 73.4% in females, a split by sex within one method rather than a gap between methods. Quote neither figure without saying which criteria set was applied and to whom.

19.4 What the syndrome actually buys in risk

Prospective studies show that metabolic syndrome raises the risk of developing coronary vascular disease by over 50% and the risk of type 2 diabetes by approximately threefold compared with individuals without metabolic syndrome. Both figures carry that comparator inside them. The **approximately threefold** diabetes risk is why the cluster is called prediabetic rather than a risk marker, and the thread is **insulin resistance**, which is why these abnormalities cluster at all. In the United States over 96 million adults, or 1 in 3 adults aged 18 or older, have prediabetes.

IN INDIA

Every prevalence figure here is United States or Western, the sharpest limitation in this topic for Indian practice. The harmonised waist threshold is its own source's United States and Canada value, and no South Asian threshold appears in these references at all; since central adiposity at a given waist means different things across populations, a North American cut-point applied to Indian patients is not neutral. There is likewise no Indian general-population prevalence, no Indian prevalence in serious mental illness, and no Indian or South Asian mortality-gap figure. Record the waist in centimetres rather than only the verdict against an imported threshold, and the number stays usable when a local cut-point arrives. Lipids and glucose cost the patient money; the tape, the scale and the cuff cost nothing, and the free measurements should never be the omitted ones.

19.5 Obesity: the thresholds, and the number that triggers action

Obesity is the component the psychiatrist sees first. It is about twice as prevalent in people with schizophrenia as in the general population, and substantial evidence attributes part of that excess to psychotropic treatment, particularly certain antipsychotics. The drug-by-drug ranking belongs with antipsychotic metabolic effects, and drug selection with the Schizophrenia: management, antipsychotics and adverse effects notes.

Body mass index is weight in kilograms divided by the square of height in metres. Kaplan and Sadock give greater than 25 kg/m2 for overweight and greater than 30 kg/m2 for obesity, and record approximately 42% of United States adults obese as of 2019, up from 30% in 2000, with severe obesity rising from about 5% to 9%: Centers for Disease Control figures. The American Psychiatric Association practice guideline bands the same construct as 25 to 29.9 for overweight and 30 or higher for obesity, and adds waist as a risk indicator at above 35 inches for women and above 40 inches for men.

In patients on antipsychotic medication, except for those with a body mass index below 18.5, an increase in body mass index of 1 unit suggests a need for intervention: closer weight monitoring, a weight management programme, adjunctive treatment to reduce weight, or changing the antipsychotic.

GOOD TO REMEMBER

The threshold for action is **an increase in body mass index of 1 unit**, not a crossing of the obesity line. It is set that low because weight gained early on an antipsychotic is rarely lost later, so waiting for formal obesity wastes the whole period in which the trajectory could have been altered.

Why body mass index rather than the waist that the metabolic syndrome criteria make central? Stahl's The Clozapine Handbook is explicit: waist circumference shows significant variability between examiners to an extent that does not exist with body mass index, so changes in body mass index serve as a more accurate measure. Diagnosis asks whether a threshold was crossed once, monitoring asks whether a number is moving, and inter-rater noise wrecks the second question while barely touching the first.

19.6 Diabetes and cardiovascular comorbidity in serious mental illness

Kaplan and Sadock count almost 100 systematic reviews and meta-analyses of physical health comorbidity in mental illness since 2000, of which 15 concerned schizophrenia between 2000 and 2019, spanning cardiovascular disease, cancer, diabetes, metabolic syndrome, osteoporosis and arthritis, and conclude that physical comorbidities are the rule and not the exception.

For type 2 diabetes, prevalence is substantially higher than in the general population, with estimates ranging from two to four times higher. Three pooled estimates in the same passage must not be collapsed: Stubbs and colleagues reviewed 25 studies and found 9.5%; Vancampfort and colleagues pooled 22 studies for 11.5%, with a risk of nearly double the general population; and Ward and Druss estimated a median prevalence of 13%. The source attributes the spread to study design, detection and sample size, and leaves standing the tension between the two-to-four-times headline and a pooled estimate of nearly double. The diabetes-depression relationship and hypoglycaemia are taught with diabetes, depression and hypoglycaemia.

Cardiovascular disease is the leading cause of mortality in schizophrenia. Fan and colleagues reviewed 13 studies with 422,698 patients with schizophrenia carrying cardiovascular outcome data and calculated pooled relative risks:

- 1.53 for cardiovascular disease overall
- 1.2 for coronary heart disease
- 1.7 for stroke
- 1.81 for congestive heart failure

Correll and colleagues, in more than 3 million patients, give prevalence rather than risk: a pooled cardiovascular disease prevalence of 9.9% across all patients with serious mental illness, significantly higher than normal controls. The populations differ, Fan being schizophrenia-specific and Correll covering serious mental illness as a whole. Correll's effect estimate is corrupt in the available text, its point estimate falling outside its own confidence interval, and is not reproduced.

Bipolar disorder enters these data at one point only, and it is cardiovascular: patients with schizophrenia and bipolar disorder are twice as likely to die from cardiovascular disease as the general population. The same passage makes it a health-systems problem, since patients with diabetes and schizophrenia are treated less aggressively for their cardiovascular risk than patients with diabetes and no mental disorder, and carry an elevated rate of depression. Part of the gap is not a property of the illness but of the care it attracts.

19.7 The mortality gap: how many years, and for whom

DSM-5-TR asserts the reduction and declines to quantify it, attributing it to associated medical conditions, with weight gain, diabetes, metabolic syndrome, cardiovascular and pulmonary disease all commoner than in the general population, and adds a hedge: a shared vulnerability for psychosis and medical conditions may explain some of the medical comorbidity.

SOURCE	POPULATION AS STATED	ESTIMATE
Kaplan and Sadock's Comprehensive Textbook of Psychiatry	Schizophrenia *and other chronic psychotic disorders*	About 10 to 15 years prematurely; men about 15, women on average 12
Shorter Oxford Textbook of Psychiatry	Schizophrenia	Men approximately 20 years, women 15 years
Stahl's Essential Psychopharmacology	Schizophrenia	"May be" 20 to 30 years shorter
Child and Adolescent Psychopathology	Serious mental disorder, undifferentiated	Averaging 10 to 25 years (Chang et al., 2011)
DSM-5-TR	Schizophrenia	Reduction asserted, no figure given

TRAP **"People with serious mental illness die twenty years early."** No single source supports that sentence. The two sex-disaggregated estimates contradict each other for the same illness, and the only estimate whose population genuinely *is* serious mental illness is the broadest and vaguest, at **10 to 25 years**. Give the range, name the sources, and say why it varies: different populations, different eras, different metrics.

Excess mortality was originally reported by Odegaard in Norway in 1951, and the estimate has moved: an early meta-analysis by Harris and Barraclough (1998) found all-cause mortality increased 1.6-fold, while subsequent studies found a higher figure, typically around threefold, and suggested that the mortality gap is increasing (Saha et al., 2007). The **mortality gap** also widens unevenly: all-cause mortality is increased several-fold further in patients who have comorbid alcohol and substance misuse (Hjorthoj et al., 2015). Physical illness rarely comes singly: perhaps as many as two-thirds of these patients with comorbidity have more than one physical disease, that is, multimorbidity, and they are less likely to receive and benefit from appropriate medical treatment and more likely to experience unfavourable clinical outcomes.

19.8 What patients actually die of, and the contradiction the sources leave standing

The references split into two irreconcilable camps. Kaplan and Sadock, reporting the Global Burden of Disease analysis, put the weight on physical disease: cardiovascular disease alone accounted for more than 33% of premature deaths, while suicide, homicide and accidents together accounted for less than 15% of the excess deaths, with Brown and colleagues, following 370 schizophrenia patients over 25 years, finding 81% died from medical diseases. The Shorter Oxford Textbook of Psychiatry states the opposite: about 60% of the excess early mortality in schizophrenia is accounted for by unnatural causes, meaning suicide and accidents, and the rest by natural causes, chiefly cardiovascular, attributed to smoking, poor diet, sedentary lifestyle,

obesity and type 2 diabetes, with lower rates of diagnosis and less active treatment also contributing (Shiers et al., 2015).

Under 15% against about 60% for what looks like the same quantity, and neither passage can be dismissed. Two reconciling possibilities, neither asserted: a share of *all* premature deaths is not a share of *excess* deaths over general-population expectation; and cohorts differ in era and in weighting towards early illness, when suicide risk is concentrated. A merged sentence would create a fact neither source supports.

The **standardised mortality ratios** are less contested. Cohort studies consistently show all-cause mortality two to four times higher than the general population. In Osby and colleagues' sample of 7,784 inpatients, the ratio for death from any cause was 2.8 in men and 2.4 in women, an inpatient sample, which the source notes tends to yield smaller increases. In Olfson and colleagues' study of over 1 million United States Medicaid patients, those with schizophrenia were 3.7 times more likely to die during follow-up, with cardiovascular disease at a ratio of 3.6 and the highest mortality rate of any single cause, 403.2 per 100,000 person-years, and elevated ratios for chronic obstructive pulmonary disease at 9.9, influenza and pneumonia at 7.0, and diabetes mellitus at 4.2 with a rate of 61.8 per 100,000 person-years. Against most clinicians' intuition, accidental deaths at 119.7 per 100,000 person-years accounted for more than twice the deaths attributable to suicide at 52.0 per 100,000 person-years.

Suicide nonetheless contributes heavily: between 25% and 50% of schizophrenia patients attempt suicide and up to 10% eventually succeed, contributing to a mortality rate eight times greater than that of the general population. That eight-fold figure belongs to the suicide sentence and is not a free-standing all-cause ratio.

19.9 What follows for practice

The gap is partly iatrogenic, partly behavioural and partly a failure of medical care, and only the last is quickly fixable. LOCUS. Almost all of this work happens in the outpatient psychiatric clinic, where the psychiatric contact is often the patient's only reliable medical contact of the year. Admission is the opportunity for the baseline anthropometry and bloods that outpatient attendance never quite delivers; emergency presentation belongs to the acute diabetic and cardiac decompensations.

FOCUS. Acutely the target is the measurement itself: nothing can be acted on that has not been recorded. In the short term it is trajectory rather than category; in the medium term the individual components, each separately treatable; in the long term, the mortality gap.

MODUS. The American Psychiatric Association practice guideline supplies the metabolic syndrome criteria used here and the body mass index action threshold; the Maudsley Guidelines on Advanced Prescribing in Psychosis supply the alternative waist-obligatory set used in psychosis services. Management of established disturbance is set out with the management of antipsychotic metabolic disturbance, and the schedule with the metabolic monitoring protocols. Diet, activity and above all smoking cessation address the causes the epidemiology identifies.

PITFALL

Concluding that because antipsychotics cause metabolic syndrome, less antipsychotic means longer life. The data run the other way: moderate levels of antipsychotic use are associated with the lowest mortality in schizophrenia, and even high doses are associated with lower mortality than no treatment at all (Torniainen et al., 2015). This is observational association rather than demonstrated causation and no dose is specified, but the direction is not what the metabolic story predicts: untreated psychosis carries its own lethality through suicide, accident and disengagement from medical care. From the same passage, the incidence of, and mortality from, some cancers and autoimmune disorders is lower than expected in individuals with schizophrenia and in their relatives (Catts et al., 2008), by unknown mechanisms.

Metabolic syndrome is any three of five risk factors in one definition and an obligatory waist plus two others in another, so no prevalence figure means anything without its criteria set; and every standard source agrees life expectancy in schizophrenia is substantially reduced but not on the years or the causes, so the defensible answer gives the range with its populations, never a single confident number.

20 · SIADH and hyponatraemia: mechanisms, psychiatric drug causes and management

Hyponatraemia is the electrolyte disturbance this specialty actually causes. Nearly every class we prescribe has been implicated, the presentation is a confusional state that looks like the illness being treated, and the drug responsible is usually one started weeks ago. Marks cluster on the definition, the single test separating the two routes to a low sodium, drug-class risk where candidates guess, and a short set of action thresholds. Four sources carry the territory, and where two disagree the disagreement is the question: the Maudsley Prescribing Guidelines for epidemiology, risk and thresholds, Kaplan and Sadock's Comprehensive Textbook of Psychiatry for mechanism and anticonvulsants, Brazis's Localization in Clinical Neurology for the criteria, Goodman and Gilman's The Pharmacological Basis of Therapeutics for treatment.

AS HIGH AS 11%	**1 IN 300**	**30 DAYS**	**0.004% TO 26.1%**
SIADH PREVALENCE, ACUTELY ILL PSYCHIATRIC PATIENTS	HYPONATRAEMIA ADMISSION ON ANY ANTIDEPRESSANT, OLDER ADULTS	USUAL ONSET WINDOW AFTER STARTING	REPORTED ANTIPSYCHOTIC PREVALENCE RANGE

20.1 The defining biochemistry, and where normal ends

The **syndrome of inappropriate secretion of antidiuretic hormone** is defined biochemically, not clinically. Brazis states the conditions, satisfied together, as serum hyposmolarity below 280 mOsm/kg with hyponatraemia below 135 mEq/L, normal renal excretion of sodium, and an inappropriately high urine osmolality without body fluid depletion, with renal and adrenal function normal and serum ADH elevated. His subtitle, elevated ADH release with normal thirst, states what makes the secretion inappropriate: the hormone appears when the signals that normally drive it are absent.

Two elements do the diagnostic work and are the most often dropped. Absence of fluid depletion matters because a dry patient has every reason to secrete the hormone, so this is a euvolaemic diagnosis. Normal renal and adrenal function excludes renal salt wasting and adrenal insufficiency, a hyponatraemia that will not answer to anything done about the psychotropic. The Maudsley gives the normal serum sodium range as **136-145 mmol/L**.

TRAP **The lower limit of normal is 135 or 136 depending on which book you revised from.** Brazis treats a sodium below 135 mEq/L as the abnormality, leaving that value itself normal; the Maudsley range begins at 136 mmol/L, putting the Brazis value already below it. Neither is a misprint, so do not harmonise them and do not assume the paper you are sitting has. The reassurance is clinical: no decision turns on that unit, because every action threshold sits far below it.

20.2 The mechanism, and the one discrimination made at the bedside

Kaplan and Sadock are mechanistically direct: excessive secretion of **arginine vasopressin** increases retention of fluid in the body, and the retained water produces the hyponatraemia. Total body sodium is not the problem; the solvent is in excess. It may develop after injury to the brain or from medication, including phenothiazines, butyrophenones, carbamazepine, oxcarbazepine and SSRIs among many other agents, and the hyponatraemia may produce delirium. Delirium as a syndrome belongs to the Stroke, TBI, delirium and focal brain syndromes notes; here, new confusion in a recently medicated patient calls for electrolytes, not a dose increase.

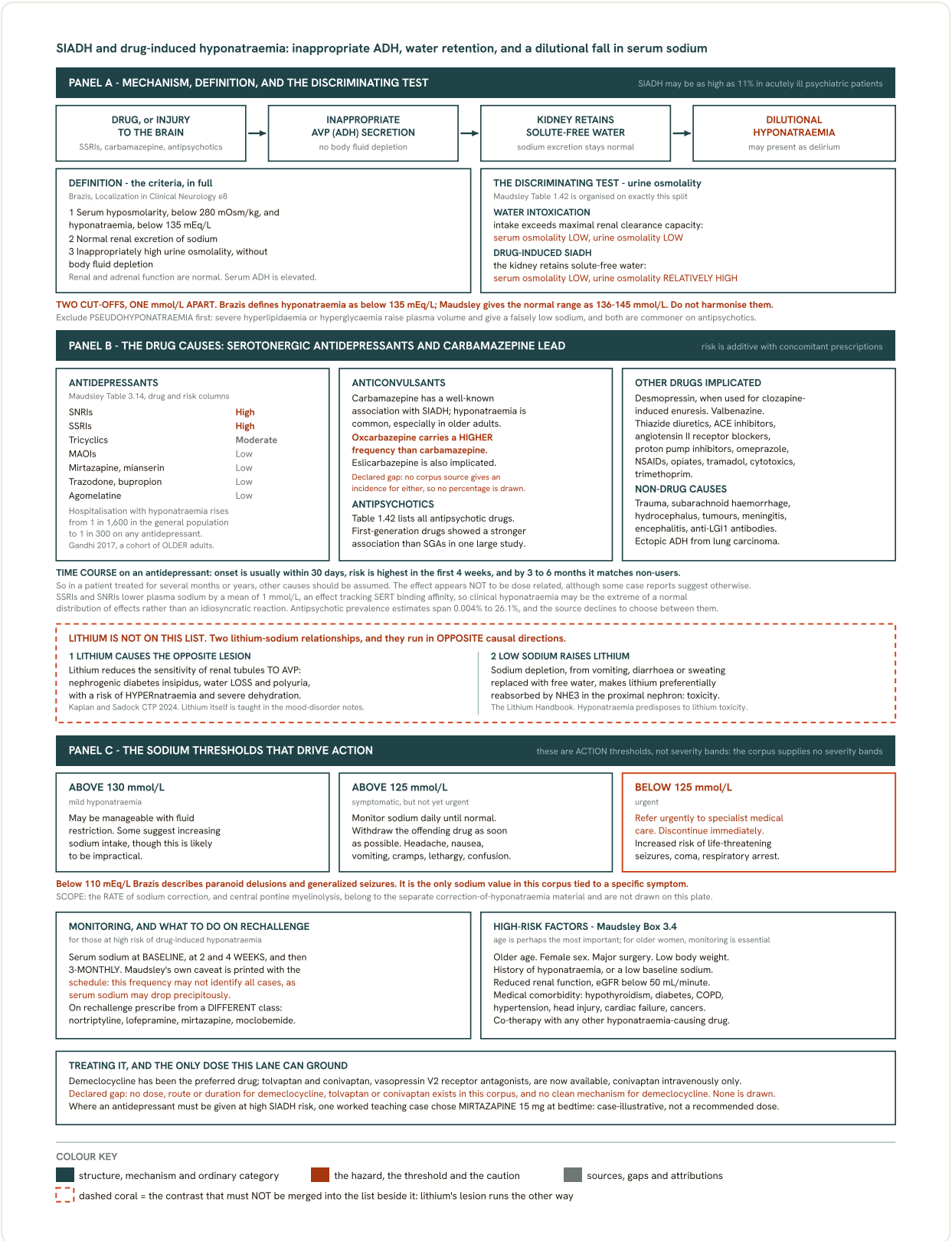

Fig 33.8 SIADH and drug-induced hyponatraemia: the mechanism, the discriminating test, the drug causes, and the sodium thresholds that drive action. Excess AVP makes the kidney retain solute-free water, so sodium falls by dilution while renal sodium excretion stays normal; the bedside discriminator is urine osmolality, low in water intoxication and relatively high in SIADH. Serotonergic antidepressants and carbamazepine lead, and oxcarbazepine carries the higher frequency of the two, though no corpus source attaches an incidence to either. Lithium is deliberately absent: its lesion runs the opposite way. (Maudsley 15th edition; Kaplan and Sadock's CTP 2024; Brazis, Localization in Clinical Neurology e8; Goodman and Gilman; The Lithium Handbook; Geriatric Psychiatry Study Guide.)

Psychiatric patients reach a low sodium by two routes needing opposite logic. In **water intoxication** intake outruns maximal renal clearance and both serum and **urine osmolality** are low. In drug-induced SIADH the kidney retains solute-free water, so serum osmolality is low while the urine stays concentrated: suspect it when a patient is hyponatraemic and the urine is concentrated, that is, when urine osmolality or specific gravity is high. Compulsive drinking in its own right is taken up where this chapter deals with psychogenic polydipsia, the sodium-correction risk and mineral disturbance.

AXIS	WATER INTOXICATION	DRUG-INDUCED SIADH	LITHIUM-ASSOCIATED NEPHROGENIC DIABETES INSIPIDUS
Primary lesion	Intake exceeds renal clearance	Kidney retains solute-free water	Tubules less sensitive to vasopressin
Water moves	In, in excess	Retained under vaso-pressin drive	Out, as polyuria
Serum osmolality	Low	Low	Not characterised in these sources
Urine	Osmolality low	Osmolality relatively high	Cannot be concentrated
Sodium moves	Down	Down	Up, with dehydration risk

RULE **Serum osmolality is low in both psychiatric mechanisms; only the urine tells you which.** A dilute urine says the kidney is working against an intake it cannot match: stop the drinking. A concentrated urine says it is obeying a signal it should not be receiving: find the drug. One paired serum and urine osmolality separates two managements sharing no steps.

20.3 Antidepressants: the best-quantified cause

The Maudsley's SIADH prevalence of as high as 11% in acutely ill psychiatric patients is an upper bound, not a point estimate. As risk, hospitalisation with hyponatraemia rises from 1 in 1,600 in the general population to 1 in 300 on any antidepressant, from a cohort of older adults; quote the population with the number, since the effect is age-loaded and reads as alarming in a young outpatient otherwise.

Onset is usually within 30 days of starting, risk is highest in the first 4 weeks, and falls until by 3 to 6 months it equals that of patients not taking antidepressants. Against intuition, the effect appears not to be dose related, although some case reports suggest otherwise, so dose reduction is not rational and the choice lies between stopping and monitoring. Across the treated population the magnitude is small: a 2022 Japanese study found SSRIs and SNRIs caused an average plasma sodium fall of **1 mmol/L**, absent from the other antidepressants examined and linked to binding affinity for the serotonin transporter. If the whole distribution shifts, clinical hyponatraemia is plausibly its tail rather than an idiosyncratic reaction in a few.

ANTIDEPRESSANT CLASS	LEVEL OF HYPONATRAEMIA RISK
SNRIs	High
SSRIs	High
Tricyclics	Moderate
MAOIs	Low
NaSSAs (mirtazapine, mianserin)	Low
Trazodone	Low
Bupropion	Low
Agomelatine	Low

The narrative agrees: a 2024 meta-analysis suggests risk may be highest with SNRIs, then SSRIs, and lowest with mirtazapine and trazodone, fitting the transporter-affinity finding. The pharmacovigilance literature agrees with neither. One large regulatory database study found the strongest association with mirtazapine, a French study the greatest risk with duloxetine, another a signal for agomelatine, not previously reported to cause hyponatraemia at all.

TRAP **Quoting a spontaneous-reporting signal as though it were a risk estimate.** The Maudsley explains its own divergent findings: disproportionate reporting arises for drugs whose adverse effect is believed rare, confounding by indication cannot be adjusted for because drugs thought low risk go preferentially to patients already at high risk, and concomitant prescriptions distort the signal. The mirtazapine finding reads as an artefact of who receives mirtazapine. Give the table's ranking, then name the artefact. Note too that no antidepressant has been definitively shown not to be linked with hyponatraemia.

GOOD TO REMEMBER

A patient stable on the same antidepressant for a year who becomes hyponatraemic probably has another cause. Risk has fallen to a non-user's by 3 to 6 months, so look for the new diuretic, the chest lesion or the intercurrent illness before stopping a drug that works.

20.4 Antipsychotics, and the anticonvulsant direction candidates reverse

The antipsychotic evidence is broad and far less precise. Case reports and series implicate various phenothiazines, haloperidol, pimozide, risperidone, paliperidone, quetiapine, olanzapine, aripiprazole, cariprazine and clozapine, and one large Swedish study found a stronger association for first-generation than second-generation drugs. The Maudsley tabulates the implicated agents as all antipsychotic drugs. Two further points are examinable: antipsychotic treatment was suggested to be five times more likely than water intoxication to be the cause, and reported prevalence spans 0.004% to 26.1%, the source assuming the truth lies between two widely different extremes. Offer no single figure; the refusal to pick one is the point. Age, sex, comorbidity and polypharmacy are said to matter less here than for antidepressants.

Among anticonvulsant mood stabilisers carbamazepine is the archetype, its association called well known by the Maudsley. Kaplan and Sadock add that hyponatraemia is common with

carbamazepine, particularly in older adults, that baseline electrolytes may reasonably be taken in vulnerable populations, and that neurocognitive change on it should prompt a sodium check, an effect shared with oxcarbazepine and eslicarbazepine.

TRAP **Naming carbamazepine as the worst anticonvulsant offender.** Kaplan and Sadock state that oxcarbazepine is structurally similar to carbamazepine but has fewer drug interactions and fewer side effects, with the exception of an increased frequency of clinically significant hyponatraemia. Because it is chosen as the gentler option, the sodium is what nobody checks. Learn the direction, not a percentage: no source here quantifies incidence for either drug, so a confident figure is an invented one.

20.5 The rest of the causal field, and the sodium that is not really low

Psychotropics rarely act alone. The Maudsley notes that desmopressin, used for clozapine-induced enuresis, can itself cause hyponatraemia, and that antidepressants, anticonvulsants, valbenazine and many drugs for physical health conditions, including diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and proton pump inhibitors, have been implicated, with risk probably additive across concomitant prescriptions, adding thiazides, opiates, NSAIDs, tramadol, omeprazole and trimethoprim. Reconcile the whole list, not only your part of it.

Non-drug causes come from the neurology side. Brazis records that although the syndrome is more often extrahypothalamic, partial damage to the supraoptic and paraventricular nuclei or neighbouring areas can produce it, through trauma, subarachnoid haemorrhage, hydrocephalus, tumours, meningitis, encephalitis or autoimmune disease such as anti-LGI1 antibodies, and that ectopic ADH production by a tumour, classically a carcinoma of the lung, does the same. His drug list independently names vincristine, chlorpropamide, cyclophosphamide, carbamazepine and chlorpromazine, corroborating the psychotropic causes from a neurological source.

Confirm the sodium is real before acting on it. **Pseudohyponatraemia** arises because severe hyperlipidaemia or hyperglycaemia produces a secondary increase in plasma volume, and both are commoner in people treated with antipsychotic drugs than in the general population, so both should be excluded as causes. The same antipsychotic that produces a genuine SIADH can manufacture a spurious low sodium. The metabolic criteria sit where this chapter deals with metabolic syndrome, obesity and mortality in serious mental illness.

20.6 Who is at risk, what to warn about, and how to monitor

The Maudsley's **high-risk factors for drug-induced hyponatraemia** are asked as straight recall.

- Older age and female sex, age perhaps the most important, so monitoring is essential in older people and especially older women.
- Major surgery.
- Previous hyponatraemia, or a low baseline sodium.
- Co-therapy with diuretics, NSAIDs, antipsychotics, carbamazepine, chemotherapy, calcium antagonists, angiotensin-converting enzyme inhibitors or laxatives.

- Reduced renal function, taken as a glomerular filtration rate below 50 mL/minute.
- Medical comorbidity such as hypothyroidism, diabetes, COPD, hypertension, head injury, cardiac failure, stroke and cancers, plus low body weight.

MNEMONIC

Old, One sex, Operations, Other drugs, Organ trouble, Once before

The six headings of the high-risk list. Low body weight is the seventh and sits outside the pattern.

Warning precedes testing. Everyone starting an antidepressant should be told about and watched for dizziness, nausea, lethargy, confusion, cramps and seizures, the gradient running from confusion, nausea, headache and lethargy in mild to moderate hyponatraemia to increasingly severe symptoms with seizures and coma as plasma sodium falls. Only Brazis attaches a number, at the severe end: anorexia, nausea, vomiting and irritability may progress to paranoid delusions and generalised seizures once serum sodium falls below **110 mEq/L**. The delusions matter: a patient with schizophrenia growing more paranoid on treatment reads as relapse, and increasing the antipsychotic makes everything worse.

For high-risk patients on antidepressants the schedule is serum sodium at baseline, at 2 and 4 weeks, then 3-monthly, with a caveat that should never be stripped: this frequency may not identify all cases, as serum sodium can drop precipitously. For antipsychotics no schedule is given, only that plasma sodium monitoring is desirable for everyone receiving them, particularly where several risk factors are present. The wider metabolic cadence belongs where this chapter deals with metabolic monitoring protocols and parameters for patients on antipsychotics.

20.7 Lithium: two sodium relationships running in opposite directions

Lithium is absent from the SIADH lists, and knowing why is worth a mark. Its characteristic lesion is the opposite one: lithium decreases the sensitivity of renal tubules to vasopressin and is a common cause of acquired **nephrogenic diabetes insipidus**, so fluid intake and urine output need close monitoring and patients risk hypernatraemia and severe dehydration where an impaired ability to drink to thirst meets an impaired ability to concentrate urine. SIADH retains water and drives sodium down; lithium loses water and drives sodium up. Lithium as a drug belongs to the Mood disorders: pharmacotherapy notes.

The second relationship runs the other way and reaches the ward. Any state inducing sodium depletion can cause lithium toxicity, because the relative paucity of sodium leads lithium to be preferentially reabsorbed by NHE3 in the proximal nephron. The scenario is specific: season, ambient temperature, sweating and strenuous exercise do not by themselves significantly alter lithium levels, and the common path is a patient depleted by gastrointestinal losses or heavy sweating who replaces them with free water rather than a balanced electrolyte solution. Here low sodium is cause and high lithium effect, the reverse of the arrow above; separating the two is what is tested.

IN INDIA

The sodium-depletion route to lithium toxicity is seasonal here in a way the source literature does not convey: outdoor work through the hot months, gastroenteritis through the wet ones, and the instinct to drink plain water afterwards assemble the described scenario exactly. A patient on lithium losing fluid to vomiting, diarrhoea or heavy sweating should rehydrate with oral rehydration solution, available in any chemist, rather than water alone. Monitoring diverges downward: the sodium schedule assumes repeat electrolytes are affordable and the patient returns to the same clinic, and where neither holds, the warning given to patient and family does more work than the calendar.

20.8 Management: LOCUS, FOCUS, MODUS

No dedicated national guideline covers this here; the Maudsley supplies the thresholds and rechallenge advice, Goodman and Gilman the drug options. **LOCUS** is set by the number. Mild hyponatraemia above 130 mmol/L may be manageable with fluid restriction, some suggesting increased sodium intake though this is likely impractical, with the antidepressant discontinued if symptoms persist: outpatient work. Above 125 mmol/L, monitor sodium daily until normal and withdraw the offending antidepressant as soon as possible, watching for headache, nausea, vomiting, muscle cramps, restlessness, lethargy, confusion and disorientation. Below **125 mmol/L**, refer urgently to specialist medical care and discontinue immediately, given the increased risk of life-threatening seizures, coma and respiratory arrest: emergency transfer, not a review appointment. The same passage warns that over-rapid correction may itself be harmful; the safe rate of rise and the demyelinating syndrome that follows breaching it are taught where this chapter deals with psychogenic polydipsia, the sodium-correction risk and mineral disturbance.

FOCUS shifts by phase: acutely the falling sodium and the offending drug together; short term, the daily sodium until back in range; mid term, whether antidepressant treatment resumes, since untreated depression is not a safe alternative; long term, the modifiable risk, most of which is co-prescription.

MODUS begins with subtraction: withdraw the offending drug and any additive co-prescription, then restrict fluid. Goodman and Gilman record that demeclocycline has been the preferred drug but that the **vasopressin V2 receptor antagonists** are now available: tolvaptan, a selective oral V2 antagonist FDA approved for clinically significant hypervolaemic and euvolaemic hyponatraemia, and conivaptan, a non-selective V1a and V2 antagonist FDA approved for hospitalised patients with euvolaemic and hypervolaemic hyponatraemia and available only for intravenous infusion. The Maudsley calls the vaptans aquaretics because they induce a highly hypotonic diuresis, with promise in hyponatraemia of various aetiologies including drug-related SIADH. No dose or duration for the three appears in this material, and no dosing regimen should come from memory. The Maudsley also lists lithium, cautioning that hyponatraemia predisposes to lithium toxicity, a poor choice in exactly the patient who would need it.

Restarting is the part candidates skip. **Rechallenge** carries real recurrence risk: hyponatraemia may recur with the same or a different SSRI but may be less likely with an antidepressant from another class. The strategy is to withdraw other drugs associated with hyponatraemia, since risk increases exponentially when antidepressants are combined with diuretics; prescribe from a different class, considering nortriptyline, lofepramine, mirtazapine or moclobemide, starting low and monitoring closely; consider water restriction and careful use of demeclocycline where it recurs and continued treatment is essential; and consider ketamine or esketamine, or ECT, where no standard antidepressant can be given. For antipsychotics the advice is deliberately weaker: switching is suggested, but data are insufficient to guide the choice and cross-sensitivity may occur, the individual perhaps being predisposed overall and the drug chosen unimportant. In a worked teaching case of depression in a medically ill older adult at high SIADH risk, where SSRIs and tricyclics are avoided, mirtazapine 15 mg at bedtime is preferred, to improve sleep and appetite and reduce nausea; read it as one case-illustrative starting dose, not a recommended regimen. The same logic applies where lung cancer with central nervous system metastasis already places SIADH risk unusually high.

PITFALL

One widely used text points the wrong way, and copying it would be dangerous. Kaplan and Sadock's Comprehensive Textbook of Psychiatry, in its eating-disorders section, states that whatever the aetiology fluid restriction is the treatment of choice, and that intranasal arginine vasopressin should be considered where fluid restriction does not sufficiently improve sodium. Every other source here runs the other way: the Maudsley lists desmopressin, given for clozapine-induced enuresis, among the causes, and the drugs named as treatment are vasopressin antagonists, the mechanistic opposite. A specialist nephrological manoeuvre does exist, in which desmopressin prevents over-rapid autocorrection while sodium is raised controllably, but that is not what the sentence conveys and is not a psychiatric procedure. Do not give desmopressin for hyponatraemia; refer for specialist medical care.

Serum osmolality is low in both mechanisms and only the urine discriminates; risk peaks in the first weeks and is gone by three to six months; oxcarbazepine is worse than carbamazepine; and below 125 mmol/L the drug stops today and the patient goes to a medical unit.

21 · Psychogenic polydipsia, the sodium-correction risk and mineral disturbance

Three questions sit inside this topic and examiners like all of them. One is behavioural, the drinking itself; one is iatrogenic and is the one that maims, a pons lost to the correction; one is the wider mineral field of calcium, magnesium, potassium and phosphate. One discipline ties them: establish the mechanism before acting on the number. A low sodium from drinking, one from inappropriate antidiuresis and one the body is defending on purpose behave differently, and two of the three call for doing less than the number invites. Inappropriate antidiuretic hormone secretion and the drug causes of hyponatraemia are treated separately in this chapter.

At least 20%	6 to 17%	Over 12 mEq/L/day	Under 10%
POLYDIPSIA AMONG CHRONIC PSYCHIATRIC INPATIENTS	WATER INTOXICATION, CHRONICALLY ILL HOSPITALISED PATIENTS	RISE AT WHICH PONTINE MYELIN BREAKS DOWN	PSYCHIATRIC SYMPTOMS IN HYPERPARATHYROIDISM

21.1 What primary polydipsia is, and what it is not

Primary polydipsia is increased water intake occurring in the absence of any impairment in water excretion. The kidney is working; the patient is drinking faster than a normal kidney can clear. That separates it from **secondary polydipsia**, where water is being lost obligatorily, the classic psychiatric example being the lithium-treated patient with nephrogenic diabetes insipidus replacing what the kidney throws away.

Both groups may show a low urine osmolality, and that shared finding is where candidates come unstuck. The discriminator is the serum: in lithium-driven secondary polydipsia sodium and osmolality stay normal because intake matches loss; in primary polydipsia both fall during binges, sometimes severely. Lithium as a drug and its non-thyroid organ-system adverse effects belong to the Mood disorders: pharmacotherapy notes.

TRAP **Assuming the lithium patient who drinks a great deal is therefore hyponatraemic.** Heavy drinking, dilute urine and lithium invite you to call it water intoxication. It is not: the drinking is compensatory, serum sodium and osmolality are normal, and fluid restriction dehydrates the patient and pushes the lithium level up. Read the serum, not the story.

The named variants appear in single-best-answer stems. Patients may drink from conditioned behaviour, which supplies the two eponymous presentations, **beer drinker's hyponatraemia** and **tea party epilepsy**, or from other psychogenic factors. A second group has hyperangiotensinaemia, described in renal patients who stay thirsty despite an electrolyte balance kept normal by haemodialysis. A third, rare group has hypothalamic disease, where the drinking compensates for a mild diabetes insipidus, the mirror image of the trap above.

21.2 How common, and in which population

Three different numbers get merged into one wrong number. They do not share a denominator.

CONSTRUCT	FIGURE	POPULATION IT IS BOUND TO
Excessive water intake, historical observation	approximately 25% of patients, noted by 1936	The severely mentally ill of the era, in whom it was called the commonest metabolic abnormality and was already linked to life-threatening hyponatraemia.
Polydipsia, the drinking behaviour, modern prevalence	at least 20%	Chronic psychiatric inpatients, from data gathered over 5 years in a state hospital. Note the direction: at least, not up to.
Water intoxication, the biochemical consequence	6 to 17%	Cross-sectional studies of chronically ill, hospitalised psychiatric patients.
Episodic hyponatraemia secondary to fluid overload	10%	A longitudinal study of severely ill patients with a diagnosis of schizophrenia.

One caution about independence: the modern figure in the clozapine literature and those in the prescribing literature rest substantially on the same body of work, so quoting both is not two confirmations. The ordering is the teaching point: a common behaviour, a smaller fraction of drinkers becoming biochemically water-intoxicated, a smaller group again cycling through it. That argues for screening, not for waiting.

21.3 Why they drink: two accounts that do not agree

The aetiology is poorly understood and the standard sources offer different accounts. The clozapine literature is unambiguous that the drinking is not due to excessive thirst but is motivated by delusions or by a psychic discomfort that the water binge relieves, making the behaviour closer to a delusionally motivated ritual than to a homeostatic drive.

The prescribing literature offers two drug-mediated hypotheses instead. The first is an extreme compensatory response to the anticholinergic adverse effects of some antipsychotic drugs, a dry mouth taken to its dangerous conclusion. The second is a receptor argument: post-synaptic dopamine receptor antagonism produces receptor supersensitivity, increased presynaptic dopamine release and elevated dopamine in the hypothalamus, driving thirst and polydipsia. Three observations support it: many reported cases occur in patients with long illness histories, many occur on antipsychotics with high D2 receptor affinity, and clozapine can improve polydipsia independently of improvement in psychosis.

That last observation cuts against the purely psychopathological account: if water intake falls while the delusions do not, the drinking was not simply a delusional act. Antipsychotic receptor pharmacology and drug selection belong to the Schizophrenia: management, antipsychotics and adverse effects notes. The correct answer names both accounts and settles neither.

21.4 Telling it apart at the bedside

Polydipsia with polyuria has a short differential a psychiatrist must run. It may reflect impaired renal concentrating capacity from deficiency of antidiuretic hormone, which is cranial diabetes

insipidus, or from failure of its action, which is nephrogenic diabetes insipidus. The nephrogenic form may be inherited or acquired, hypercalcaemia and hypokalaemia both impairing that action: a calcium or potassium disturbance can itself manufacture a polyuria that looks like drinking. Or it may simply follow vastly excessive intake.

The bedside sign is **nocturnal polyuria**, generally not a feature of psychogenic polydipsia because the drinking stops when the patient sleeps, whereas a kidney that cannot concentrate keeps producing urine through the night. Hutchison's own hedge must travel with the sign: this is not an absolute distinction, and further investigation of urine concentrating capacity is usually required.

PITFALL

Sodium in water intoxication shows diurnal variation, dropping as the day progresses because the drinking accumulates across waking hours. A morning-round sample is drawn at the patient's best moment, and a ward that samples only then will keep recording acceptable sodium in a patient who is seizing by evening. Where the concern is water intoxication rather than a drug effect, time the sample to the risk.

Eating disorders are a second, quite separate population. Hyponatraemia occurs commonly in bulimia nervosa and often in anorexia nervosa, from increased water intake diluting the serum sodium or from a syndrome of inappropriate antidiuretic hormone secretion. The intake is deliberate: patients may drink to suppress appetite and support restriction, or, where treatment involves weigh-ins, practise **water loading** to inflate the recorded weight. Because hyponatraemia increases seizure risk it must be addressed quickly, and whatever its aetiology here, fluid restriction is the treatment of choice.

21.5 Management of polydipsia and water intoxication

LOCUS. Managed where the patient already is, on the ward or in the outpatient clinic, because the behaviour is chronic and the monitoring longitudinal. The escalation point is explicit: refer urgently to specialist medical care if the serum sodium falls below **125 mmol/L**. Below that line the psychiatrist's job is handing over an accurate account of the mechanism rather than managing the electrolyte.

FOCUS. Acutely, the water intoxication and the seizure risk that rides with it, plus anything exogenous making the sodium worse. Longer term, the drinking behaviour, the only durable fix.

MODUS. Three evidence-based options are named for preventing water intoxication: **targeted fluid restriction**, clozapine therapy, and removal of agents that may themselves be causing hyponatraemia, the examples given being carbamazepine, valproate and sodium-wasting diuretics. Fluid restriction is coupled to careful sodium monitoring, which must take the diurnal variation above into account. Note what the sources do not supply: none states a volume, so no litre-per-day target belongs in the plan.

Clozapine has demonstrated efficacy in schizophrenia with psychogenic polydipsia at doses as low as **300 mg per day**. The evidence base is thin and should be quoted as thin: a 24-week open-

label study of eight male patients with schizophrenia and polydipsia who had already met treatment-resistance criteria, run as sequential 6-week blocks of clozapine at 300, then 600, then 900 mg per day where tolerated. On typical antipsychotics serum and urine osmolality stayed grossly abnormal; on clozapine mean plasma osmolality normalised, rising by 15.2 mosm/kg (95% CI 5.5 to 25.0), the effect evident at the lowest dose step. There is no polydipsia-specific titration to learn: it is that of treatment-resistant schizophrenia. The prescribing literature agrees clozapine raises plasma and urine osmolality, while cautioning that this is consistent with reduced fluid intake and not clearly related to mental state.

Two negatives are as examinable as the positives. There is no evidence that reducing or increasing the antipsychotic dose improves serum sodium in water-intoxicated patients, so dose manipulation is not a treatment. And a long list of other agents has been tried with limited data behind any, which is reason to distrust a confidently named second-line drug.

TRAP **Reaching for demeclocycline because a guideline mentions it.** It is included in some practice guidelines for psychogenic polydipsia. Against that, its mechanism is to interfere with antidiuretic hormone and increase water excretion, already running at capacity in a pure water-intoxication patient, so the rationale is debatable and some published cases may have been complicated by undiagnosed inappropriate antidiuresis. A single small randomised trial showed no benefit. The same source nonetheless keeps it for inappropriate antidiuresis, recording the conflict without resolving it. The question is whether you established the mechanism first, and urine osmolality is what establishes it.

21.6 The correction, not the illness, is what maims

Overly rapid correction of hyponatraemia can produce central pontine myelinolysis, the prime example of the **osmotic demyelination syndrome**. Vulnerable patients lose myelin in the pons and are often left with permanent nystagmus, quadriparesis and ataxia. Three groups are named repeatedly: malnourished alcoholics, liver transplant recipients, and pregnant women with hyperemesis gravidarum, alongside others prone to hyponatraemia. The prescribing literature calls it irreversible.

> The pons is destroyed by the correction and not by the hyponatraemia, and it is chronic hyponatraemia whose correction destroys it.

The timing is what makes central pontine myelinolysis a psychiatric problem. It occurs days after the overly rapid correction of chronic hyponatraemia, so the patient improves first and deteriorates afterwards, by which point the causal link is easy to miss. It typically presents with delirium and a flaccid quadriparesis, and uncommonly with delirium alone, and that second version is the one a psychiatrist is asked to see. In alcohol-dependent patients the picture is quadriplegia with pseudobulbar palsy. Delirium as a syndrome belongs to the Stroke, TBI, delirium and focal brain syndromes notes; what belongs here is that a new delirium in a patient whose sodium was corrected days earlier is a structural event until proven otherwise.

RULE **In hyponatraemia, every decision is a decision about rate.** The single number the corpus supplies for the rate of sodium correction is a threshold for harm: correction faster than **12 mEq/L per day** is what leads to myelin breakdown in the pons. Read the direction carefully: that figure says where damage occurs, not where treatment should aim, and must not be converted into a target. No recommended maximum safe rate is stated anywhere in the standard psychiatric references, and a rate quoted from memory is a rate you cannot attribute.

21.7 The other end of the range, and a sodium that should be left alone

Essential hypernatraemia is a rare syndrome of decreased antidiuretic hormone release with absence of thirst, diagnosed on four criteria: hypernatraemia without a corresponding fluid deficiency, preserved renal responsiveness to the hormone, impaired secretion in the face of hypernatraemia, and absence of thirst despite preserved conscious behaviour. Lesions have affected the tuberal region or the whole hypothalamus. Some patients tolerate a high sodium well enough to develop water intoxication when treated, an iatrogenic hazard that runs opposite to central pontine myelinolysis. Sodium reaching 170 mEq/L here is attended by muscle cramping, tenderness and weakness, fever, anorexia, paranoia and lethargy. That figure is bound to this syndrome and its unusual tolerance; generalising it into a symptom threshold for hypernatraemia at large misuses it. No source in the standard references defines hypernatraemia by a serum sodium value.

Reset osmostat hyponatraemia is the third mechanism and the one most likely to be mismanaged. Its criteria are normovolaemic hypotonic hyponatraemia; normal renal, adrenal and thyroid function; the ability to concentrate urine when serum tonicity is raised above the reset level; the ability to excrete a water load; and maintenance of normal sodium balance without correction of the hyponatraemia during salt loading. The last pair does the work: preserved excretion of a water load separates it from inappropriate antidiuresis, and the failure of salt loading says the body is defending a lower set point rather than failing to reach a normal one. This is the stable, asymptomatic, treatment-resistant low sodium that keeps prompting intervention, and precisely the patient in whom chasing the number carries the demyelination risk for no gain.

21.8 Calcium: the mineral with a psychiatric reputation it does not quite deserve

Hypercalcaemia is the classic examinable mineral cause of psychiatric presentation, and it is not a common one. Hyperparathyroidism is usually diagnosed after an incidental hypercalcaemia on routine bloods, and 50% of patients are asymptomatic. Where symptoms occur they are principally those of the hypercalcaemia itself: fatigue, malaise, proximal muscle weakness, renal colic, abdominal pain and cognitive decline. Psychiatric symptoms belong to the classic tetrad, but their prevalence is likely to be **less than 10%**, and they correlate with both the duration and the severity of the hypercalcaemia.

MNEMONIC

Bones, stones, moans and psychic groans

The symptomatic tetrad of hyperparathyroidism. Worth holding for the viva with the qualifier attached: the psychic groans are the least frequent of the four, not the headline.

The psychiatric profile is reasonably specific. Affective disorders, predominantly depressive, are the most frequently recorded, with anxiety often comorbid; psychotic disorders are reported but infrequent, with persecutory and paranoid delusions predominating; cognitive changes usually take the form of short-term memory loss, disorders of attention and acute confusional states; and severe derangement of calcium metabolism may present with somnolence and coma. Neuropsychiatric symptoms are often the initial presentation in older adults or those with limited cognitive reserve, the group most likely to be read as dementia. Symptoms generally respond to treatment such as parathyroidectomy. The severity correlation is stated repeatedly, but no calcium value is ever attached to it.

IN INDIA

Two practical points bite here. Where parathyroid hormone is mildly raised against a normal calcium, most commonly from vitamin D insufficiency, psychiatric disturbance is uncommon. Given how often that insufficiency is met in practice here, the combination is a finding to note, not an explanation for the presentation, and treating it as the cause closes an inquiry that should stay open. Second, magnesium is not on the routine electrolyte panel in most laboratories and must be requested by name at additional cost. Given how much of what follows turns on it, a psychiatrist who does not ask will not get it.

At the other end, hypocalcaemia announces itself through neuromuscular excitability: paraesthesiae, muscle cramps, carpopedal spasm and facial grimacing progressing to laryngeal spasm and convulsions. Examination may reveal tetany, reduced or absent deep tendon reflexes, papilloedema, and QT prolongation, which matters directly before any QT-lengthening psychotropic is added. The elicited sign is **Chvostek's sign**: gentle percussion over the proximal facial nerve as it exits the parotid gland is positive if it evokes involuntary facial twitching.

Delirium is now understood to be the commonest neuropsychiatric manifestation of hypocalcaemia. One large study reported cognitive impairment in 39%, non-specific affective disturbance in 21%, affective or neurotic symptoms in 12% and psychotic symptoms in 11%. Those categories are not mutually exclusive and belong to that study's population, so quote them as a profile rather than summing them. Severity again tracks the degree of hypocalcaemia and normalisation resolves the symptoms, with one exception.

21.9 Magnesium, potassium and the corrections that will not hold

RULE **Correct the magnesium, or the correction you are proud of will not hold.** This appears three times in three separate contexts across the standard references. Persistent psychosis has been recorded in hypocalcaemia where coexisting **hypomagnesaemia** was not addressed. Refractory cramping after apparently adequate correction of hypocalcaemia can be due to an associated hypomagnesaemia. And hypomagnesaemia, which may co-occur with hypokalaemia, must also be addressed because it inhibits prolonged normalisation of potassium. Whenever a corrected electrolyte drifts back down or a corrected patient fails to improve, magnesium is the first thing to check.

Hypokalaemia is the disturbance a psychiatrist is most likely to meet outside the ward, and it is dangerous rather than merely abnormal: it can cause cardiac arrhythmias and occurs commonly in individuals with recurrent vomiting. Potassium should be monitored regularly where purging is self-reported, with electrocardiograms for arrhythmias and QT and QTc prolongation. The caveat that is easy to lose: that prolongation may occur in eating disorders even without any electrolyte abnormality, so a normal potassium does not license skipping the tracing. In the opposite direction, hyperkalaemia tends to produce bradyarrhythmias and heart block rather than the lethal tachyarrhythmias of hypokalaemia.

The eating-disorder risk assessments give the only numeric mineral thresholds here. Among the blood-test markers of high physical risk are **hypokalaemia below 3.0 mmol/L** and hypophosphataemia below 0.5 mmol/L, alongside a very low body mass index, hypothermia, bradycardia, hypotension, postural hypotension, arrhythmia, hypoglycaemia and neutropenia. Both values are internally plausible, but the table they come from cannot be fully attributed, so treat them as indicative rather than quotable. Beyond them the standard references supply no reference range for serum calcium, ionised calcium, magnesium or potassium, which is why this material is examined as phenomenology and mechanism rather than numbers.

Refeeding is where all of this becomes predictable rather than incidental. Electrolytes should be monitored during refeeding even when normal at initial presentation, because hypophosphataemia and hypomagnesaemia may develop during the early phases; liver enzymes are usually normal but may increase transiently. No numeric threshold or calorie-escalation schedule for refeeding is given in these sources, and neither should be improvised.

GOOD TO REMEMBER

Intermittent cramps and bilateral pins and needles can be due to a decreased level of circulating ionised calcium, and that fall does not require hypoparathyroidism. Any rise in extracellular pH lowers the ionised fraction, and the best recognised setting is the respiratory alkalosis of a hyperventilatory state, with hypokalaemia producing the same effect through a metabolic alkalosis. That is the mechanism behind the perioral and peripheral paraesthesiae and the carpopedal spasm of a panic attack, worth explaining to the patient because the phenomenon is frightening and the explanation itself therapeutic. One rider: paraesthesiae confined to the hand may be median nerve compression at the wrist.

Hold the whole mineral set together as one line on the delirium screen. The metabolic causes of delirium listed in the standard texts include hyponatraemia and hypernatraemia, hypoglycaemia and hyperglycaemia, hypocalcaemia and hypercalcaemia, and hypomagnesaemia and hypermagnesaemia, with the general medical lists adding liver dysfunction, uraemia, thyroid dysfunction and nutritional deficiency, particularly of vitamin B12, thiamine and niacin.

- Sodium: low from drinking, from inappropriate antidiuresis or from a reset set point; the mechanism decides the response.
- Calcium: high produces depression and cognitive change; low produces tetany, seizures and delirium.
- Magnesium: rarely the presenting abnormality, frequently the reason another correction fails.
- Potassium: low in the purging patient, arrhythmogenic, not normalisable while magnesium is low.
- Phosphate: the refeeding mineral, falling early even when admission bloods were clean.

Encephalopathies, reproductive endocrinology and toxins

22 · Hepatic encephalopathy: grading, pathophysiology and psychiatric management implications

The psychiatrist usually meets this condition before the physician names it. The referral arrives as a behavioural problem: a man with cirrhosis irritable and muddled overnight, or a woman on a de-addiction ward whose attention has narrowed over a week. Kaufman's Clinical Neurology for Psychiatrists sets out the sequence. With hepatic insufficiency, mental function and consciousness steadily decline, and mild confusion with either lethargy or, less frequently, agitation may precede coma and overtly abnormal liver function tests. That last clause inverts the order most trainees expect.

Marks concentrate here for a reason only partly about the disease. Almost every specific a candidate confidently recalls, the numbered grades, the ammonia cut-off defining each one, the millilitres of lactulose, is either unsourced or contradicted by the standard references. Delirium as a syndrome belongs to the Stroke, TBI, delirium and focal brain syndromes notes; choosing and dosing a psychotropic in liver failure belongs where this chapter deals with prescribing in hepatic and renal impairment.

22.1 The disease, its nosological place and the full constellation

Kaplan and Sadock's Comprehensive Textbook of Psychiatry places hepatic encephalopathy as a **delirium due to another medical condition**. That places the disease; it does not license re-deriving the delirium construct. The corollary matters: fluctuation, inattention and altered arousal are expected, and a stable, well-oriented presentation should prompt another explanation.

The picture is far wider than confusion, which is why it lands on a psychiatric desk. The same source describes a condition commonly encountered in significant liver disease, presenting as a constellation: altered consciousness up to stupor or coma, cognitive impairment, confusion or disorientation, affective and emotional dysregulation, psychosis, behavioural and bioregulatory disturbance, and motor signs including asterixis, tremor, brisk reflexes, increased tone, ataxic gait, bradykinesia, slurred speech and incoordination. An apparent first psychotic episode, a manic disinhibition and a personality change in liver disease all sit on that list, and none defers the metabolic assessment.

RULE **Normal liver function tests do not exclude hepatic encephalopathy.** The mental state declines before the biochemistry does, so the tempting sequence, abnormal tests first and encephalopathy second, runs backwards. This is a clinical diagnosis supported by the laboratory, not gated by it.

22.2 The named forms, and the grading scheme these references do not carry

Honesty about what these references contain is what this section offers. They name forms consistently, minimal, subclinical, overt, fulminant and persistent, and never attach a numbered grade to any of those words. The numbered severity ladder in wide hepatological use is not reproduced here, because a grading scheme recalled from memory is exactly the specific that reaches a resident wrong. Take it from a hepatology source that prints it.

What they carry instead is prognostic direction. Kaplan and Sadock state that **minimal hepatic encephalopathy** predicts overt encephalopathy, and that the fulminant form is associated with intracranial hypertension, cerebral oedema, seizures and death before transplantation. Those statements bracket the condition: an abnormality detectable only on testing is a forecast, and at the other end the syndrome stops being psychiatric at all.

Reversibility ties the forms together and is why this is not a dementia. **Persistent hepatic encephalopathy** is rare, seen predominantly with extensive portacaval collateral circulation or after surgical or transjugular portosystemic stent shunting. Persistence is structural: where portal blood has a permanent route around the liver, the insult does not stop. The dementia syndrome and its workup belong to the Dementias and neurocognitive disorders notes; what belongs here is that cognitive impairment in liver disease carries a presumption of reversibility.

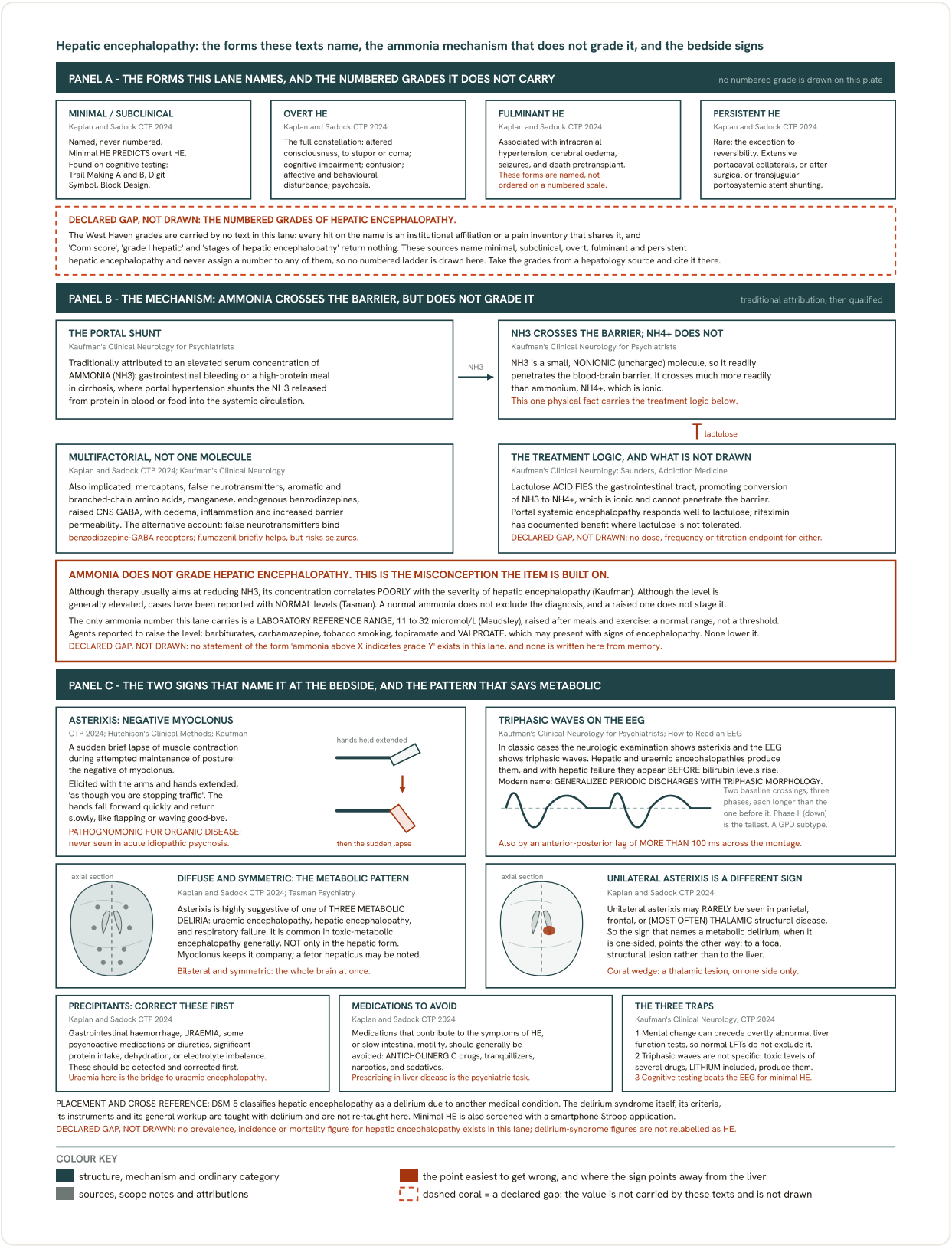

Fig 33.9 Hepatic encephalopathy: the forms these texts name, the ammonia mechanism, and the two bedside signs. No text in this lane numbers the severity: minimal, subclinical, overt, fulminant and persistent are named and none is graded, so the plate draws the vocabulary and marks the numbered ladder as a declared gap. The mechanism survives with its limit: ammonia crosses the barrier because it is small and uncharged, and lactulose converts it to ammonium, yet its concentration correlates poorly with severity and may be normal. Asterixis is pathognomonic for organic disease but not specific to the liver, and when unilateral points at structural disease instead. (Kaufman's Clinical Neurology for Psychiatrists; Kaplan and Sadock 2024; Tasman; Hutchison's Clinical Methods; How to Read an EEG; Maudsley Prescribing Guidelines; Saunders, Addiction Medicine.)

The accompanying figure sets the severity ladder alongside the mechanism and the two anchoring signs.

FORM NAMED IN THE SOURCES	WHAT THE SOURCES STATE	WHY IT MATTERS
Minimal	Predicts overt encephalopathy	Detectable only on testing; not benign
Subclinical and overt	Named; given no numbered grade in these texts	See a hepatology source
Fulminant	Intracranial hypertension, cerebral oedema, seizures, death before transplantation	A transplant and intensive-care problem
Persistent	Rare; portacaval collaterals or post-shunting	The structural exception to reversibility

22.3 The ammonia route, and why one molecule's charge decides everything

The traditional account drives the treatment. Kaufman records the classical attribution to a raised serum ammonia, operating in the common scenario of gastrointestinal bleeding or a high-protein meal in cirrhosis, where cirrhosis-induced portal hypertension shunts ammonia released from protein in blood or food straight into the systemic circulation. The mechanism is as much anatomical as biochemical: the nitrogen load is ordinary, but it bypasses a liver that would have cleared it. A gastrointestinal bleed is a reliable precipitant because it is a high-protein meal in the gut lumen.

Access to the brain is decided by charge alone. Ammonia is small, non-ionic and uncharged, so it penetrates the blood-brain barrier readily and far more readily than the ionic form, **ammonium**. That is the hinge of the topic: shift the equilibrium between the two species and you change how much nitrogen reaches the brain.

This is what the first-line treatment does. **Lactulose** is given to acidify the gastrointestinal tract, promoting conversion of ammonia to ammonium, which is ionic and cannot penetrate the blood-brain barrier. It is not a systemic scavenger; it traps nitrogen in the gut lumen in a form that cannot follow the portal shunt. That guards against calling lactulose a purgative: catharsis contributes, but the stated mechanism is a pH-driven speciation shift.

22.4 Ammonia is a treatment target and not a severity marker

Here the standard references genuinely disagree, and the disagreement is worth teaching rather than flattening. Kaplan and Sadock write that although the pathogenesis is multifactorial, the predominant treatment strategy is to reduce ammonia production from intestinal protein and reduce its absorption. Read alone, that invites treating the ammonia level as the disease. Two sources block the inference. Kaufman states that although therapy aims at lowering ammonia, its concentration correlates poorly with the severity of hepatic encephalopathy, and prints the opposite proposition as the wrong answer to a review question. Tasman's Psychiatry closes the loop: although the level is generally elevated, cases have been reported with normal levels.

Ammonia is a valid therapeutic target and an invalid severity marker: lowering it helps, while measuring it tells you neither how ill the patient is nor, when normal, that the patient is well. No numeric threshold for diagnosing, staging or grading appears in these references. The one figure available is a laboratory reference range from The Maudsley Prescribing Guidelines, **11-32 micromol/L**, rising after meals and exercise: a normal range for the assay, not a threshold for the disease.

One entry in that same table is squarely a psychiatric problem. The Maudsley lists the agents reported to raise ammonia, barbiturates, carbamazepine, tobacco smoking, topiramate and valproate, noting that valproate may present with signs of encephalopathy, and records none known to lower it. Valproate-induced hyperammonaemic encephalopathy is the one situation in which a psychiatrist sends an ammonia level on a structurally normal liver; the prescribing decisions belong to the Mood disorders: pharmacotherapy notes.

TRAP **Writing that ammonia levels are used to grade hepatic encephalopathy.** No source supports it and two contradict it. The trap is built on a true premise, that ammonia is the main treatment target. Learn the two negatives instead: the concentration correlates poorly with severity, and cases with normal levels have been reported.

Ammonia is a treatment target, never a severity marker: a normal level does not exclude hepatic encephalopathy, a raised level does not grade it, and the only ammonia figure worth carrying is a laboratory reference range.

22.5 The multifactorial account and the GABA hypothesis

Ammonia tracks severity poorly because it is one contributor among many. Kaplan and Sadock implicate mercaptans, false neurotransmitters, the aromatic amino acids phenylalanine, tyrosine and tryptophan, the branched-chain amino acids, manganese, endogenous benzodiazepines and raised central gamma-aminobutyric acid, alongside oedema, inflammation and increased blood-brain barrier permeability. The list is dominated by neurotransmitter precursors and neuromodulators rather than toxins, which is why the picture is behavioural before it is neurological, and its last three items are processes rather than metabolites, which is why a patient deteriorates at an unchanged ammonia level when sepsis or dehydration supervenes.

The best-developed alternative is testable. Kaufman describes an account emphasising **false neurotransmitters** that bind benzodiazepine-gamma-aminobutyric acid receptors and increase GABA activity, and notes that **flumazenil**, a benzodiazepine antagonist acting at those receptors, temporarily reduces symptoms though it carries some risk of precipitating seizures. Hold on to the word temporarily: this is a mechanistic demonstration, not a strategy, and the seizure risk is stated in the same breath. No dose appears in these references and none is offered here.

GOOD TO REMEMBER

The endogenous benzodiazepine account has a prescribing consequence easily lost on a busy ward. If part of the encephalopathy is driven by activity at the benzodiazepine-GABA receptor complex, a benzodiazepine given for the agitation adds to the mechanism producing it. That is the reason behind the blunt instruction to avoid sedatives.

22.6 Asterixis: what it is, how to elicit it, and what it does not mean

The first of the two bedside signs is a movement disorder defined by absence. Kaplan and Sadock build it from its positive counterpart: myoclonus is a sudden, jerky, shock-like movement, more discontinuous than chorea or tremor, and its negative is **asterixis**, a sudden lapse of muscle contraction during attempted maintenance of posture. Hutchison's Clinical Methods records a negative myoclonus, a sudden brief loss of tone, particularly associated with hepatic encephalopathy. The term is not pedantry: the sign exists only while a posture is actively held, which dictates how it is sought.

Kaufman describes the manoeuvre. Asterixis is elicited by having the patient extend the arms and hands as though stopping traffic; the hands then intermittently and quickly fall forward and slowly return, as though flapping or waving goodbye. The asymmetry is the diagnostic detail: a fast drop with slow recovery is a lapse of tone, a symmetrical oscillation a tremor. Kaplan and Sadock add that it should be carefully sought, because it is pathognomonic for organic disease and is never seen in acute idiopathic psychosis or other non-organic disorders, and Addiction medicine, listing the findings in alcohol-related liver disease, says to check for asterixis if hepatic encephalopathy is suspected. Tasman adds the accompanying olfactory sign, a characteristic bad breath or **fetor hepaticus**.

The trap runs the other way. Kaplan and Sadock note that both phenomena, but more sensitively asterixis, are common in toxic-metabolic encephalopathy and not just in hepatic encephalopathy. Tasman narrows it: asterixis is highly suggestive of one of three metabolic deliria, namely uraemic encephalopathy, hepatic encephalopathy and respiratory failure. One refinement is counter-intuitive. Unilateral asterixis may rarely be seen in parietal, frontal or, most often, thalamic structural disease. A flap on one side only is a localising sign, not a metabolic one.

MNEMONIC

Liver, kidney, lung: the three organs that flap

Asterixis in a delirious patient points at **liver**, **kidney** or **lung**. Then ask the question that is not an organ: is the flap bilateral? If one-sided, think structurally, thalamus first.

TRAP **Reading asterixis as specific to liver failure.** Candidates learn the sign attached to hepatic encephalopathy and use it as though it named the organ. The safe formulation has two halves: it is pathognomonic for organic disease, but within organic disease it is a metabolic pointer with more than one destination.

22.7 The electroencephalogram, the triphasic wave and the cognitive tests

The second sign is electrographic, and Kaufman's classic case pairs the two: the examination demonstrates asterixis and the electroencephalogram shows triphasic waves. Most of what a metabolic encephalopathy does to an EEG is non-specific. Background slowing and disorganisation are typical but shared by numerous conditions; a few findings do suggest an aetiology, and **triphasic waves** often indicate hepatic or uraemic encephalopathy. In hepatic failure, triphasic waves usually appear before bilirubin levels rise, the electrographic version of the rule that mental change precedes the laboratory. And the finding may also be seen with toxic levels of several medications, including lithium: triphasic waves in a lithium-treated patient are not automatically hepatic, and that side of the question belongs to the Mood disorders: pharmacotherapy notes.

The modern term is worth a mark. How to Read an EEG classifies it as **generalized periodic discharges with triphasic morphology**, a common subtype seen in toxic and metabolic encephalopathies such as the hepatic and uraemic ones, but also with hypoxic and epileptic encephalopathies, and less commonly as the electrographic manifestation of non-convulsive status epilepticus. That last possibility is why morphology is read rather than pattern-matched. The same source cautions that no feature reliably separates ictal from non-ictal triphasic waves, and that on one retrospective study almost one-third of metabolic triphasic waves may show a definitive response to medication.

ELECTROGRAPHIC FEATURE	WHAT IT CONTRIBUTES
Two baseline crossings, three lengthening phases, tallest middle positive phase	Establishes triphasic morphology
Anterior-posterior lag of more than 100 ms	Supports the triphasic identification
Overriding spikes or sharp waves	Suggests an ictal pattern
Frequencies faster than 2.5 Hz	Suggests an ictal pattern
No change with state change or stimulation	Suggests an ictal pattern

At the mild end, testing wins. Kaplan and Sadock hold that although the electroencephalogram may show generalised slowing of the dominant rhythm, cognitive testing is more efficient and perhaps more sensitive to minimal hepatic encephalopathy. They name the Trail Making Tests A and B, Digit Symbol and Block Design, useful for minimal disease but not commonly employed because of time and expertise limitations, and a smartphone application using the Stroop cognitive screening test, validated against a standard neurocognitive battery and possibly a more feasible way to detect and track it. The instruments and their norms belong to the Dementias and neurocognitive disorders notes.

11-32
MICROMOL/L, LAB RANGE, NOT A THRESHOLD

>100 ms
ANTERIOR-POSTERIOR LAG, TRIPHASIC WAVE

>2.5 Hz
FASTER RUNS SUGGEST ICTAL

ALMOST ONE-THIRD
METABOLIC TRIPHASICS MAY RESPOND TO MEDICATION, ONE STUDY

IN INDIA

Neither the formal neuropsychological battery nor the electroencephalogram is realistically available where most of this work happens. District psychiatry units and de-addiction services see decompensated alcohol-related liver disease constantly, without same-week access to an EEG technician or a neuropsychologist, and the paper tests above are already described as not commonly employed for want of time and expertise. So the bedside asterixis check carries disproportionate weight in every confused patient with liver disease: it is free and, unlike the EEG, available at midnight. A validated smartphone-based screen is the one feasible route to tracking the minimal form.

22.8 Management implications for the psychiatrist: locus, focus and modus

LOCUS. Care happens in three places, all of them the psychiatrist's. The emergency and acute medical locus owns the fulminant form. The general hospital ward and the consultation-liaison referral own the common presentation, where the psychiatrist is asked to manage behaviour and should instead sequence an aetiological search. The outpatient and de-addiction locus owns the minimal form and relapse prevention. The hepatology society guidance governing the medical arm is not carried by the psychiatric references drawn on here: the positions below come from Kaplan and Sadock's Comprehensive Textbook of Psychiatry, Kaufman's Clinical Neurology for Psychiatrists and the addiction medicine literature.

FOCUS. The first target is not the mental state but the precipitant, and the instruction is explicit that these problems should be detected and corrected first:

- Gastrointestinal haemorrhage.
- Uraemia.
- Use of some psychoactive medications or diuretics.
- Significant protein intake.
- Dehydration or electrolyte imbalance.

Two of those are iatrogenic, and uraemia is the bridge to the other systemic encephalopathies dealt with elsewhere in this chapter. The short-term target is the encephalopathy once the precipitant is addressed; the mid-term target is recurrence, meaning the drinking, the diuretics and the nutritional state; the long-term target is the transition to overt disease.

MODUS. The gut-directed drug modes are the mainstay. Addiction medicine records that portal systemic encephalopathy responds well to lactulose, with **rifaximin** now increasingly available and of documented benefit where lactulose is not tolerated. No dose, frequency or titration endpoint for either agent appears in any reference used here, and none is invented: know the mechanism and the order of preference, and take the regimen from a prescribing source. The psychiatric mode is largely subtractive. Medications that contribute to the symptoms of hepatic encephalopathy or slow intestinal motility, namely anticholinergic drugs, tranquillisers, narcotics and sedatives, should generally be avoided. That covers most of what a liaison psychiatrist is tempted to prescribe here; which psychotropic may then be used is dealt with where this chapter

covers prescribing in hepatic and renal impairment. The procedural mode matters for its shadow: shunting is where the rare persistent form appears, so an encephalopathy that does not clear deserves a question about shunt anatomy. The social mode is the most decisive, because abstinence, nutrition and adherence to a gut-directed regimen determine whether any of the above holds.

PITFALL

Sedating the agitated, disinhibited cirrhotic patient because the presentation looks behavioural. The reasoning is ordinary: the patient is disturbed, the referral asked for sedation, the drug settles people. It does three unhelpful things at once. It adds to the receptor activity implicated in the mechanism, it slows intestinal motility in a patient whose treatment depends on gut transit, and it obscures the conscious level that is the main index of improvement.

23 · Uraemic, hypoxic and other systemic encephalopathies

These are the encephalopathies in which the failing organ is never the brain, and the psychiatrist is called first. A dialysis patient stops sleeping, turns irritable, then frankly paranoid. A patient with advancing neuromuscular weakness becomes overwhelmingly anxious overnight. A young man resuscitated after a hanging attempt opens his eyes and says nothing that means anything. In each the reflex psychiatric response is the wrong one.

Hepatic encephalopathy and its grading belong where this chapter deals with hepatic encephalopathy; dose adjustment in renal failure belongs where this chapter deals with prescribing psychotropics in hepatic and renal impairment. Delirium as a syndrome belongs to the Stroke, TBI, delirium and focal brain syndromes notes; the dementia syndrome and its investigation belong to the Dementias and neurocognitive disorders notes.

23.1 Why uraemia poisons the brain, and why no single molecule is to blame

Kaplan and Sadock's Comprehensive Textbook of Psychiatry frames **uraemic encephalopathy** as the endpoint of broad systemic failure rather than of one toxin. Chronic renal failure frequently produces multiple pathophysiologic changes across catabolic, metabolic and endocrinologic processes, and the accumulation of organic substances acting as neurotoxins is believed to drive the encephalopathy. The substances named are urea, uric acid, guanidine compounds, hippuric acid, various amino acids and indoleacetate among others, but no single metabolite has been identified as the sole cause.

That last clause is the examination point: as with ammonia in hepatic encephalopathy, the marker everyone measures explains none of the mental state.

A second set of contributors is the correctable one: hormonal elevations, electrolyte imbalances including acidosis, hyponatraemia, hyperkalaemia, hypocalcaemia and hypermagnesaemia, anaemia, malnutrition, and central nervous system factors comprising increased calcium with decreased GABA and glycine activity. That is a management list disguised as a pathophysiology list: the neurotoxins leave only with dialysis or a new kidney, while the electrolytes, the anaemia and the nutritional state can be addressed tonight.

RULE **In a systemic encephalopathy the brain is the readout, not the lesion.** Imaging excludes a structural competitor rather than finding the cause; the electroencephalogram grades severity but does not name the organ; the treatment that works is directed at the systemic derangement. A psychiatrist who answers uraemic paranoia with an antipsychotic before asking when the patient last dialysed has answered the wrong question.

23.2 The clinical picture, from insomnia to coma

The fluctuation is what identifies the disease as metabolic. Symptoms typically fluctuate and can begin insidiously, with patients reporting mild irritability, insomnia, or cognitive, attentional and memory impairment. Patients may complain of slurred speech, muscle twitches or restless legs. Symptoms can then progress, slowly or rapidly, to confusion, lethargy, seizures, overt delirium, psychosis, catatonia, and stupor or coma.

Three features matter. Irritability, insomnia and inattention in chronic kidney disease get referred as depression or non-compliance; the discriminator is the attentional deficit, which does not belong to a mood disorder. Psychosis and catatonia are explicitly on the list, so a catatonic presentation in renal failure is not a coexisting psychiatric diagnosis. And restless legs are routinely misread as akathisia once the patient is on an antipsychotic.

Kaufman's Clinical Neurology for Psychiatrists records that renal insufficiency is a common cause of neuropathy and occurs almost universally in patients on maintenance haemodialysis, so stocking-glove sensory loss is expected. The negative that follows is more useful: cancer chemotherapy agents and antibiotics, including those used for tuberculosis and HIV disease, routinely cause neuropathy, whereas antipsychotics, antidepressants and antiepileptic drugs, with the exception of phenytoin, do not.

23.3 Asterixis and myoclonus: the two signs that localise to an organ

Two involuntary movements do most of the bedside work. Tasman's Psychiatry states that **asterixis** is highly suggestive of one of three metabolic deliria: uraemic encephalopathy, hepatic encephalopathy and respiratory failure.

MNEMONIC

Liver, Kidney, Lung

The three organs behind asterixis in an unexplained encephalopathy, worked in the order of the examination: sclerae and abdomen, then when the patient last passed urine and last dialysed, then the respiratory rate and accessory muscles. All three are answered before any investigation returns.

Myoclonus discriminates within that group. Kaufman notes that patients with hepatic or uraemic encephalopathy have asterixis, while myoclonus occurs in uraemia, in penicillin or bismuth intoxication, with meperidine treatment, and in several other metabolic encephalopathies. Uraemia therefore produces both. Tasman widens the differential: myoclonus may be seen in toxic deliria such as the serotonin syndrome, in metabolic deliria such as uraemic encephalopathy and hyperglycaemia, and in certain others such as Hashimoto's encephalopathy. The first arises

from our own prescribing; the last is taught where this chapter deals with subclinical thyroid disease and autoimmunity.

> Asterixis narrows an unexplained encephalopathy to liver, kidney or lung; myoclonus alongside it leans renal.

Discriminating the systemic encephalopathies at the bedside and on the electroencephalogram

CONDITION	ASTERIXIS	MYOCLONUS	ELECTROENCEPHALOGRAM
Uraemic encephalopathy	Yes	Yes	Generalised slowing of the dominant rhythm; triphasic waves when uraemia is severe
Hepatic encephalopathy (taught elsewhere in this chapter)	Yes	Not among those listed	Triphasic waves
Respiratory failure	Yes	Not listed	Not characterised in these sources
Hypoxic-ischaemic encephalopathy	Not listed	Not listed	Generalised periodic discharges

23.4 What the electroencephalogram adds, and the seizure it hides

The electroencephalogram does two jobs. Kaplan and Sadock state that an electroencephalogram can aid diagnosis, typically showing a generalised slowing of the dominant rhythm, and can detect seizures including **nonconvulsive status epilepticus**, which can occur in uraemia and could be mistaken for uraemic encephalopathy. Grading is the first: diffuse slowing confirms the disturbance is global and metabolic rather than focal and structural, the question a confused patient with a normal scan raises. The second changes management, because no bedside observation reliably separates an obtunded, twitching uraemic patient who is encephalopathic from one in nonconvulsive status, and the wrong call leaves a patient in status while dialysis is awaited.

Kaufman records that **triphasic waves** develop in hepatic encephalopathy and in several other toxic-metabolic encephalopathies, such as severe uraemia. The qualifying adjective is load-bearing: Kaufman's worked example shows mild to moderate derangement producing diffuse background slowing rather than triphasic waves, so the waves imply uraemia well beyond the threshold at which the patient first became confused. Their absence excludes nothing.

PITFALL

Accepting a normal or non-specific electroencephalogram report as evidence against a metabolic encephalopathy, when the study was recorded on a lucid day between dialysis sessions. The picture fluctuates and so does the tracing, which cannot answer a question about a state it never sampled.

23.5 Three mimics that live inside the uraemic patient

Uraemic encephalopathy is a diagnosis of exclusion in a population unusually rich in things to exclude. The first mimic is thiamine deficiency. Kaplan and Sadock record that reduced levels of thiamine, a water-soluble vitamin, have been noted in haemodialysis patients, and cases of Wernicke encephalopathy have been mistaken for uraemic encephalopathy. Dialysis is a filter and does not distinguish a neurotoxin from a water-soluble vitamin. A confused, ataxic dialysis patient with eye signs therefore has a treatable deficiency until proved otherwise, and this is not the alcohol-related presentation the syndrome is usually taught through. The acute syndrome and its treatment regimens are taught where this chapter deals with Wernicke encephalopathy and the Korsakoff boundary.

The second is nonconvulsive status, above. The third is radiological. Uraemic encephalopathy has also been associated with a cliniconeuroradiologic syndrome termed **posterior reversible (leuko) encephalopathy syndrome**, whose characteristic findings on computed tomography or magnetic resonance imaging lie in the posterior cortical and subcortical white matter. Imaging here is ordered to exclude a bleed or an infarct and the negative filed as reassurance, yet a positive finding is available in exactly this population: posterior, often subtle on computed tomography, and reversible when recognised.

IN INDIA

Maintenance haemodialysis in much of Indian practice is intermittent by economics rather than by prescription: sessions are missed when money, transport or a working machine is unavailable. Presentations skew late, so overt delirium, seizures and catatonia are commoner first contacts than insidious irritability and insomnia, and the clinician waiting for a gradual prodrome will meet the patient in coma. Electroencephalography is concentrated in teaching and tertiary hospitals, so the investigation that separates encephalopathy from nonconvulsive status is often unavailable. Where it cannot be obtained, hold that question open, escalate dialysis, and do not commit to a psychiatric formulation of a confusional state that has never had a tracing. Thiamine, by contrast, is cheap and everywhere, and empirical use costs almost nothing.

23.6 When dialysis is the cause: disequilibrium and the aluminium dementia

Two encephalopathies arise from the treatment rather than the disease, and candidates confuse them because both are called dialysis something. The first is **dialysis disequilibrium**, an osmotic event. KDT's Essentials of Medical Pharmacology gives its basis as a fall in the osmolality of plasma and extracellular fluid due to rapid haemodialysis or peritoneal dialysis, and lists mannitol as the countermeasure. Goodman and Gilman independently name dialysis disequilibrium syndrome among the indications for mannitol. Beyond that mechanism and its countermeasure these sources give no clean account and no dose; the timing, symptom sequence, severity spectrum and risk factors are stated here as not established rather than filled in from recollection.

The second is the chronic dementing syndrome of aluminium exposure, to which ICD-11 gives a diagnostic home without the traditional name. The code is **6D85.2**, Dementia due to exposure to heavy metals and other toxins. Its essential requirements are that all the diagnostic requirements for dementia are met and that the dementia is presumed attributable to toxic exposure to specific

heavy metals, such as aluminium from dialysis water, lead, mercury or manganese, demonstrated by neuropsychological test data, neuroimaging data, medical tests or clinical history. Two things follow: the classification does not recognise dialysis dementia as an entity, so a candidate searching the manual for that phrase will not find it, and the attribution is presumptive rather than confirmed by any test.

ICD-11 holds that the neurocognitive impairments depend on the particular metal or toxin and can affect any cognitive domain, that onset is related to exposure and progression can be rapid, particularly with acute exposure, and that in some cases symptoms are reversible once the exposure is identified and ceases. A reversible dementia is rare enough to deserve a place on the list whenever a dialysis patient's cognition declines. The dementia syndrome itself and its workup belong to the Dementias and neurocognitive disorders notes.

23.7 Managing uraemic encephalopathy

No guideline-level protocol for the psychiatric management of uraemic encephalopathy appears in these sources; what they give is a treatment logic. **LOCUS.** Once the mental state has changed this is not outpatient work: the patient belongs where dialysis, biochemistry and cardiac monitoring are available, meaning a medical or renal ward with liaison psychiatry attending, and intensive care once there are seizures or a depressed conscious level. The commonest system error is a transfer in the wrong direction, to a psychiatric unit that cannot dialyse, on the strength of a psychotic or catatonic presentation.

FOCUS. Acutely the targets are the derangement and the seizure, not the psychopathology. Kaplan and Sadock give the sequence: removal of uraemic toxins by haemodialysis, correction of electrolyte imbalances and of anaemia, and treatment of malnutrition can diminish symptoms and improve cognition, while seizures may be treated with anticonvulsants. Over the short and medium term the focus shifts to sustaining that correction and to reassessing cognition once the biochemistry settles, because a mental state assessed in the uraemic trough is not the patient's baseline. Long term, definitive renal replacement.

MODUS. Dialysis is the effective modality; anticonvulsants cover the seizure; psychological and social work belongs to adherence and the family burden of sustaining a dialysis schedule, which determines whether the correction holds. Sedation needs the most caution, and the source says why: drugs that are sedating, or that require elimination of the parent compound or an active metabolite by renal clearance, should be avoided, or their dosages appropriately adjusted for the degree of impaired renal function. Making that adjustment agent by agent is taught where this chapter deals with prescribing psychotropics in hepatic and renal impairment.

Definitive treatment does not guarantee a clean cognitive result. Kaplan and Sadock report a cross-sectional study of kidney transplant recipients an average of 3.4 years afterwards in which **58%** met criteria for cognitive impairment. That figure describes transplant recipients at that interval and nothing else; it is not a prevalence in uraemia, and quoting it as one is an error of population.

58%	3.4 YEARS	3	6D85.2
COGNITIVELY IMPAIRED AFTER TRANSPLANT	MEAN INTERVAL IN THAT STUDY	METABOLIC DELIRIA WITH ASTERIXIS	ICD-11 CODE, DIALYSIS ALUMINIUM

TRAP **Sending a serum ammonia to diagnose uraemic encephalopathy.** Two standard sources disagree and the disagreement is unresolved; know both positions. Kaplan and Sadock name the uraemic neurotoxins, insist no single metabolite is the sole cause, and never invoke ammonia in the renal context. Against that, a widely reproduced differential table in Saunders and colleagues' Addiction medicine lists serum ammonia among the differentiating features of uraemic encephalopathy. That table shows clear row displacement, one value repeated verbatim down five unrelated rows and another carrying two competing values, so the ammonia entry may have migrated from the adjacent hepatic line. Ammonia is the hepatic marker, its role in uraemia is unsupported by the major textbook account, and no metabolite test diagnoses this condition.

23.8 Hypoxia and hypercapnia: the encephalopathy referred as anxiety

Respiratory failure is the third organ behind asterixis, and the one most often handed to psychiatry as a psychiatric problem. Kaufman puts it as a vignette: a man with rapidly advancing Guillain-Barre syndrome develops confusion, overwhelming anxiety and agitation, and the answer is that he may be developing hypoxia, hypercapnia or both because of chest and diaphragm muscle paresis. Guillain-Barre syndrome, also called acute inflammatory demyelinating polyradiculoneuropathy, is not directly associated with central nervous system dysfunction; however, respiratory insufficiency is a common complication of the illness and might cause the anxiety and agitation.

That is hypoxic and hypercapnic encephalopathy arriving under a psychiatric label. Acute anxiety and agitation in any patient with neuromuscular or respiratory compromise is a blood-gas problem until proved otherwise, and the request that arrives on the phone is almost always for a benzodiazepine, which sedates the respiratory drive that is the only thing keeping the gases survivable. The first response is an arterial blood gas and an assessment of ventilation; the second, if the gases are deranged, a call to intensive care rather than a prescription. ICD-11's list of conditions to consider in a disturbed mental state includes Wernicke's encephalopathy, electrolyte disturbance, systemic infection, and hypoxia or hypercapnia: a bare list rather than a diagnostic rule, quoted only to place the gases in the standard differential.

GOOD TO REMEMBER

Arterial carbon dioxide is a less reliable guide to encephalopathy than arterial oxygen, because chronic retainers adapt and tolerate levels that would confuse an acutely deranged patient. The same principle governs uraemia: an acute derangement produces symptoms at a degree of abnormality a slowly progressive one is tolerated at. A single gas read without the trajectory decides nothing. The thresholds conventionally quoted for the two partial pressures could not be verified from a clean reading of these sources and are deliberately not printed.

23.9 Anoxic injury, its end states, and the encephalopathy treatment causes

Anoxia is the exception to the reassuring rule that metabolic encephalopathies reverse: most patients recover from delirium if the underlying illness responds to treatment, but sometimes, as

in anoxic encephalopathy, they are left with permanent cognitive impairment. To a neurologist **watershed** denotes areas of cerebral cortex perfused by the terminal branches of arteries, whose already tenuous blood supply falls to an insufficient level during hypotension or anoxia. What remains once the insult ends is structural loss, not biochemical disturbance.

Kaufman describes a severe and extensive, though incomplete, cerebral cortical anoxic insult, an injury also suffered by survivors of cardiac arrest and by those who have attempted suicide by hanging or carbon monoxide poisoning, in whom the well-perfused language arc may be preserved while almost the entirety of the other cortical regions is destroyed. That preserved arc surrounded by destroyed cortex is the **isolation aphasia** picture: the patient who repeats fluently but comprehends nothing and initiates nothing. Two of the three causes named are suicide attempts, which is why the survivors are our patients.

Where the cortical injury is more complete the outcome is a **persistent vegetative state**, which typically follows cerebral cortical anoxia from cardiac arrest, drug overdose, carbon monoxide poisoning or traumatic brain injury. The cortical injury is extensive, so cognitive impairment is profound, yet vegetative functions such as respiration and digestion continue and the eyes open and close, mostly randomly or in response to light. That extensive cortical damage produces slow and disorganised electroencephalographic activity. That tracing discriminates against locked-in syndrome, which follows infarction at the base of the lower brainstem or extensive cranial and peripheral nerve disruption: hemispheres and thalamus intact, those patients retain normal cortical function and a normal tracing. At the far end, electroencephalographic activity is completely absent, or **electrocerebral silence**, in brain death, in which by definition brain function is utterly abolished.

The surviving anoxic patient often shows a periodic pattern. **Generalised periodic discharges** are commonly seen in toxic or metabolic encephalopathies including sepsis, where triphasic waves are especially characteristic; in extensive structural cerebral damage such as hypoxic ischaemic encephalopathy, diffuse intracranial haemorrhage or neurodegeneration; in the epileptic encephalopathies; with medications; and in infections such as Creutzfeldt-Jakob disease or subacute sclerosing panencephalitis. The medication list is the one to memorise, because one of its members is ours:

- Cefepime.
- Lithium.
- Ifosfamide.
- Baclofen.
- Metrizamide.

Lithium as a drug, its pharmacokinetics, therapeutic range and non-thyroid organ-system adverse effects belong to the Mood disorders: pharmacotherapy notes.

TRAP **Reading generalised periodic discharges as an independent marker of death.** Candidates reproduce the traditional teaching that they imply a poor prognosis. The source describing the pattern corrects it: recent studies have not found an independent association with increased mortality; the discharges are associated with nonconvulsive status epilepticus, which does itself carry increased mortality; and the underlying aetiology and the severity of the primary disease process are most often the key determinants of prognosis. The pattern is a prompt to look for treatable status and to characterise the primary illness, not a prognostic verdict to deliver to a family.

One systemic encephalopathy is produced entirely by treatment. Kaufman warns that overly rapid correction of metabolic derangements, such as hyponatraemia, can lead to **central pontine myelinolysis**, the prime example of the osmotic demyelination syndrome. The syndrome itself, the populations at risk, the safe correction rate and the management of the hyponatraemia that provokes it belong where this chapter deals with psychogenic polydipsia and the sodium-correction risk; no numeric ceiling for the rate is stated in these sources and none is printed here. The principle: a chronic derangement must be corrected slowly, because it is the speed of correction and not the abnormality that demyelinates.

24 · Prescribing psychotropics in hepatic and renal impairment

This is the commonest real prescribing problem in liaison psychiatry and one of the easiest places to lose marks. Most answers turn on one insight: the drugs safest in liver disease are the drugs most dangerous in kidney disease.

Two standard references dominate and do not always agree; where they diverge, both positions are given rather than harmonised. Only the organ-impairment modifier is owned here: dose and titration for the psychiatric indication belong with that disorder's pharmacotherapy, lithium as a drug to the Mood disorders: pharmacotherapy notes, and antipsychotic selection to the Schizophrenia: management, antipsychotics and adverse effects notes.

ONE-THIRD	4%	0.5% TO 3%	1.65%
ON ANTIPSYCHOTICS, ONE ABNORMAL LFT	AN LFT OVER THREE TIMES ULN	ON ANTIDEPRESSANTS, TRANSAMINASE RISE	SEVERE HEPATIC TOXICITY, QUETIAPINE

24.1 What the liver function tests do not tell you

Liver function tests evaluate hepatic damage; they say little about **hepatic metabolising capacity**, and many people with chronic liver disease are asymptomatic or fluctuate clinically. A normal panel does not license a normal dose, nor a deranged one a reduced dose. There are few clinical studies of psychotropics in hepatic disease, so almost all of what follows is kinetic inference rather than trial evidence.

Advanced organ disease shifts perfusion, fluid status, protein binding, hepatic metabolism and excretion, with pretransplant patients additionally prone to encephalopathy, arrhythmia and drug interactions. Two dosing consequences follow. Highly protein-bound drugs, the tricyclics, the SSRIs other than citalopram, trazodone and the antipsychotics, may carry raised free levels initially, and this is not reflected in the measured total plasma level, which is why therapeutic

drug monitoring misleads here. Second, agents with extensive **first-pass metabolism**, the tricyclics and haloperidol, need lower doses.

24.2 The principles, and the four drugs that escape the liver

The general principles of prescribing psychotropics in hepatic impairment generate most correct answers without a table.

- Be cautious with extensively hepatically metabolised drugs, which is most psychotropics; lower doses may be needed.
- The exceptions are sulpiride, amisulpride, lithium and gabapentin, undergoing no or minimal hepatic metabolism.
- Avoid very sedative drugs, for the risk of precipitating hepatic encephalopathy.
- Avoid very constipating drugs, for the same reason.
- Avoid drugs hepatotoxic in their own right, the examples given being the monoamine oxidase inhibitors and chlorpromazine.

Both rules earn their place: sedation and constipation slow clearance of ammoniagenic load from the gut and mask worsening encephalopathy. That syndrome is set out where this chapter deals with hepatic encephalopathy, and delirium belongs to the Stroke, TBI, delirium and focal brain syndromes notes. Clozapine is disqualified twice over, being both.

RULE **Reach for the drug the failing organ does not handle.** In hepatic impairment the answers are the renally cleared agents: amisulpride and sulpiride need no reduction provided renal function is normal, and paliperidone, mainly excreted unchanged, may be a good choice in pre-existing hepatic disease. Turn the failing organ around and the list inverts: be cautious with extensively renally cleared drugs such as sulpiride, amisulpride and lithium, and avoid nephrotoxic drugs, lithium and the non-steroidal anti-inflammatories among them.

The four drugs that escape the liver are sulpiride, amisulpride, lithium and gabapentin. They are the hepatic-impairment answers and, gabapentin partly excepted, the renal-impairment dangers. Learn the list once and read it both ways.

24.3 How often psychotropics disturb the liver tests

Abnormal transaminases on a psychotropic are common; significant injury is not. On antipsychotics, a third of patients have at least one abnormal test and 4% have one above three times the upper limit of normal, transaminases most often affected, generally within 1 to 6 weeks of initiation. On antidepressants, 0.5% to 3% develop asymptomatic mild transaminase elevation, normally several days to 6 months after initiation, the elderly more vulnerable. Frank damage is rare and mostly **idiosyncratic**, being unpredictable, unrelated to dose, and with cross-toxicity within a class described. Within-class substitution after a hepatic reaction is therefore not automatically safe.

Transient asymptomatic rises appear in 20% of patients on haloperidol, and on clozapine elevations of AST, ALT and GGT to over twice normal occur in up to a third, resolving

spontaneously in 6 to 12 weeks. Only one agent carries a mandated schedule: agomelatine needs liver function tests at baseline and at 3, 6, 12 and 24 weeks during initiation and at each dose increase, stopping if transaminases exceed three times the upper limit of normal.

TRAP **The consequence rises, not the probability.** Pre-existing liver disease does not increase the risk of drug-induced hepatotoxicity, but it may be more catastrophic if it occurs. Candidates reverse this and answer that cirrhosis makes hepatotoxic reactions likelier. The corollary: shun a drug with a hepatic signal in the patient with no reserve to absorb the hit.

24.4 Antidepressants in hepatic impairment

Nearly every antidepressant is hepatically cleared, so most differences are of degree. Three are outright prohibitions. Duloxetine's clearance is markedly reduced even in mild disease, with hepatocellular injury beyond ten times the upper limit of normal and fatal hepatic failure reported; agomelatine likewise; non-selective monoamine oxidase inhibitors are contraindicated in hepatic impairment.

AGENT	INDICATION	MODIFIER IN HEPATIC IMPAIRMENT
Sertraline	Depression, anxiety	Low or less frequent dose in mild disease; avoid in moderate and severe. Itself used for **cholestatic pruritus**
Citalopram	Depression	Maximum **20 mg daily**; higher exposure, greater QT risk
Escitalopram	Depression	60% higher exposure in mild to moderate disease; 5 mg daily for the first 2 weeks, maximum 10 mg daily
Fluoxetine	Depression	Accumulates in compensated cirrhosis; reduce by at least 50% or dose on alternate days
Mirtazapine	Depression	50% dose reduction on kinetic data, though sedative
Agomelatine	Depression	Contraindicated, including cirrhosis and active liver disease
Moclobemide, reboxetine	Depression	Moclobemide to half or one-third of the dose; reboxetine a 50% reduction in starting dose
Venlafaxine	Depression	Reduce the total daily dose; watch blood pressure
Bupropion	Depression	In severe disease, 150 mg extended-release every other day or 100 mg per day sustained-release

AGENT	INDICATION	MODIFIER IN HEPATIC IMPAIRMENT
Vortioxetine, esketamine	Depression	Neither recommended in severe disease; esketamine needs longer monitoring in moderate disease

Sertraline is where the references part company: one permits reduced or less frequent dosing at any severity, the other prohibits it in moderate and severe disease. Sertraline being otherwise a natural first choice in the medically ill, the disagreement is real and unresolved, compounded because the severity scores printed against it overlap and cannot both be correct.

24.5 Antipsychotics in hepatic impairment

Aripiprazole needs no reduction in mild to moderate disease, with caution in severe disease, and pimavanserin none at all. Clozapine is contraindicated in active liver disease with nausea, anorexia or jaundice, in progressive disease and in hepatic failure; in milder disease start treatment-resistant schizophrenia at 12.5 mg, increasing slowly, plasma levels gauging metabolising capacity. Olanzapine changes little kinetically even in severe impairment but is sedative and anticholinergic, so start psychosis or mania at 5 mg per day in moderate or severe disease, plasma target 20 to 40 mcg per litre; with clozapine it is the antipsychotic most often linked to drug-induced liver injury. For psychosis in severe disease, risperidone starts at 0.5 mg twice daily, rising by 0.5 mg twice daily no faster than weekly above 1.5 mg twice daily.

In moderate or severe hepatic failure, brexpiprazole should not exceed 3 mg per day for schizophrenia or 2 mg per day for depression or agitation in Alzheimer's disease, its half-life long at around 90 hours. For schizophrenia or bipolar depression, lurasidone starts at 18.5 mg, capped at 74 mg per day in moderate disease, where exposure rises 1.7-fold, and 37 mg per day in severe disease, where it trebles; the American reference gives the same ceilings in salt-equivalent strengths, starting at 20 mg per day and not exceeding 80 mg per day in moderate or 40 mg per day in severe hepatic impairment. For psychosis, briefly: asenapine is avoided in severe disease, exposure rising sevenfold; iloperidone is reduced in moderate disease, active metabolites doubling, and avoided in severe; cariprazine is not advised in severe failure, half-life about 2 to 4 days; lumateperone has a manufacturer-recommended dose of 21 mg daily in moderate and severe disease, exposure being increased; and the phenothiazines, sedative and constipating to a drug, are best avoided, chlorpromazine being particularly hepatotoxic.

TRAP **Haloperidol and quetiapine are where the two standard references give opposite advice.** For psychosis, agitation or delirium, one position holds haloperidol extensively hepatically metabolised, so halve initial doses and adjust in smaller increments at longer intervals; the other records that typical agents such as haloperidol need no dosage adjustment in renal or hepatic impairment. Each is internally consistent, one reasoning from first-pass extraction, the other from the near-absence of renal excretion. Quetiapine splits identically: one holds that clearance falls by a mean of 30%, so psychosis or bipolar disorder starts at 25 mg per day of the immediate-release or 50 mg per day of the extended-release preparation, the other that no adjustment is needed. The sources also print two different lurasidone starting figures, and impairment tables have carried a millilitre where a milligram was meant; an oral tablet dose is never in millilitres.

24.6 Sedatives, mood stabilisers, transplantation and the substance-use agents

Benzodiazepine choice in liver disease follows metabolic route, not half-life. Impaired hepatic oxidation delays clearance and raises adverse effects, so agents needing only **conjugation** are preferred for anxiolysis or sedation in hepatic impairment: lorazepam, oxazepam and temazepam, with respiratory depression the residual risk.

MNEMONIC

Lorazepam, Oxazepam, Temazepam

LOT: the three benzodiazepines needing no hepatic oxidation, and so the choices in liver disease. In the cirrhotic patient in withdrawal, offered diazepam or chlordiazepoxide alongside these three, this is the answer.

Among anticonvulsant mood stabilisers the most examinable adjustment: for bipolar disorder or epilepsy in severe hepatic impairment, lamotrigine has initial, escalation and maintenance doses reduced by **50%** with ascites and by 25% without. Valproate is the conspicuous hole: both references say only to avoid it where possible, since clearance falls and low albumin raises the free fraction, and neither offers a percentage or a ceiling.

Transplantation adds an interaction problem to the kinetic one. Immunosuppressants are largely CYP3A4 substrates and psychotropics differ widely in inhibiting it: in decreasing order, fluvoxamine and nefazodone, then fluoxetine, then sertraline, the tricyclics and paroxetine, then venlafaxine. Nefazodone has produced toxic immunosuppressant levels and is best avoided outright. Induction is no safer: carbamazepine and oxcarbazepine, as CYP3A4 inducers, lower immunosuppressant levels and risk organ rejection.

GOOD TO REMEMBER

Before starting any antidepressant in a transplant candidate or recipient, check the immunosuppressant regimen and speak to the transplant team. The commonest avoidable harm is not hepatotoxicity but a graft lost to a predictable interaction.

Naltrexone carries a black box warning for hepatotoxicity and is not recommended in active liver disease, hepatitis or liver failure; above the recommended range, at more than 300 mg per day, it

becomes a direct hepatotoxin. Methadone needs a lower initial dose and slow titration in either impairment and can prolong the QT interval. For ADHD, atomoxetine is reduced by 50% in moderate and 75% in severe hepatic impairment, modafinil by 50% in severe, while methylphenidate and amphetamine need no adjustment in either organ.

24.7 Estimating renal function, and the general renal principles

CKD-EPI is more accurate than MDRD and is preferred; for most drugs and most adults of average build its estimated glomerular filtration rate can guide dose adjustment. For nephrotoxic drugs, patients aged 75 years and over, and either extreme of muscle mass, body mass index below 18 or above 40 kg/m2, calculate **creatinine clearance** instead, by the **Cockcroft and Gault equation**. Regulatory advice extends creatinine clearance to direct-acting oral anticoagulants and to narrow therapeutic index drugs mainly renally excreted, lithium among them. The psychiatric point: the drug most likely to need renal dosing is the one for which the routinely reported estimate is the wrong number.

Five principles frame dose adjustment in renal impairment and the choice of agent. renal function significantly affects elimination when the fraction excreted unchanged in urine is **30% or more** of the dose, which is why lithium, sulpiride, amisulpride and paliperidone dominate the renal tables and clozapine and haloperidol barely appear. Age is a silent modifier: adults over 65 should be assumed to have at least mild renal impairment, serum creatinine perhaps not raised because muscle mass is smaller. Renal failure slows hepatic clearance too, the point most often missed: elimination of hepatically metabolised drugs can fall in kidney disease, possibly through inhibition of enzyme activity by **uraemia**, so start low and go slowly, half-life and time to steady state often being prolonged. Long-acting preparations such as depots should be avoided, since their dose and frequency cannot easily be adjusted if renal function changes, as should QTc-prolonging drugs, electrolyte disturbance being common in established renal failure. Trajectory matters as much as the current value: a 30% change over 2 years carries a fivefold increase in the risk of end stage renal disease.

> **PITFALL**
>
> Manufacturer bands are written variously in filtration rate or in creatinine clearance, and for a narrow therapeutic index drug the two are not interchangeable. The pragmatic bands used by the drug tables also do not map cleanly onto the chronic kidney disease stages, so do not translate between them.

24.8 Lithium, and the drugs the kidney clears

Lithium is the paradigm case, being both the drug most affected by renal impairment and a cause of it. It is nephrotoxic and contraindicated in severe renal impairment, **95%** excreted unchanged in urine. For bipolar maintenance at a filtration rate of 10 to 50 mL/min, avoid it or reduce to 50% to 75% of the normal dose with level monitoring; below 10 mL/min avoid if possible, and if used, 25% to 50% is essential. It can be used successfully during haemodialysis. The renal risk is cumulative rather than acute: risk factors include increasing age, treatment duration, cumulative dose, lower initial eGFR, female sex, hypertension and diabetes, concomitant nephrotoxic drugs,

nephrogenic diabetes insipidus and previous toxicity, and damage is likelier with chronic than acute toxicity. Prevention rests on once daily dosing, tight adherence to recommended plasma levels, avoiding intoxication, treating comorbidity assertively and monitoring kidney function actively.

IN INDIA

Wherever lithium is prescribed, the creatinine clearance instruction becomes a daily problem: laboratories report an estimated filtration rate with every creatinine, while Cockcroft and Gault needs a recorded body weight that outpatient notes frequently lack. Non-steroidal anti-inflammatories, among the nephrotoxic drugs to avoid where renal reserve is limited, are bought across the counter and rarely volunteered unless asked for by name. And long-acting injectables, attractive where follow-up is distant and adherence fragile, are the preparations to avoid when renal function may change, because the dose cannot be taken back.

AGENT	INDICATION	MODIFIER BY RENAL FUNCTION
Amisulpride	Psychosis	50% unchanged. 50% of the dose at GFR 30 to 60 and 33% at 10 to 30 mL/min; no recommendation below 10, so avoid
Sulpiride	Psychosis	Almost wholly renal. 70%, 50% and 34% of the normal dose at GFR 30 to 60, 10 to 30 and below 10 mL/min, or lengthen the interval 1.5-, 2- and 3-fold
Paliperidone	Psychosis	59% unchanged. GFR 50 to 80: 3 mg daily, maximum 6 mg. GFR 10 to 50: 3 mg alternate days or 1.5 mg daily. Clearance falls 71% in severe disease; oral contraindicated below GFR 10, depots below 50 mL/min
Risperidone	Psychosis	Clearance falls 60%. Below GFR 50: 0.5 mg twice daily for at least 1 week, then up by 0.5 mg twice daily to 1 to 2 mg twice daily; injection only after oral titration
Olanzapine	Psychosis	7% unchanged. UK labelling: 5 mg daily below GFR 50, injection from 150 mg every 4 weeks. US labelling: no adjustment
Lurasidone	Schizophrenia, bipolar depression	9% unchanged; levels 1.5-, 1.9- and 2.0-fold higher in mild, moderate and severe disease. Below GFR 50: start 18.75 mg, maximum 74 mg per day; avoid below 15 mL/min

AGENT	INDICATION	MODIFIER BY RENAL FUNCTION
Clozapine, chlorpromazine, aripiprazole, lumateperone, pimozide, haloperidol, quetiapine	Psychosis, delirium	All excreted overwhelmingly as metabolites, under 1% of haloperidol and under 5% of quetiapine unchanged, and none needs routine adjustment. Clozapine and chlorpromazine: no adjustment above GFR 10 mL/min, cautious titration in very severe disease, though clozapine is contraindicated by its manufacturer in severe renal disease. Haloperidol: normal dosing at GFR 10 to 50, lower start below 10. Quetiapine clearance falls 25% below GFR 30 with no change advised
Ziprasidone	Psychosis	Under 1% unchanged, no adjustment above GFR 10, but the injection carries **cyclodextrin sodium**, a renally eliminated excipient
Valproate	Bipolar disorder, epilepsy	About 2% unchanged; normal dosing, but free levels rise and below GFR 10 dose to free valproate levels. Interstitial nephritis and renal tubular acidosis reported
Topiramate, gabapentin, oxcarbazepine	Bipolar disorder, epilepsy, neuropathic pain	Topiramate halved in moderate to severe disease. Gabapentin 600 mg per day in moderate and 150 to 300 mg per day in severe disease, supplemented after dialysis. Oxcarbazepine from 300 mg per day in severe disease
Desvenlafaxine, acamprosate, varenicline, buspirone	Depression, dependence, anxiety	Desvenlafaxine no more than 50 mg per day in moderate and 50 mg every other day in severe disease. Acamprosate 333 mg three times daily in moderate disease, contraindicated in severe; varenicline from 0.5 mg per day to 0.5 mg twice daily in severe disease. Buspirone not recommended in severe renal or hepatic impairment

Two points close the table. Amisulpride and sulpiride, always taught together, carry different percentage schedules at the same bands and must be learned apart. And risperidone warns about triggers, not doses: three references give the same 0.5 mg twice daily start for psychosis but

attach it to a filtration rate below 50 mL/min, to severe impairment, and to a creatinine clearance below 30 mL/min respectively, materially different populations.

24.9 Choosing a regimen and following it up

Management here is a sequence, not a lookup. The LOCUS of care is set by the organ, not the psychiatric diagnosis: decompensated cirrhosis or established renal failure needing psychotropic initiation belongs on a medical or liaison inpatient service where electrolytes and fluid balance are already followed; stable compensated disease sits in outpatient psychiatry under a shared plan with a named physician; agitation in the encephalopathic patient is handled where the medical team is. Three bodies of guidance frame the decision: the Maudsley Prescribing Guidelines for drug-by-drug kinetic adjustment, Kaplan and Sadock's Comprehensive Textbook of Psychiatry for the transplant and advanced organ disease perspective, and the American Psychiatric Association practice guideline where it specifies initial doses and titration rates in impairment.

The FOCUS moves by phase: acutely, the symptom threatening the medical course, at the smallest effective exposure of the safest molecule; in the short term, whether the syndrome is primary or a manifestation of organ failure, which decides whether the drug continues at all; in the mid term, titration against a moving kinetic target, time to steady state being prolonged; in the long term, surveillance of the organ itself.

The MODUS. Pharmacologically, choose by clearance route first and receptor profile second, and lengthen the dosing interval rather than shaving a tablet where licensed strengths do not divide. Psychological treatment carries no hepatic or renal penalty and is underused in exactly these patients; electroconvulsive therapy remains available when the pharmacological field has narrowed to nothing safe; socially, address alcohol, over-the-counter analgesia and dehydration. One instruction generalises: pretransplant patients call for lower starting dosages and slower titration until clinical effectiveness is reached.

25 · Reproductive hormones and mood: PMDD, perimenopause and the pituitary

Four clinical territories sit under one axis. Premenstrual dysphoric disorder, perimenopausal depression, polycystic ovary syndrome with its prolactin and pituitary differential, and androgen-related mood disturbance share one hypothalamic-pituitary-gonadal axis. The marks sit at the thresholds, where the sources contradict each other and sometimes themselves.

1.3%	2 TO 5-FOLD	10.5%	5%
PMDD BY PROSPECTIVE DAILY RATING, UNITED STATES	RISE IN DEPRESSION RISK DURING THE PERIMENOPAUSE	INCIDENT PCOS ON VALPROIC ACID VERSUS 1.4% ON OTHER MOOD STABILISERS	MANIC OR HYPOMANIC SYNDROMES UNDER BLINDED HIGH-DOSE ANDROGEN EXPOSURE

25.1 The axis, and why change matters more than level

The hypothalamus releases gonadotropin-releasing hormone in a pulsatile fashion, driving luteinising hormone and follicle-stimulating hormone from the anterior pituitary and then gonadal oestrogen, progesterone and testosterone. Oestrogen rises through the follicular phase

until a critical concentration triggers the luteinising hormone surge, and progesterone rises in the luteal phase; fluctuating oestrogen is held to dysregulate monoamines, producing luteal-phase mood and anxiety symptoms. The axis belongs to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

Progesterone becomes **allopregnanolone**, and serotonergic antidepressants are believed to enhance gamma-aminobutyric acid type A receptor sensitivity, or promote allopregnanolone formation by increasing 3-alpha-hydroxysteroid dehydrogenase activity. Testosterone runs the same route, its metabolite **3-alpha-androstanediol** likewise a positive allosteric modulator of gamma-aminobutyric acid receptors.

RULE **Mood follows the change in hormone concentration and the individual's sensitivity to it, not the absolute level.** It is the change in hormone levels rather than the levels themselves that triggers the symptomatic state. Under blinded conditions, acute oestradiol withdrawal induced depressive symptoms in asymptomatic postmenopausal women with a past perimenopausal depression, but not in those without. Same hormone, opposite outcome, decided by who the woman is.

25.2 Premenstrual dysphoric disorder: the criteria and their arithmetic

Criterion A fixes timing and count: in the majority of cycles, **at least five symptoms** must sit in the final week before menses, improve within a few days after menses begin, and become minimal or absent in the week postmenses. Criterion B makes an affective symptom compulsory: one or more of marked affective lability, marked irritability or anger with increased interpersonal conflict, marked depressed mood with hopelessness, or marked anxiety and tension.

Criterion C supplies the remainder: decreased interest in usual activities, difficulty concentrating, lethargy, marked appetite change with food cravings, hypersomnia or insomnia, feeling overwhelmed, and physical symptoms such as breast tenderness, joint or muscle pain, bloating or weight gain. These count together with the Criterion B symptoms to reach a total of five, never five from Criterion C alone.

MNEMONIC

Lability, Irritability, Depressed mood, Anxiety

The four Criterion B items, at least one mandatory. Somatic symptoms cannot carry it: bloating, breast tenderness, hypersomnia, food craving and fatigue is five symptoms and no diagnosis.

Criterion D requires clinically significant distress or interference with work, school, usual social activities or relationships; Criterion E excludes what is merely an exacerbation of another disorder, though co-occurrence is allowed; Criterion G excludes a substance, a medication or another medical condition, with hyperthyroidism the worked example, the hook to the hypothyroidism and hyperthyroidism in psychiatry notes. A note requires that Criteria A to C have been met for most cycles in the preceding year.

25.3 Confirming it, and the three things it is not

Criterion F makes this a measurement diagnosis: Criterion A should be confirmed by prospective daily ratings during at least two symptomatic cycles, though the diagnosis may be made provisionally beforehand, with the word provisional appended. The validated prospective instrument is the **Daily Rating of Severity of Problems**; the Premenstrual Symptoms Screening Tool is retrospective and screening only.

IN INDIA

The two-cycle rating requirement fails here structurally, not clinically: the woman with cyclical irritability is seen once and will not return two months later with a completed diary, and literacy and privacy compound it. Use the manual's own provision, since a provisional diagnosis before rating confirmation is explicitly permitted, and treat the retrospectively-screened patient as a candidate for rating, not a confirmed case.

CONDITION	WHAT DEFINES IT	THE DISCRIMINATING OBSERVATION
Premenstrual syndrome	Requires neither a minimum of five symptoms nor mood symptomatology, and is generally less severe	Prevalence about 20% in the manual against 80 to 95% in a text counting any premenstrual symptom. Different constructs, so neither is the prevalence.
Premenstrual exacerbation	Luteal worsening of a pre-existing mood or anxiety disorder, in approximately 50 to 66% of women	After menses start, residual depression and anxiety symptoms persist. No symptom-free postmenstrual interval rules the diagnosis out.
Premenstrual dysphoric disorder	The full criteria set, confirmed prospectively	Symptoms confined to the luteal phase, resolving completely when the period starts.

25.4 How common, and what each number counts

A large German study gives a 12-month community prevalence of 5.8%; a United States study following two cycles found 1.3%, the most rigorous estimate, requiring impairment and no comorbidity, since retrospective estimates are often higher than those based on prospective daily ratings. The wider published band is 1.3 to 7.7%. Heritability is a grammatical trap: no studies have examined heritability in the disorder itself, and estimates of **30% to 80%** apply to premenstrual dysphoric symptoms, where it remains unclear whether the symptoms are heritable or simply associated with other heritable traits. Symptoms cease after the menopause, though cyclical hormone replacement can trigger their re-expression.

25.5 Treating premenstrual dysphoric disorder

LOCUS. Outpatient and shared, since the contraceptive option here is usually prescribed by primary providers and gynaecologists. The Royal College of Obstetricians and Gynaecologists guideline places selective serotonin reuptake inhibitors first line, supported by a meta-analysis finding similar efficacy between agents, and also places the combined oral contraceptive pill first

line, prescribed cyclically or back to back, typically for 3 months. Three antidepressants are approved by the United States Food and Drug Administration, all selective serotonin reuptake inhibitors - fluoxetine, controlled-release paroxetine and sertraline - plus the combined oral contraceptive drospirenone with ethinyl oestradiol, though all agents in the class could be used and venlafaxine extended-release has also been shown effective. Every approval named in this topic is a United States one; Indian licensing status is a separate question and none of these sources state it.

FOCUS. Response is fast and partial: improvement may be seen during the first week, and mood, irritability and anxiety improve while physical symptoms such as swelling, bloating and breast tenderness are less responsive. Warn the patient, or a working drug reads as failure.

MODUS. Starting doses are all the sources supply. Sertraline is usually started at 50 mg per day, with upward titration not uncommonly required. Fluoxetine is often started at 10 to 20 mg per day. Controlled-release paroxetine starts at 12.5 mg per day, as a single morning dose, daily or only during the luteal phase. No source states a target or ceiling, so titrate to response. Intermittent treatment for the last 2 weeks of the cycle can be as efficacious as continuous administration and does not produce discontinuation symptoms; call that window roughly the two weeks from ovulation to menses, since no source defines it by cycle number.

The hormonal ladder: the approved contraceptive is dosed daily for 24 days, followed by 4 days of placebo, but a 2021 meta-analysis reported that combined oral contraceptives improved overall premenstrual symptomatology but not premenstrual depressive symptoms. Second line is continuous percutaneous bioidentical oestradiol, with a progestogen in women with a uterus; beyond it, **gonadotrophin-releasing hormone agonists** give a reversible medical menopause, used therapeutically and as a diagnostic test. Suppression works in about two-thirds of women, as many as are successfully treated by selective serotonin reuptake inhibitors though not necessarily the same individuals, while non-response in about 30% despite adequate ovarian suppression makes a reproductive hormone aetiology unlikely, with a ceiling of not greater than 3 months without gynaecology consultation. Adjunctively, cognitive behavioural therapy is effective, anxiety or irritability may warrant as-needed benzodiazepines, buspirone or hydroxyzine, and zuranolone is being studied rather than approved here. There is no allopregnanolone assay to order.

25.6 Staging the menopausal transition, and the follicle-stimulating hormone question

The menopause is a date in time, 12 months after the last menstrual period, normally between 45 and 55 years; the perimenopause is the phase before it, with erratic ovarian function, symptoms typically arising 2 to 7 years beforehand. Two variants matter: early menopause before 45 years and premature ovarian insufficiency below 40 years, against the instruction that menopausal symptoms should be considered in women older than 40. The transition lasts a median of 4 years, with median age of onset 47 and the final menstrual period at 51 to 52. Staging is menstrual: the 2012 revision of the **Stages of Reproductive Aging Workshop** criteria define the early transition by persistent differences of 7 days or more in the length of consecutive cycles and the late transition by intervals of amenorrhoea longer than 60 days.

TRAP **There is no free-standing follicle-stimulating hormone cut-off for the menopause, and a question offering a bare number is testing whether you know that.** The staging criteria treat elevated plasma follicle-stimulating hormone above 25 IU/L as confirmatory evidence only. The prescribing guidelines answer a different question: in women younger than 45, two raised levels above 30 mIU/mL taken 6 weeks apart, sampled between the second and fifth days of the cycle, may help confirm a diagnosis if clinical symptoms are not conclusive, the Greene Climacteric questionnaire being sufficient in most women older than 40. A psychopharmacology text rejects measurement outright, since hormone testing is neither necessary nor recommended, because these hormones fluctuate during the same day. The two units are numerically the same, so the thresholds genuinely differ. Construct and population separate them: one confirms perimenopause, one confirms menopause in women younger than 45 only, one denies single measurements any value.

25.7 Perimenopausal depression and what to prescribe

There is a 2 to 5-fold increase in the risk of depression during the perimenopause, and suicidal ideation is present in around 6% of women experiencing menopause-related psychological symptoms. Lifetime prevalence is 28% in women with no previous history of major depressive disorder and 59% in women with such a history. Nosologically, research strongly suggests perimenopausal depression is an entity of its own, but the manual contains no specifier or classification for it, so the clinician must use the diagnosis of major depressive disorder.

TRAP **"Is hormone replacement a treatment for perimenopausal depression?" has three published answers, two from the same textbook, and quoting any one alone is the error.** The prescribing guidelines call hormone replacement first-line for menopausal insomnia, anxiety and depression. The comprehensive textbook, on antidepressant augmentation, reports that recent studies of oestrogen augmentation of selective serotonin reuptake inhibitors in both pre- and postmenopausal women have not shown a consistent benefit. The same book, on gonadal steroids, reports that several randomised placebo-controlled trials of oestradiol therapy in perimenopausal depression have demonstrated both short-term antidepressant efficacy and preventative benefits. Population and role separate them: oestrogen as a general antidepressant, or as augmentation in depressed women at large, fails; oestradiol in symptomatic perimenopausal women has trial support.

The usable version is narrow. Oestrogen with the progestin medroxyprogesterone acetate may increase coronary heart disease and stroke risk during the first year, so estradiol prophylaxis can no longer be recommended, but it may still be indicated in women with perimenopausal symptoms and depression who fail standard antidepressant treatment. The preparation suggested is the 50 microgram transdermal estradiol patch, giving levels slightly above the 60 pg/mL threshold necessary to preserve bone: a patch strength and a serum concentration, never merged. In a woman with a uterus endometrial protection is not optional, since unopposed oestrogen for more than 1 year gives a 2 to 12-fold increased relative risk of endometrial cancer, the optimal regimen being 12 to 13 days of progestin treatment each month when oestrogens are administered. On antidepressants, the only antidepressant approved by the United States Food and Drug Administration for perimenopausal vasomotor symptoms is paroxetine, with off-label venlafaxine and desvenlafaxine, and also oestrogen replacement and a neurokinin 3 receptor antagonist, while perimenopausal depression itself can be treated with all approved

antidepressants for major depressive disorder. Approved antidepressant, not approved treatment: that is the trap. Antipsychotic selection in these women belongs to the Schizophrenia: management, antipsychotics and adverse effects notes.

25.8 Polycystic ovary syndrome and the psychiatric interface

This is the most widespread endocrine disorder among women, occurring in up to 15% of women in the general population of reproductive age but in 30% to 75% of women presenting for menstrual irregularities or hirsutism, a referral statistic. The **Rotterdam criteria** run in two steps candidates collapse into one. First, exclude other causes of hyperandrogenism such as congenital hyperplasia, Cushing syndrome and androgen-secreting tumours. Only then diagnose on two of three conditions: oligo-ovulation or anovulation, clinical or biochemical signs of hyperandrogenism, or ultrasound-documented polycystic ovaries, noting that normal-appearing ovaries no longer rule out this diagnosis if the other two criteria are met. The exclusions to order: hyperprolactinaemia and thyroid disorders are associated with menstrual irregularities and should always be ruled out through serum prolactin levels and thyroid function tests, while rapid onset of marked virilisation should raise suspicion of an androgen-secreting tumour.

Mechanistically, gonadotropin-releasing hormone appears insensitive to ovarian steroids, increased luteinising hormone pulse amplitude and frequency drive thecal androgen synthesis, and insulin stimulates thecal androgen production while lowering sex hormone-binding globulin. An elevated luteinising hormone to follicle-stimulating hormone ratio is one of the most common laboratory results, with no numeric threshold given. The metabolic burden is not simply obesity: insulin sensitivity is decreased by 35% to 40% independent of obesity, approximately 50% are obese, and undiagnosed type 2 diabetes is 7 to 10 times more common than in women without it of similar age, with a homeostatic model assessment of insulin resistance greater than 2.3 indicating insulin resistance. The metabolic syndrome criteria belong to the metabolic syndrome, obesity and mortality in serious mental illness notes.

Comorbidity is poorly explained: major depression is commoner than in age-matched controls, a meta-analysis controlling for body mass index finding rates as high as four times greater, yet androgen levels do not consistently differ between depressed and non-depressed women with the syndrome, insulin resistance being a possible common link. Treatment carries a psychiatric tail: metformin decreases insulin resistance, acne, hirsutism and bioavailable testosterone, low-dose oral contraceptives are frequently first-line for acne and hirsutism, and clomiphene citrate is first-line for women who desire pregnancy, while spironolactone may be difficult to tolerate, producing mood changes, decreased libido and fatigue - a profile otherwise read as relapse. One published case used metformin 850 mg per day, titrated to 2,550 mg per day, with spironolactone 100 mg per day: a worked case, not a dose range.

25.9 Valproate and the reproductive endocrine system

in the most extensive study to date of bipolar disorder patients, 10.5% of women on valproic acid developed PCOS compared to 1.4% of women on other mood stabilizers. An independent reference corroborates both figures, gives the phenotype as oligomenorrhoea and

hyperandrogenism, meaning hirsutism, acne, male-pattern alopecia and elevated androgen levels, and supplies the relative risk of 7.5, noting the effect is apparently reversible.

TRAP **The valproate and polycystic ovary syndrome disagreement is about attribution, not observation, and answering it as yes or no is the error.** The same textbook that supplies that figure states elsewhere that the relationship remains controversial because patients with epilepsy and obesity appear to be at increased risk for the syndrome, studies in women with bipolar disorder taking valproate or lithium have reported conflicting results, and in bipolar disorder exacerbation by valproate is less apparent and more inconsistent. The prescribing guidelines take an intermediate line: valproate can cause hyperandrogenism in women and has been linked with the development of polycystic ovaries, the evidence being conflicting. Note the asymmetry: hyperandrogenism asserted as caused, polycystic ovaries only linked. They disagree on causation, not on observation, because obesity, epilepsy itself and pre-treatment menstrual abnormality are independent risks the studies could not separate.

All four converge on conduct. Menstrual history and weight should be followed carefully in women of reproductive potential who begin treatment with valproate; all aspects of the syndrome are reversible in patients with epilepsy, especially if valproate is discontinued and lamotrigine substituted, the effect being apparently reversible in the bipolar series, where no source extends the lamotrigine substitution finding; the syndrome can be mitigated by birth control pills; and this should not preclude women with bipolar illness from treatment with valproate. No source states what to measure or at what interval, so no monitoring schedule exists beyond that instruction. The far larger reason to avoid valproate in women of childbearing potential is teratogenicity, taught with the drug in the Mood disorders: pharmacotherapy notes.

25.10 Prolactin, the pituitary and their psychiatric consequences

Prolactin is produced by the anterior pituitary and inhibited by dopamine from the tuberoinfundibular neurons of the arcuate nucleus. Normal levels run from 5 to 25 ng/mL in women and from 5 to 15 ng/mL in men, and because levels fluctuate during the day, peak during sleep, and rise with exercise and emotional stress, a single raised sample settles nothing. Symptoms usually develop once **prolactin reaches 60 to 100 ng/mL**, with amenorrhoea, gynaecomastia in men, low libido, decreased fertility and galactorrhoea, and headache and visual impairment where there is an adenoma. That is a symptom threshold only: no standard source states a concentration above which a **prolactinoma** becomes likely, so the imaging decision stays qualitative and disproportionate or symptomatic elevation warrants endocrine referral.

The reproductive and pituitary causes, otherwise blamed on a drug: prolactinomas and idiopathic hyperprolactinaemia are commonest, both more common in women. Beyond them:

- Hypothyroidism, since thyrotropin-releasing hormone stimulates prolactin release: the reason thyroid function is checked before the antipsychotic is blamed.
- Acromegaly, through the lactogenic properties of growth hormone, and hypothalamic disease such as craniopharyngioma.
- Pregnancy, breastfeeding and nipple stimulation, and stress, seizures and renal impairment.

The antipsychotic material belongs to the managing antipsychotic metabolic disturbance and hyperprolactinaemia notes. All the SSRIs have case reports, and the one completed study reported that 4.5% of men and 22% of women developed hyperprolactinaemia after 12 weeks of fluoxetine, with oral contraceptives, tricyclic antidepressants, metoclopramide and verapamil also implicated; one study is thin evidence, and that hedge travels with the figure. Sustained elevation suppresses the hypothalamic-pituitary-gonadal axis, producing sexual dysfunction, menstrual disturbance and galactorrhoea, with long-term reductions in bone mineral density. Also, pituitary tumours are found in up to 20% of adults at autopsy, and as many as 30% are non-secretory.

PITFALL

Simple, non-formed visual hallucinations in a patient who retains insight are treated as psychosis and answered with an antipsychotic. Visual hallucinations have been reported where a pituitary tumour impinges the optic chiasm, are more often simple and non-formed, are associated with insight, and can be exacerbated by bromocriptine; the accompanying sign is a field defect, since large pituitary tumours produce the classic bitemporal hemianopia, oculomotor palsies and headache. Confrontation fields take a minute and are almost never done in a psychiatric clerking.

Bromocriptine normalises serum prolactin in 70% to 80% and decreases tumour size in more than 50% of patients with prolactinomas. Cabergoline is the preferred drug for hyperprolactinaemia, initiated at 0.25 mg twice a week or 0.5 mg once a week; the pharmacology text's escalation sentence is truncated mid-clause, so no maximum dose is quoted. Medication must continue indefinitely, since discontinuation usually leads to relapse. The hazard runs both ways, since psychosis has been described on bromocriptine for a prolactinoma, and impulse control disorders such as pathological gambling with cabergoline.

25.11 Androgens, anabolic steroids and mood

In general, 200 mg of testosterone cypionate taken every 2 weeks will restore physiologic testosterone concentrations in a hypogonadal male, and illicit use escalates beyond that because a eugonadal male given physiologic dosages gains nothing, exogenous steroid shutting down endogenous production via feedback inhibition of the hypothalamic-pituitary-testicular axis. So illicit users take dosages 10 to 100 times greater than therapeutic doses, while transdermal gels or patches are generally inadequate to produce massively supraphysiologic levels. Testosterone and hypogonadism sit at the opposite end of the same axis: where it is genuinely deficient, testosterone improves mood and decreases irritability in hypogonadal men.

WEEKLY TESTOSTERONE-EQUIVALENT EXPOSURE	PSYCHIATRIC EFFECT REPORTED	WHAT THE BAND IS GOOD FOR
300 mg of testosterone a week or less	Psychiatric effects appear rare	Why negative laboratory trials do not reassure about illicit use.
Between 300 and 1,000 mg of testosterone equivalent per week	Mood syndromes appear more frequent, albeit still uncommon	Where most gym-population field studies sit.
More than 1,000 mg a week	Mood syndromes become quite common and are occasionally severe; described psychotic cases are primarily in this band	The exposure to ask about in a young muscular man presenting manic or paranoid.

These are exposure bands, never a prescribing range. Across four blinded placebo-controlled studies giving at least 500 mg a week, 5 of 109 men exhibited prominent hypomanic or manic syndromes, and that crude rate of approximately 5% may represent a lower bound for illicit users, who stack drugs. Psychotic symptoms usually consist of grandiose or paranoid delusions within a manic episode, disappearing within a few weeks of discontinuing the agent.

Withdrawal is where a psychiatrist usually meets this. Because these agents suppress hypothalamic-pituitary-testicular function, male users often become hypogonadal after stopping a course; function usually recovers within a few weeks to a few months, but hypogonadism may persist for more than a year and appears partially or completely irreversible in some cases. Withdrawal depression is usually brief and self-limited, but some episodes have continued for months and required fluoxetine, tricyclic antidepressants or ECT, and completed suicides on withdrawal have been reported. The loop is self-sustaining: stopping produces hypogonadism and depression, the user resumes to self-treat it, and some develop brittle mood disorders with mixed symptoms and prominent impulsivity - the authors' clinical experience, and the differential for a young man with a rapid-cycling mixed state.

PITFALL

A testosterone result is read against a memorised cut-off rather than the reporting laboratory's reference interval, and one textbook shows why that fails. One chapter gives normal testosterone plasma concentrations for men as 300 to 1,000 ng/dL. Another, reporting former users, classifies against a normal reference limit of 12.1 nanomoles per liter, 350 nanograms per deciliter. The conversion is internally correct, so the disagreement about where normal starts is genuine, most plausibly because the second is one laboratory's limit. Neither is a diagnostic threshold for hypogonadism, and these sources state none.

GOOD TO REMEMBER

Recovery is sequenced and endocrinologist-led, though these sources give no doses for it. Physiologic doses of exogenous testosterone first, after supraphysiologic doses stop; then clomiphene, stimulating the pituitary to resume luteinising hormone and follicle-stimulating hormone production; simultaneously human chorionic gonadotropin to stimulate the testis; then a gradual taper as the axis reawakens. The point is relapse prevention, since withdrawal symptoms untreated will strongly tempt a man to resume use.

No assay makes any diagnosis in this topic: premenstrual dysphoric disorder is confirmed by prospective daily ratings during at least two symptomatic cycles, the perimenopause is staged on menstrual pattern, and a raised prolactin or low testosterone is read against the reporting laboratory's interval, never a remembered number.

26 · Toxic, occupational and environmental encephalopathies

These are the encephalopathies whose cause is written on a payslip, a water source or a bottle, and never on the referral letter. A battery-factory worker, irritable, forgetful and constipated, is referred with depression; a farmer arrives sweating and confused and nobody mentions the tin in the shed. The diagnosis turns on an exposure question the history never reaches.

Four axes make the agents memorable: route of entry, anatomical target, assay and reversibility. Heavy-metal toxicity is where those axes separate most cleanly, because lead, mercury, arsenic and manganese differ on every one of them at once. Delirium as a syndrome belongs to the Stroke, TBI, delirium and focal brain syndromes notes; the dementia syndrome and its workup to the Dementias and neurocognitive disorders notes; antipsychotic movement disorders to the Schizophrenia: management, antipsychotics and adverse effects notes.

26.1 Lead: how it gets in, where it goes, and what it does to a neurone

Gut absorption varies with age and diet, children absorbing about **40%** of ingested lead against less than 20% in adults, and fasting, calcium deficiency or iron deficiency increases it further. Inhaled lead is absorbed at about 90%, and tetraethyl lead crosses skin while inorganic lead does not.

A blood level maps the body burden poorly. Lead binds haemoglobin, distributes to renal tubular epithelium and liver, then redistributes to bone, teeth and hair, so that **95%** of the adult body burden sits in bone. Growing bone accumulates more and can form **lead lines** on radiography. Bone lead is slowly reabsorbed, faster when calcium is depleted, including in pregnancy. Only small quantities reach brain, mostly grey matter and basal ganglia, and lead crosses the placenta.

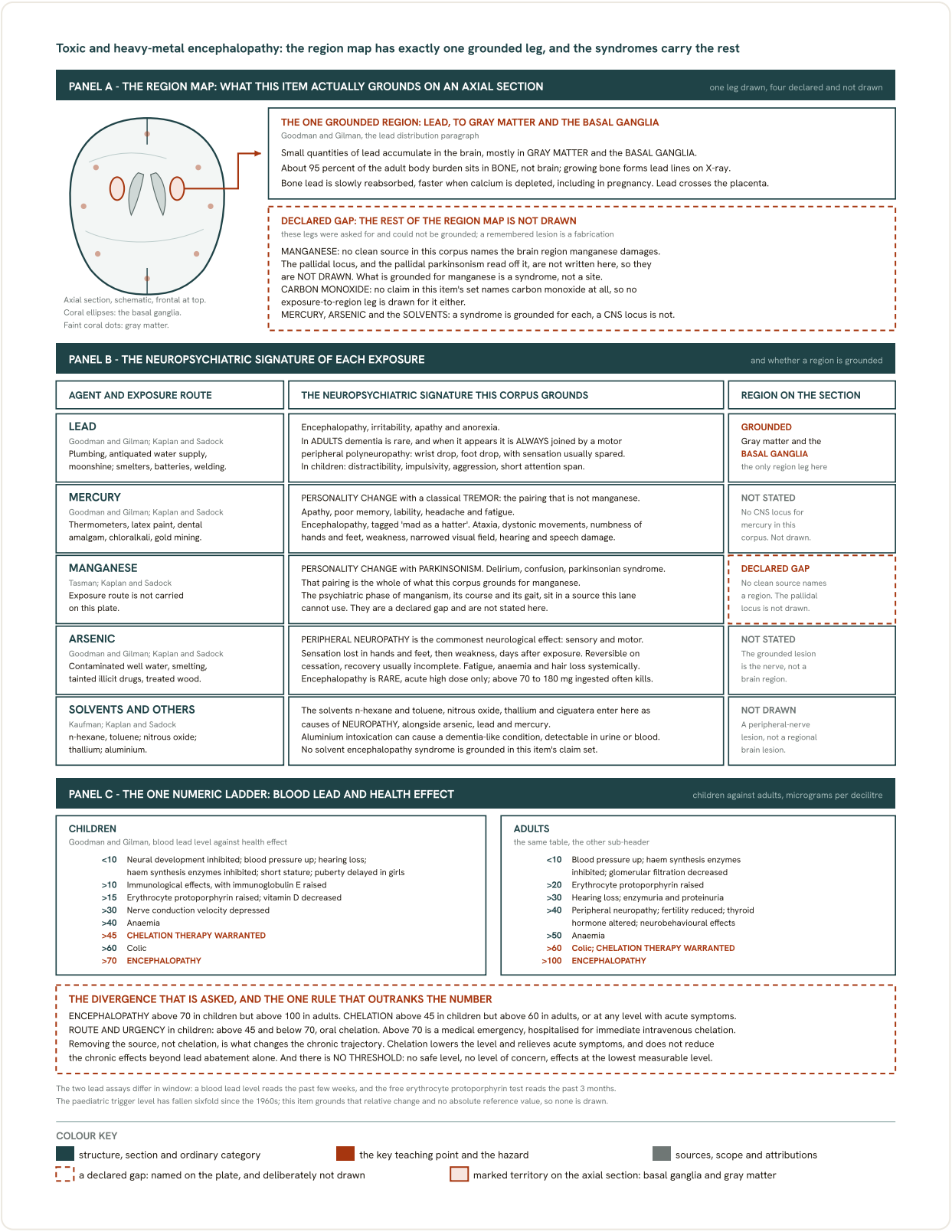

Fig 33.10 The toxic and heavy-metal region map, drawn only as far as the sources go: one grounded anatomical leg, the declared gaps named beside it, and the syndromes that carry the teaching instead. Lead is the only exposure this item maps to tissue, to gray matter and the basal ganglia; the manganese-to-pallidum and carbon monoxide legs are named on the plate and deliberately not drawn. The differentiating triad is syndromic: manganese gives personality change with parkinsonism, mercury personality change with a tremor, and adult lead intoxication only rarely a dementia, then always with a motor polyneuropathy. (Goodman and Gilman's The Pharmacological Basis of Therapeutics; Tasman Psychiatry; Kaplan and Sadock's Comprehensive Textbook of Psychiatry 2024; Kaufman's Clinical Neurology for Psychiatrists.)

Lead injures by **molecular mimicry** of zinc and calcium, altering protein structure. Centrally, inhibition of calcium channels and of calcium-responsive proteins such as protein kinase C and calmodulin drives inappropriate transmitter release across dopaminergic, cholinergic and glutamatergic pathways, while high concentrations disrupt the blood-brain barrier. Encephalopathy is the same lesion with a failing barrier added.

26.2 The blood lead ladder, and why no level is reassuring

>45	>70	>60	>100
UG/DL, CHELATION WARRANTED, CHILDREN	UG/DL, ENCEPHALOPATHY, CHILDREN	UG/DL, CHELATION WARRANTED, ADULTS	UG/DL, ENCEPHALOPATHY, ADULTS

Blood lead concentration and health effect, children against adults

EFFECT	CHILDREN (UG/DL)	ADULTS (UG/DL)
Present at the lowest measurable levels	Below 10: inhibited neural development, raised blood pressure, hearing loss, inhibited haemoglobin synthesis enzymes, short stature, delayed sexual maturation in girls	Below 10: raised blood pressure, inhibited haemoglobin synthesis enzymes, reduced glomerular filtration
Immunological effects (raised IgE)	Above 10	Not listed
Raised erythrocyte protoporphyrin	Above 15	Above 20
Reduced vitamin D	Above 15	Not listed
Hearing loss	Below 10	Above 30
Enzymuria and proteinuria	Not listed	Above 30
Depressed nerve conduction velocity	Above 30	Not listed
Peripheral neuropathy	Not listed	Above 40
Reduced fertility, altered thyroid hormones, neurobehavioural effects	Not listed	Above 40
Anaemia	Above 40	Above 50
Chelation therapy warranted	Above 45	Above 60
Colic	Above 60	Above 60
Encephalopathy	Above 70	Above 100

At the bottom of the ladder there is no line at all: lead disturbs synaptic pruning, neuronal migration and neurone-glia interaction, producing falls in IQ, language and motor deficits, distractibility, impulsivity and aggression, with no evidence of a threshold and associations evident at the lowest measurable levels.

RULE **A blood lead level can confirm poisoning; it can never exclude harm.** Regulation has followed the biology: there is no safe level of lead exposure for children, the CDC no longer provides a level of concern, and the emphasis has moved to primary prevention. The paediatric trigger level has fallen sixfold since the 1960s, an administrative concession rather than a threshold.

26.3 The adult lead patient, and the management of metal poisoning

Adults present differently. **Lead palsy**, wrist drop and foot drop from degeneration of motor neurones, was classical in painters and is now rare. Tasman gives the discriminator: lead intoxication in adults only rarely produces a dementia, and when it does it is always accompanied by a motor peripheral polyneuropathy with wrist or foot drop. Exposure is inhalational and trade-specific: greatest in smelter and storage-battery workers, with further risk in welding, construction, printing and radiator repair, to which Kaplan and Sadock add plumbing trades, an antiquated water supply and illegal moonshine.

Management of any heavy-metal toxicity turns on one uncomfortable fact: the chelator treats the number, removal from exposure treats the disease. LOCUS is set by concentration and symptoms: chelation is warranted above 45 in children and above 60 ug/dL in adults, or where there are acute symptoms of lead poisoning, and oral chelation is recommended for a child above 45 but below 70 ug/dL, and above 70 is a medical emergency requiring hospitalisation and immediate intravenous chelation, on the American Academy of Pediatrics position. That is the only guideline-level statement available here. FOCUS by phase: lower the burden, then keep the patient away from the workplace or water source. MODUS is narrow. Removing the source is the most important response; chelation lowers the blood level and relieves acute symptoms but does not reduce the chronic effects of lead beyond abatement alone, and in rats chelators mobilise lead into the brain.

Chelator selection is a matching exercise: edetate for acute lead poisoning; dimercaprol for acute arsenic, gold and mercury poisoning and for acute lead poisoning combined with edetate; succimer for children with elevated blood lead; penicillamine for copper; trientine for Wilson disease. Copper chelation is taught where this chapter deals with Wilson's disease. Succimer is preferred because it is orally bioavailable and, being hydrophilic, does not mobilise metals to the brain, and it does not significantly chelate essential metals such as zinc. Dimercaprol is given by deep intramuscular injection as a 100 mg/mL solution in peanut oil, contraindicated in peanut allergy. A formulation strength, not a dose: no milligram-per-kilogram regimen exists in these sources.

PITFALL

Reaching for the intravenous route in the sickest lead-poisoned patient because they are the sickest. Edetate is principally nephrotoxic, so adequate urine output must be established before and during treatment; and in lead encephalopathy with cerebral oedema the intravenous route can produce a potentially fatal rise in intracranial pressure, so the intramuscular route is preferred.

26.4 Arsenic: well water, neuropathy and arsine gas

Arsenic's signature is peripheral, not central, and the route that matters in South Asia is drinking water: massive ingestion, smelting of lead and copper ore, contaminated well water, tainted illicit drugs and the burning of preserved wood. Goodman and Gilman add: the commonest effect of acute or subacute exposure is a peripheral neuropathy involving both sensory and motor neurones, appearing several days after exposure and reversible on cessation though recovery is usually incomplete; encephalopathy is rare and follows only acute high-dose exposure. Arsenic is a poor answer to a chronic confusional state.

TRAP **Merging the two standard descriptions of arsenic neuropathy into one sentence.** Goodman and Gilman describe loss of sensation in the hands and feet, often followed by muscle weakness, a negative sensory phenomenon in both territories at once. Kaplan and Sadock's table describes burning and numbness of the feet followed by the hands, a positive, painful, length-dependent ascent from the feet. Hold both: the narrative account is the stronger because the table cell is positionally reconstructed. Answer the picture the stem describes.

Chronic vascular disease is the other signature. **Blackfoot disease** is cyanosis of the extremities progressing to gangrene, endemic in regions of Taiwan where well water contains arsenic at 170 to 800 ug/L, a water concentration and not a human threshold. Ingestion above 70 to 180 mg is often fatal, immediate death coming from cardiac and gastrointestinal effects. **Arsine gas**, formed industrially by reduction of arsenic, causes rapid and often fatal haemolysis, with haemoglobinuria and anuria hours later and jaundice after 24 hours; roughly **25%** of exposures are fatal. Treatment splits acute from chronic: chelation works after short-term exposure but has little or no benefit in the chronically exposed, and exchange transfusion is often warranted after arsine exposure.

26.5 Mercury and manganese, and separating the metals at the bedside

Mercury is a three-syndrome metal because it exists in three forms: elemental mercury, met as vapour; inorganic mercurous and mercuric salts; and organic compounds, of which **methyl mercury**, generated environmentally by aquatic microorganisms, is the one of concern. Covalent bonding with sulfhydryl residues at very low concentrations accounts for most biological effects. The form predicts the target. Inhaled elemental vapour is acutely toxic to lung, progressing to interstitial pneumonitis. The salts strike the kidney: acute exposure, typically in suicide attempts, produces renal tubular necrosis, while chronic exposure causes predominantly glomerular injury. Occupationally, the chloralkali industry carries the highest risk, with exposure also in dentistry and gold mining. The index case is Minamata, where fish contaminated with methylmercury caused severe learning disability in Japan in the 1950s.

Separating the metals by neuropsychiatric signature and confirmatory specimen

METAL	NEUROPSYCHIATRIC SIGNATURE	DETECTED IN
Lead	Dementia only rarely, always with a motor polyneuropathy; encephalopathy, irritability, apathy, anorexia	Blood lead level for the past few weeks; free erythrocyte protoporphyrin for the past 3 months
Mercury	Personality change with a classical tremor; apathy, poor memory, lability, headache; encephalopathy tagged mad as a hatter, with ataxia, dystonic movements and narrowed visual fields	Urine, blood, hair
Manganese	Personality change with parkinsonism; delirium, confusion, parkinsonian syndrome	Urine, blood, hair
Arsenic	Fatigue, loss of consciousness, anaemia, hair loss	Urine, blood, hair
Aluminium	A dementia-like condition	Urine or blood

Personality change is shared by manganese and mercury, separated only by the motor sign beside it, parkinsonism against tremor. The assays are asymmetrical: lead has a quantified ladder and a second test with a longer memory, the others only a specimen. So is the anatomy. Lead has a stated locus, but **manganism** is recorded only as parkinsonism produced by high-level manganese exposure, with no locus stated anywhere here, so the accompanying figure carries no grounded manganese leg. Kaufman places heavy-metal toxicity among the toxic causes of neuropathy, beside ciguatera fish poisoning, thallium, nitrous oxide, n-hexane and toluene.

GOOD TO REMEMBER

A worker removed from a smelter a month before presentation can show a falling blood lead level beside a still-abnormal protoporphyrin. The pair dates the exposure, which matters when the question is whether the workplace poisoned them, not whether they are poisoned now.

26.6 Carbon monoxide: the gas that leaves a hypoxic footprint

Carbon monoxide binds haem tightly to form **carboxyhaemoglobin**, which can no longer carry oxygen. Smokers of one to two packs daily typically run 3% to 8% and non-smokers under 2%; after acute poisoning 5% to 10% is associated with impaired alertness and cognition, and **30% to 50%** causes significant falls in tissue oxygen delivery. The smoker's baseline overlaps the symptomatic band, so a single carboxyhaemoglobin figure cannot grade the severity of carbon monoxide poisoning in a smoker.

Poisoning usually arises from deliberate self-harm with car exhaust and, more recently, from charcoal burning in the Far East, though it also follows badly ventilated boilers and fires. anoxia, hypoglycaemia and carbon monoxide produce similar patterns of injury, in which cerebral and cerebellar atrophy may occur and the hippocampus and globus pallidus are particularly

vulnerable. The lesion is hypoxic rather than gas-specific: a hypoglycaemic coma and a charcoal-burning attempt leave the same deficits, and the amnesia follows hippocampal vulnerability.

The recovery trajectory is relatively brief compared with traumatic brain injury; parkinsonism is not infrequent after a latent interval; the commonest cognitive impairment is poor memory. The latent interval is the examinable phenomenon: the patient improves, is discharged, then deteriorates. No numeric latency is given. Nor is a complication rate: the prevalence of complications is unclear, with a wide range of figures reported. That refusal is the citable fact.

26.7 Organophosphates: the toxidrome, ageing, and the emergency

Organophosphate exposure is the toxic encephalopathy an Indian psychiatrist meets most often, and the only one here in which minutes matter. Organophosphate insecticides bind and inactivate acetylcholinesterase, so acetylcholine accumulates and irreversibly depolarises postsynaptic neuromuscular junctions; people committing suicide, especially in India, often deliberately drink organophosphate pesticides, and the nerve gases including sarin act identically.

Goodman and Gilman organise the syndrome into three compartments. Acute intoxication produces muscarinic and nicotinic features and, except with quaternary compounds of low lipid solubility, central signs; effects appear within minutes of inhaled vapour but are delayed after gastrointestinal and percutaneous absorption. Route decides which system declares first: vapour brings ocular and respiratory features first, with marked miosis, ciliary spasm and brow ache; ingestion brings gastrointestinal features earliest; percutaneous exposure produces localised sweating and fasciculation at the site.

MNEMONIC

DUMBBELLSS

Diarrhoea, urination, miosis, bronchorrhoea, bradycardia, emesis, lacrimation, lethargy, salivation, sweating: the muscarinic effects of the **cholinergic toxidrome**. Against the anticholinergic row of the same table the discriminators are three paired opposites: mydriasis against miosis, decreased against increased bowel sounds, decreased against increased diaphoresis.

The nicotinic and central compartments carry the mortality. Nicotinic action at the neuromuscular junction gives weakness, fasciculation and finally paralysis, gravest at the respiratory muscles; central effects include confusion, ataxia, convulsions, coma and central respiratory paralysis. Death ranges from under 5 minutes to nearly 24 hours and is primarily respiratory. Respiratory failure arrives by three converging routes, so airway management outranks every antidote.

LOCUS is the emergency department and then intensive care, never the psychiatric ward; assessment of suicidal intent waits until the crisis is over. FOCUS by phase is decontamination and airway, then muscarinic blockade and enzyme reactivation, then the later syndromes. MODUS begins before any drug: terminate exposure, remove contaminated clothing, wash skin copiously or lavage the stomach, maintain a patent airway, give oxygen, and alleviate persistent

convulsions with diazepam 5 to 10 mg intravenously. For muscarinic effects, atropine is given in doses sufficient to cross the blood-brain barrier, beginning with 2 to 4 mg intravenously, then **2 mg every 5 to 10 minutes** until muscarinic symptoms disappear or signs of atropinisation appear.

Atropine alone is not enough. It antagonises the muscarinic actions but is virtually without effect against the peripheral neuromuscular compromise, which pralidoxime reverses, the oxime acting most markedly at the skeletal neuromuscular junction. No pralidoxime dose is printed; none is recoverable in clean form here. The urgency rests on mechanism: stability of the phosphorylated enzyme is enhanced by **ageing**, the loss of one alkyl group, after which recovery depends largely on synthesis of new enzyme protein. An aged enzyme cannot be reactivated by any oxime, making the oxime a race rather than a routine.

PITFALL

Excluding organophosphate poisoning because the pupils are not small. With acute systemic absorption, miosis may not be evident because of sympathetic discharge in response to hypotension. The sickest patient is the one in whom the cardinal sign disappears.

The later syndromes are named but not defined. Kaplan and Sadock list among organophosphate central effects emotional lability, reduced alertness, cognitive impairment, convulsions and coma, with weakness of neck flexors and proximal muscles, and **organophosphate-induced delayed polyneuropathy**. Goodman and Gilman record only that an intermediate syndrome is recognised and that delayed neurotoxicity and recurrent seizures may follow severe intoxication. Latencies and the enzyme behind the delayed polyneuropathy are stated nowhere in these sources.

IN INDIA

These three exposures are the common case here, not the exotic one. The cholinergic toxidrome is a working diagnosis in any rural presentation combining altered sensorium with sweating, secretions and fasciculation. A neuropathy in a patient from a tube-well belt is a toxicological question, not only a diabetic one. A cluster of drinkers with gastroenteritis, delirium and blurred vision is a methanol outbreak until proved otherwise. Laboratory support is largely absent, so treat on the toxidrome and the atropine response, and ask about the water source, the workplace and the liquor as routinely as about mood.

26.8 Solvents and inhalants: toluene, the hexacarbons and carbon disulfide

Solvent encephalopathy divides by route into occupational and deliberate exposure, and the deliberate does far more damage. The hexacarbons are constituents of glues, lacquers and solvents, also inhaled intentionally, producing central depression or stupor acutely and, on repeated glue sniffing, cognitive deficits, motor and sensory neuropathy and autonomic dysfunction; treatment is cessation of exposure. That last clause is the prognosis: no antidote exists.

The systemic toll of chronic inhalant use spans rhabdomyolysis, renal disturbance, cardiomyopathy, hepatotoxicity, pulmonary disease and haematopoietic disorders including methaemoglobinaemia, aplastic anaemia and acute myelocytic leukaemia, with peripheral neuropathy, reversible cerebellar signs or frank cerebellar degeneration, widened sulci and basal cisterns on imaging, and two distinct dementias: lead encephalopathy from leaded petrol and **white matter dementia** from toluene. Tasman's catalogue is headed, importantly slowly reversible and/or irreversible.

Toluene is the solvent most often examined. Most reports emphasise combined cerebral and cerebellar impairment with pyramidal change, ranging from mild cognitive impairment to severe dementia with cerebellar ataxia, oculomotor abnormality, tremor, deafness and hyposmia; cognitive dysfunction is the most frequent and most disabling feature and may be the earliest sign of permanent damage. It is not the reversible fog of intoxication clinicians discount. Magnetic resonance imaging in chronic abusers shows diffuse central white matter change comprising

- cerebral, cerebellar and brain stem atrophy;
- loss of grey-white differentiation throughout the central nervous system;
- increased periventricular white matter signal on T2-weighted images.

Set that against carbon monoxide, which strikes grey matter nuclei, and methanol below. Carbon disulfide completes the set: an industrial polar solvent affecting factory workers and a major metabolite in the breakdown of disulfiram.

26.9 Toxin and non-antipsychotic medication-induced movement disorders, and methanol

Several agents causing parkinsonism are already taught above, so the toxin-induced movement disorders are largely a second pass over exposures this chapter has already met. DSM-5-TR names as toxic causes MPTP, organophosphate pesticides, manganese, methanol, cyanide, carbon monoxide and carbon disulfide. Brazis adds disulfiram, toluene, n-hexane and welding-related parkinsonism on the toxin side and reserpine, tetrabenazine, lithium, amiodarone, diltiazem and ethanol on the drug side. Kaplan and Sadock note that associations with well water, farming and rural living may reflect neurotoxins in pesticides containing homologues of MPTP. Carbon monoxide and manganese also cause secondary dystonia, beside levodopa, anticonvulsants, flecainide and ergotamines.

TRAP **Reading welding-related parkinsonism in a list as settled aetiology.** Three standard sources list manganese, one of them welding, flatly among toxin causes. Kaufman disputes the epidemiology: the relationship between welding or other manganese exposure and the risk of developing Parkinson disease is controversial, and although these were previously considered significant risk factors, more recent epidemiological studies have not indicated increased risk. His next sentence concedes that high levels of manganese, that is manganism, lead to parkinsonism. All four agree that high-level exposure produces a parkinsonian syndrome; what they dispute is whether ordinary occupational welding raises the risk of Parkinson disease itself.

Whether manganese parkinsonism improves after removal from exposure, or responds to levodopa, is stated nowhere in these sources: the one entity here whose reversibility cannot be answered. MPTP, a by-product of the synthesis of a certain opioid, kills dopaminergic cells and induces permanent parkinsonism, and it selectively poisons nigrostriatal tract neurones.

Two non-antipsychotic problems are missed for one reason, latency. DSM-5-TR lists as non-antipsychotic causes of medication-induced parkinsonism the calcium channel antagonists flunarizine and cinnarizine, the dopamine depleters reserpine and tetrabenazine, the antiepileptics phenytoin, valproate and levetiracetam, antidepressants, lithium, chemotherapeutic agents and the immunosuppressants ciclosporin and tacrolimus. Onset is unreliable: parkinsonism usually develops a few weeks after starting or raising the dose, but may develop insidiously after many months, and mainly with calcium channel blockers a second peak of onset is reported after about 1 year. Tasman supplies the longest latency: valproic acid may, albeit very rarely, cause a combination of parkinsonism and dementia, and because this evolution is delayed for from 6 months to 4 years the connection may be missed. It is also the closest these sources come to a medication-induced encephalopathy, since the other non-antipsychotic drugs named here are credited with a movement disorder alone. Lithium as a drug belongs to the Mood disorders: pharmacotherapy notes.

> In a new parkinsonian or cognitive syndrome, take a drug and exposure history covering the preceding several years, not the preceding several weeks.

Methanol has the tightest anatomy here and the most preventable outcome. Alcohol-dependent patients may inadvertently drink methanol, a component of antifreeze and cooking fuels and an illicit adulterant of everyday ethanol, producing gastroenteritis, delirium and visual disturbance, particularly blurred vision and a scotoma; with severe intoxication or merely chronic intermittent consumption the optic nerves atrophy and victims go blind. Methanol preferentially damages the optic nerves and also the putamen, where it may cause parkinsonism. Management has three limbs: bicarbonate for the acidosis; ethanol to divert the metabolism that yields formaldehyde and formic acid; and haemodialysis, with fomepizole possibly more effective than ethanol. No dose for any of the three is stated in these sources. Kaplan and Sadock list arsenic, lead, N-hexane, organophosphates, pyridoxine, cisplatin, vincristine and dapsone among environmental and medication toxicities, where pyridoxine is the reminder that a vitamin in excess belongs in a toxicology chapter.

Consolidate and apply

27 · Worked vignettes

A vignette in this territory is written so that the psychiatric syndrome is easy and the body is not. The stem hands over a recognisable picture of depression, psychosis, anxiety, confusion or personality change, then buries the discriminating evidence in items that read like background: a bowel habit, a skin change, a drug bought without prescription, an occupation, a value quoted in

passing. Candidates who read for the psychiatric label find it within two lines and elaborate a diagnosis the examiner never doubted. The marks sit in the items that were skipped.

These cases consolidate the chapter rather than replacing its disease sections. Each is followed by the reasoning that should be audible in a written answer or a viva: the syndrome, the system that could have produced it, the finding that most changes the ranking, and what must happen before the patient leaves. Criteria, reference ranges, thresholds, doses, correction rates and monitoring intervals belong to the sections that own them.

27.1 Read the stem twice: once for the syndrome, once for the body

Read these stems in two deliberate passes. The first names the psychiatric syndrome exactly as presented, without interpretation. The second ignores the mental state entirely and collects everything somatic: physical symptoms and examination findings, every drug prescribed and unprescribed, exposures, diet, reproductive and family history, tempo, and any value already quoted. Only then ask which collected item would alter the diagnosis if it were deleted from the stem.

Syndrome	System	Direction	Action
WHAT IS PRESENTED	WHAT COULD PRODUCE IT	WHICH WAY CAUSE RUNS	WHAT CANNOT WAIT

The **diagnostic pivot** is the finding, or cluster of findings, that most alters the ranking of explanations, and in this chapter it is almost never a psychiatric feature. It is a physical sign, an exposure, a temporal coincidence with a prescription, or a discordance between the psychiatric diagnosis and the age, tempo or context of onset. Nominate it explicitly: a stated pivot converts a list into an argument.

The **opening formulation** should then sit at the level the evidence supports. Lead with the syndrome, add the system you believe generated it and the strength of that belief, name the strongest competitor, and state the observation that would separate them. Naming a specific disease in the first sentence is a gamble that pays only when the somatic signature is unambiguous, and it costs the answer when the stem was built around a different organ.

RULE **Every answer here names three things: the psychiatric syndrome, the bodily system that could have produced it, and the investigation that separates them.** Missing the second reads as a psychiatric formulation that happened to be asked in a medical setting. Missing the third asserts a cause it has not tested, which is the failure this chapter exists to prevent.

27.2 Vignette: the depression that will not lift, in a body that has changed

A middle-aged woman is referred with several months of low mood, loss of interest, profound fatigue and poor concentration. Successive adequate antidepressant trials have not helped. Her family describe her as slowed rather than sad, and mention weight gain, constipation, dry skin, hair thinning and cold intolerance, all attributed to the depression. Nobody has examined her since the first referral.

This is the chapter's commonest stem shape: a **psychiatric phenocopy**, a systemic disease presenting through a psychiatric door with a mental state indistinguishable from primary illness.

The pivot is not the mood but the convergence of physical changes belonging to one axis. Each item alone is explicable as a depressive or medication effect; together, and in one direction, they point at an organ.

Apparent treatment resistance is the second pivot. Failure to respond to adequate treatment is a standing trigger for looking beyond the psychiatric diagnosis, and the correct response is to re-examine the patient rather than re-read the drug chart. Say what would be sought on examination, order the test the somatic signature calls for, and state that reference ranges and the interpretation of a borderline result belong to the thyroid sections.

The management answer has two halves and candidates write only the first. Correct the systemic disease with the physician who will manage it, expecting the psychiatric syndrome to improve alongside. Then reassess: a residual affective picture persisting after biochemical correction is a legitimate target for independent psychiatric treatment, not an argument that the endocrine finding was irrelevant. Hormone augmentation and the endocrine consequences of mood-stabilising treatment are taught in their own sections; the drug itself, with its pharmacokinetics and non-thyroid organ effects, belongs to the Mood disorders: pharmacotherapy notes.

GOOD TO REMEMBER

When a depression has failed adequate treatment, the next investigation is a physical examination, not another antidepressant. Weigh the patient, look at the skin, hair and neck, take the pulse, check for a postural drop and elicit the reflexes. A stem saying nobody has examined the patient is telling you where the answer is.

27.3 Vignette: the new confusion in a patient who already has a diagnosis

A patient with established severe mental illness is admitted for a systemic medical problem and referred back to psychiatry for agitation and confusion. The picture fluctuates: lucid in the morning, disorganised and drowsy by evening, with disturbed sleep, variable attention and an abnormal movement of the outstretched wrists that the encephalopathy sections teach as organ-localising. The referral asks for sedation and says the patient has relapsed.

The correct opening is an **acute metabolic encephalopathy** until proved otherwise. Three features carry it: the change is new against the patient's own baseline, conscious level and attention fluctuate rather than thought content alone, and there is a physical sign no psychiatric illness produces. The disease that generated the state and its correction are this chapter's material. The acute confusional syndrome itself, with its criteria, structured assessment, workup and prevention, belongs to the Stroke, TBI, delirium and focal brain syndromes notes.

Make the search for the driver audible: which organ of clearance is failing, which solute has moved, which drug was started or stopped around the change, and whether the illness, its treatment, hypoxia, sepsis, deficiency or withdrawal is responsible, singly or together. Sedation before that search is the harm: it removes the fluctuating conscious level that was the diagnostic evidence, and can deepen the encephalopathy already present.

TRAP **Letting an existing psychiatric diagnosis absorb a new deterioration.** Candidates read the psychiatric history first and file every later change under it, so confusion becomes relapse, drowsiness becomes negative symptoms and a new physical sign becomes a medication effect. The discipline is the opposite: a patient with chronic mental illness who changes acutely has an acute problem until that is excluded, and the existing diagnosis makes such a presentation more likely, not less.

27.4 Three shorter stems: when to stop and think metabolic

A young adult presents with a first psychotic episode accompanied by a movement abnormality, deteriorating handwriting, mildly deranged liver enzymes and a sibling who died undiagnosed. A second has recurrent episodes combining severe abdominal pain, autonomic instability, weakness and florid psychiatric disturbance, each following a newly started drug and resolving between attacks. A third, an older adult on a restricted diet, has cognitive decline with sensory disturbance in the feet and an unsteady gait.

These test the **inherited metabolic differential** and its nutritional neighbours, and share one feature: the psychiatric syndrome is ordinary and the accompanying findings are not. Name the pattern, then hand the confirmatory test to the section that owns it: copper studies and the ocular sign to the copper-metabolism sections, the correctly timed and handled specimen to the porphyria section, the deficiency assays to the nutritional sections. The marks lie in the decision rule, not the disease names. Stop and think metabolic when the age of onset is wrong for the psychiatric diagnosis, when psychiatric, neurological and systemic features coexist without a unifying explanation, when episodes are stereotyped and drug-triggered, when there is consanguinity or undiagnosed neuropsychiatric illness in the family, or when the course does not behave like its label. Cognitive impairment from these diseases is described here in clinical language and its reversibility is this chapter's business; the dementia syndrome and its workup belong to the Dementias and neurocognitive disorders notes, and cognitive instruments to the Psychotherapies, clinical assessment, MSE and nosology notes.

STEM PATTERN	OPENING FORMULATION	THE PIVOT	WRONG TURN
Depression with convergent somatic change	Depressive presentation of systemic disorder	Findings pointing to one axis	A third antidepressant, not an examination
Anxiety with paroxysmal autonomic surges	Anxiety needing a secretory cause excluded	Stereotyped disproportionate episodes	Treating panic without asking why it began
Fluctuating confusion in known mental illness	Acute metabolic encephalopathy, cause unknown	Fluctuating conscious level plus a sign	Calling it relapse and sedating it
First psychosis with neurological and hepatic signs	Young-onset psychosis, possibly metabolic	Three systems, one young patient	Starting antipsychotics, stopping the workup
Stereotyped attacks after a new drug	Recurrent neurovisceral episode, drug-triggered	Episodicity with a drug relation	Diagnosing somatisation from normal scans
Cognitive decline with a nutritional history	Potentially reversible cognitive syndrome	Diet and neurological signs together	Assuming irreversibility from age
Derangement in a treated psychiatric patient	Treatment-attributable metabolic disturbance	Temporal relation to the prescription	Stopping the effective drug reflexively

27.5 Vignette: the patient whose treatment produced the disease

A young man treated effectively for a psychotic illness for several years has gained substantial weight, with an increase in waist circumference his family notice more than he does. Recent bloods show abnormal glucose and lipid results. His father has diabetes. He is mentally well, wants to stop the medication because of the weight, and has already halved his own dose.

The direction of causation is inverted here and the psychiatrist is the exposure rather than the detective. The reasoning turns on the **attribution question**: how much belongs to the drug, how much to the illness with its associated inactivity, diet, tobacco and social disadvantage, and how much to the baseline that preceded treatment and was never documented. Attribution decides whether changing the drug would change the outcome, and an honest answer concedes that these contributions cannot be cleanly separated in an individual.

Ownership discipline separates a good answer from a long one. The receptor-mediated mechanism by which antipsychotic treatment produces weight and metabolic change, with the comparative liability of agents, is taught in the treatment-burden section. The criteria and thresholds defining metabolic syndrome are stated once, in the metabolic syndrome and mortality section, and the monitoring parameters and their cadence once, in the monitoring section. Choosing between agents belongs to the Schizophrenia: management, antipsychotics and adverse effects notes.

The decision on top of all four has a shape. Take the covert dose reduction as the most urgent item in the stem, because relapse risk is immediate and metabolic risk is not. Treat the complaint as legitimate rather than as poor insight, since the harm is real and was prescribed. Establish the

baseline and what has changed, address modifiable contributors actively rather than advising them, then consider with the patient whether the regimen can be altered, whether a metabolic agent is indicated, and what will be monitored to know whether any of it worked.

27.6 Vignette: the drowsy patient with a low sodium

A patient on established psychotropic treatment becomes nauseated, unsteady and progressively drowsy over a short period, with headache and a witnessed seizure. The serum sodium is low. A second stem describes a long-stay patient who drinks constantly, whose weight rises measurably through the day, who is intermittently confused in the evenings, and whose sodium is also low.

The **discordant fact** in each is the route by which the sodium fell, and it is the whole question. One patient has retained water because a drug altered water handling; the other has taken in more than the kidney can excrete. The history separates them long before any calculation: what was prescribed and when, against what is being drunk and how far the weight moves within one day. Both then converge on the same urgency, because the neurological state and the speed of the fall determine how ill the patient is.

Two handovers keep this answer honest. Mechanisms of drug-induced water retention, the psychotropic classes responsible, the risk groups and the monitoring plan belong to the section owning inappropriate antidiuresis. The rate at which a low sodium may be corrected, and the demyelinating injury that follows correcting it too quickly, belong to the section owning primary polydipsia and mineral disturbance. Both are places where a confidently remembered figure is more dangerous than an admitted gap.

> **PITFALL**
>
> Treating the number instead of the patient, in either direction. A frightened team corrects a low sodium quickly because the value looks alarming, and causes an injury worse than the illness. Elsewhere a chronically low but stable sodium in a well patient is chased with intervention it never needed. Clinical state, tempo and neurological signs decide urgency; the value alone does not.

27.7 Managing the vignette: LOCUS, FOCUS and MODUS under exam conditions

Management answers here fail predictably: a competent psychiatric plan written for a patient whose problem is not, at this moment, psychiatric. LOCUS asks where care should happen and is answered first, because it governs everything after. Most of this work is outpatient and shared with a physician, but several presentations are emergencies in which a psychiatric bed cannot deliver the monitoring the body requires, and saying so explicitly earns the mark.

FOCUS asks what is treated and in what order. Acutely it is the derangement threatening the patient, with only as much behavioural containment as makes treatment possible. In the short term it is the underlying disease and the syndrome it drove. In the medium term it is whatever psychiatric picture remains after correction, where independent psychiatric treatment becomes justified rather than assumed. In the long term it is surveillance for recurrence and the accumulating physical cost of psychiatric treatment itself. MODUS then runs across four modes: pharmacological, carrying both the systemic treatment and a psychotropic chosen for the failing

organ; psychological, carrying adherence, dietary, activity and substance-use work; procedural, carrying surgical, replacement and dialytic intervention; and social, carrying cost, supervision, transport and the exposure that may need to change before the illness will.

- State the locus of care and the threshold at which this patient leaves the psychiatric setting.
- Name the immediate risk, often the derangement rather than the behaviour that prompted referral.
- Separate treatment of the disease from treatment of the syndrome, and say who owns each.
- Choose psychotropics for the organ that must clear them, and say what you would avoid.
- Define what will be monitored, by whom, and what will be done with the result.

IN INDIA

Two structural realities change these answers. The psychiatrist in a general-hospital unit is frequently the first and sometimes the only doctor to examine the patient physically, and onward referral is a plan rather than a guarantee, so the answer must contain a psychiatric management safe in the interval before the physician is actually reached. Patients also present late, so the fully developed somatic signature is more often available at first contact than the early subtle one: the pivot is easier to find and the treatment window more often closed. Long-term correction, whether replacement, chelation or a metabolic agent, is usually paid out of pocket, so a plan that ignores who will fund and supervise it for years is not a plan.

27.8 Writing the answer: the spine that survives exam pressure

Under pressure the reasoning collapses in the same order every time. The candidate names the psychiatric syndrome, recognises a disease, writes everything known about it, and never returns to the patient in the stem. The spine below is a retrieval aid rather than a diagnostic criterion, and asserts nothing this chapter has not already taught.

MNEMONIC

PIVOT

Pivot: the finding or cluster that most changes the ranking, and why. **I**mpostor: the psychiatric diagnosis this case would otherwise have received, and the systemic disease impersonating it. **V**erify: the investigation that separates them, and what each result would mean. **O**rder of correction: what is treated first, by whom, and how quickly it may safely be corrected. **T**hen reassess: what picture is expected to remain, when it will be reviewed, and what would reopen the formulation.

Be equally disciplined about what is missing. Say what was not in the stem and how it would change the ranking, since examiners write incomplete stems deliberately. Do not manufacture normal findings, and do not read silence in a short stem as evidence that a symptom is absent. Where the answer needs a threshold, rate, dose or interval that cannot be recalled with confidence, name the parameter, name the source that governs it, and move on. That is stronger

than a confidently wrong number, and better practice, because the number will be looked up before it reaches the patient.

Finish with what changes. A formulation that alters nothing is unfinished, and here something almost always changes: a test ordered today rather than next month, a drug stopped, a deficiency replaced before a window closes, a correction deliberately slowed, a transfer to a setting that can monitor the body.

> In every endocrine or metabolic vignette, name the syndrome, name the system that could have produced it, name the pivot that separates them, name the test that would settle it, and name the one action that cannot safely wait until the diagnosis is certain.

28 · Consolidation and quick review

Nothing in this material arrives labelled with the organ that caused it. These diseases have to be learned one system at a time, but that is not how they present. A patient arrives with low mood, a first psychotic episode, panic, apathy, a fall in cognitive performance or a change in behaviour the family cannot explain, and the organ responsible sits behind that presentation, silent or attributed to the mental illness. Consolidation means turning the material around: not from gland to symptom, which is how it was written, but from symptom to gland, which is how it is used.

Two further reversals matter as much. Part of this material is not bodily disease reaching psychiatry but bodily disease that psychiatry causes, where the exposure is a prescription written in good faith. And much of the benefit lies past the diagnosis, in what is corrected, how fast, what improves and who follows it up. Criteria, thresholds, doses and intervals belong to the sections that own them.

28.1 Read the material backwards, from syndrome to system

The psychiatric syndromes here are **final common pathways**. The brain has a limited repertoire of ways to fail, so disturbances as different as a depleted vitamin store, an excess of circulating steroid, a fallen sodium, an accumulated metal and a failing liver converge on the same handful of presentations: altered mood, drive, perception, arousal and cognition. The phenotype therefore under-determines the cause, which is why the mental state alone will never name the organ.

The usable consequence is an inverse index: for each presentation, the short list of systems capable of generating it, and the question that sorts that list fastest. It is recallable under pressure and more useful than a catalogue of glands, which is indexed by the one thing the patient does not bring you.

PRESENTATION	SYSTEMS CAPABLE OF GENERATING IT	THE QUESTION THAT SORTS IT FASTEST
Depressive syndrome	Thyroid disease; cortisol excess, endogenous or prescribed; adrenal insufficiency; vitamin B12 and folate deficiency; raised calcium; diabetes; organ failure	Weight direction, temperature tolerance, pigmentation, postural symptoms, the whole drug list
Mania or irritable overactivity	Prescribed corticosteroids; thyroid overactivity; thyroid hormone given for an affective indication	What was started, stopped or increased before the change
Psychosis	Copper disorder in a young patient; acute porphyria; thyroid disease; cortisol excess; vitamin B12 deficiency; the adult-onset inherited metabolic disorders; toxic exposure	What company it keeps: neurological signs, liver disease, abdominal crises, skin change, family history
Anxiety and paroxysmal autonomic symptoms	Thyroid overactivity; catecholamine-secreting tumour; hypoglycaemia; low calcium; hypoxia and carbon dioxide retention	Whether attacks are truly paroxysmal with observed autonomic change, and whether they track meals or exertion
Apathy and blunting	Thyroid underactivity; adrenal insufficiency; raised calcium; organ-failure encephalopathy; sustained toxic exposure	Whether the family describes slowing rather than sadness
Cognitive impairment	Vitamin B12 deficiency; thyroid underactivity; acute thiamine deficiency; hepatic and uraemic encephalopathy; copper disorder; recurrent hypoglycaemia; metal and solvent exposure	The tempo of decline, and whether anything correctable is still correctable
Acute confusion, stupor or catatonia	Severe derangement of sodium, glucose, calcium, oxygen, ammonia or urea; endocrine crisis; organ-failure encephalopathy; drug and toxin states	Which single derangement could account for the whole picture, and whether conscious level itself fluctuates
Behavioural change in a young adult	Copper disorder; the adult-onset inherited metabolic disorders; chronic occupational and environmental exposure	Family history, occupation, water source, home remedies, when function first slipped

RULE **The mental state names the syndrome, the body names the system, and only then does a test name the disease.** An answer jumping from a psychiatric presentation straight to a named endocrine or metabolic disease has skipped the step where the marks are, and clinically it is guesswork with a laboratory form.

28.2 The phenocopies this material exists to separate

A **phenocopy** is a systemic disease reproducing the surface of a psychiatric syndrome closely enough that the psychiatric diagnosis is made, recorded and then defended. These pairs are where examiners concentrate, because the discriminating evidence is usually available at first contact and simply not collected. Four discriminators do most of the work: tempo and periodicity; the company the symptom keeps, meaning observed physical signs rather than reported ones; its relationship to a meal, a fast, exertion, a menstrual phase or a new drug; and its behaviour under adequate psychiatric treatment.

THE PSYCHIATRIC LABEL USUALLY APPLIED	THE DISEASE IMITATING IT	WHAT SEPARATES THEM AT THE BEDSIDE
Panic disorder	Catecholamine-secreting tumour	Genuinely paroxysmal attacks with observed pallor, sweating and pressure change, without situational cueing or avoidance
Generalised anxiety in a young adult	Thyroid overactivity	Heat intolerance, weight loss with preserved appetite, resting tachycardia, tremor, eye or neck signs
Episodic anxiety, confusion or aggression	Hypoglycaemia	Timing to food, fasting or exertion, a glucose-lowering prescription, resolution with carbohydrate
Anxiety with paraesthesiae	Low calcium	Neuromuscular irritability on examination, with a precipitant such as neck surgery
Treatment-resistant depression in later life	Thyroid underactivity, vitamin B12 deficiency, raised calcium	Apathy and slowing out of proportion to reported sadness, with physical signs
A functional neurological presentation	Copper disorder	An abnormal movement of consistent form, liver disease, a specific eye sign, a family history
Relapse on maintenance treatment	Drug-induced hyponatraemia, organ-failure encephalopathy, hypoglycaemia	Impaired attention and fluctuating conscious level, which relapse rarely produces

TRAP **Explaining new physical or cognitive symptoms by the psychiatric diagnosis the patient already carries.** This is **diagnostic overshadowing**, the most reliable way this material is failed in examination and clinic alike. The longer and more severe the psychiatric history, the more readily new symptoms are absorbed into it, and that population carries the highest burden of the diseases described here.

28.3 Tempo sorts the differential; the window sets the urgency

Tempo is the most efficient discriminator available, and it costs nothing. Paroxysmal symptoms lasting minutes with objective autonomic accompaniment point to a secreting lesion or a fall in glucose or calcium. Deterioration over hours to a few days points to a solute, a glucose, an oxygen,

an ammonia or an endocrine crisis. Change over weeks to months fits a depleting nutrient store, an accumulating hormone excess or its withdrawal. Change over years fits an accumulating metal, a slowly failing organ or a sustained occupational exposure. Symptoms recurring with an external periodicity direct attention to whatever recurs around them: a menstrual phase, a dietary pattern or an intermittent exposure at home.

Tempo also sets urgency, because these diseases are correctable in four different senses and conflating them causes harm. The first must be corrected now or function is lost, and in some of them treatment properly precedes biochemical confirmation. The second must be corrected at a controlled rate, because the correction itself injures; that rate belongs to the section owning it and is never estimated at the bedside. The third is corrected and then waited on, because the syndrome lags the biochemistry, and judging response too early drives needless escalation of psychotropic treatment. The fourth is corrected expecting a remnant, so that a **residual syndrome** is recognised as a sequel to be rehabilitated rather than pursued as fresh pathology.

Inverse	Tempo	Class	After
SYNDROME TO SYSTEM	THE FASTEST SORTER	WHAT A TEST SETTLES	WHAT CORRECTION LEAVES

28.4 Know what each class of test can settle

Investigation here is not one activity but several, and marks are lost by treating every result as the same kind of evidence. A static level measures a circulating analyte at one instant and is shaped by biological rhythm, binding proteins, posture, fasting, the acute illness the patient currently has and the drugs already prescribed; it answers what the concentration was, not whether the system is regulated. **Dynamic testing**, by suppression or stimulation, answers the regulatory question directly, which is why it rather than the static level separates physiological adaptation from disease. A **functional marker**, a metabolite accumulating when a pathway is under-supplied, answers whether the tissue is genuinely deficient when the circulating level is equivocal. A timed collection answers output across an interval, so its validity depends on the collection being complete. Imaging answers structure and rarely establishes causation alone. Tissue and genetic testing answer cause, and reframe the family as well.

Two interpretive habits protect all of this. A **reference interval** describes a population and is not itself a decision threshold for the patient in front of you; the thresholds, the direction of change that matters and the situations in which the usual interval does not apply belong to the sections owning each analyte. And the pre-test question governs the reading, since the same borderline value means less in a patient screened without a hypothesis than in one whose history already pointed at that system.

PITFALL

The correct test, sent under conditions that make it uninterpretable. Several investigations here depend on the timing of the sample, the patient's clinical state, the completeness of a timed collection or how the specimen is protected in transport. Get that wrong and the result returns neither normal nor abnormal but useless, the patient has travelled home, and the working diagnosis hardens in the absence of evidence. Confirm the sampling conditions before the patient leaves.

28.5 Your own prescription is one of the exposures

Reverse the direction of causation and the psychiatrist stops being the detective and becomes the exposure. Psychotropic treatment moves weight, waist, lipids, glucose, prolactin and sodium, and it is prescribed to a population already carrying an excess burden of cardiometabolic disease and a shortened life expectancy. That is one of psychiatry's principal harms, and it is foreseeable at the moment of prescribing. Four questions belong before the pen moves.

- Which organ clears this drug, and is that the organ currently failing?
- What does the drug do to weight, glucose, lipids, prolactin and sodium, and what is this patient already carrying?
- What does the systemic disease do to the drug's margin of safety, through altered clearance, fluid shifts, seizure threshold, cardiac conduction or reduced marrow and hepatic reserve?
- What monitoring does this prescription commit me to, and can this patient complete it?

When an abnormal parameter appears, the decision turns on **attribution**. The candidates are the drug, the illness and its lifestyle, the pre-treatment baseline, and an unrelated intercurrent disease. Which one you choose determines whether you switch, add, reduce, treat or accept, and both reflexive answers are wrong: switching on a single value can cost a stable patient a hard-won remission, while accepting a value without recording that you accepted it leaves an untreated physical illness and no plan. The comparative liability of individual agents, the monitoring cadence, the criteria defining the metabolic syndrome and the management of established disturbance and raised prolactin are each stated once, in the owning section. Drug selection and receptor pharmacology belong to the Schizophrenia: management, antipsychotics and adverse effects notes, and lithium as a drug to the Mood disorders: pharmacotherapy notes.

GOOD TO REMEMBER

One sentence in the record does most of this work: which parameter changed, what its baseline was, what you attributed the change to, what you did, and when it will next be reviewed. A patient with no documented baseline cannot be shown to have deteriorated, and an accepted abnormality never written down is indistinguishable from one never noticed.

28.6 Management: one spine, whichever disease it is

Management questions here are almost always about a patient with both a systemic disease and a psychiatric syndrome, and they become answerable on the standard spine. **LOCUS** asks where

care happens. Most of this work is outpatient and shared, but a definable group of presentations are medical emergencies in which the derangement, not the psychiatric syndrome, dictates care on a medical ward or in critical care with psychiatric input rather than the reverse. Settling LOCUS early prevents the commonest structural failure here, admitting a physically deranged patient to a psychiatric bed that cannot deliver the correction the body needs. LOCUS is dynamic, and is revisited whenever the derangement, the risk or the supervision changes.

FOCUS asks what is treated, in what order. Acutely the target is the derangement that threatens the patient, with enough containment of behaviour and risk to make correction possible. In the short term it is the underlying disease and the syndrome it drove, expecting the second to follow the first. In the medium term it is whatever picture persists after correction, where independent psychiatric treatment becomes justified rather than assumed. In the long term it is relapse prevention for both illnesses and the cumulative cost of treatment itself.

MODUS asks which modes are in use: the systemic treatment and the psychotropic chosen for the organ that must clear it; adherence support, dietary and activity intervention, substance work and psychoeducation the family can act on; the procedural and replacement interventions the disease sections describe; and the social mode of cost, distance, supervision and the exposure that may have to change before the illness will. Running through all of it is **shared care**, which works only when someone is named as responsible for each parameter, the next review and the decision to escalate. Dose, eligibility and interval come from current disease-specific guidance, never from memory.

28.7 Follow-through: the part most answers omit

Correcting the abnormality is the middle of the story, and the reassessment that follows is where a formulation is confirmed or overturned. Four outcomes should be anticipated. The syndrome remits fully, so the systemic disease was the diagnosis and continued psychotropic treatment needs a reason. It improves partially, so the contribution was real but shared, and what remains is treated on its own terms. It does not change, so the two conditions were co-occurring and the psychiatric illness stands independently, which is a legitimate finding rather than a failed workup. Or the patient deteriorates during correction, raising the correction itself, an unmasked second process or a complication, and usually needing the physician back the same day.

Long-term follow-up then carries three jobs easily collapsed into one. It watches for recurrence of the systemic disease, which in several of these conditions announces itself first as a change in mental state and is misread as psychiatric relapse. It watches the parameters psychiatric treatment itself created, on the cadence set by the section owning the monitoring. And it revisits the explanation given to patient and family, since an account offered during an acute derangement is rarely the one they need a year later. Adherence deserves the scrutiny given to efficacy, because correction here means daily treatment and repeated travel for someone who feels well.

IN INDIA

The shared-care pathway that Western descriptions assume is frequently unavailable, and the psychiatrist may be the only doctor the patient sees at predictable intervals. The physical review, the repeat investigations and the coordination then fall to psychiatry, so they belong in the psychiatric plan rather than a referral letter whose outcome is never seen. Cost drives the rest: long-term replacement, chelation, glucose-lowering treatment and repeated monitoring are largely paid out of pocket, and a regimen the family cannot sustain is stopped silently rather than renegotiated, so ask what is affordable and stage the plan accordingly. Anthropometric thresholds for Indian patients differ from imported ones and are stated in the monitoring section. Since records are usually held by the patient rather than an institution, send the family home with a written summary of the correction, the parameters being followed and the signs that should bring them back.

28.8 The retrieval frame, and how to deploy it

When a stem is crowded with physical detail, frame the case before trying to solve it. The scaffold below is a retrieval aid, not a diagnostic criterion. Under pressure the steps most often dropped are the phenocopy question, because the label is already written, and the escalation question, because the physician is elsewhere.

MNEMONIC

PROBE

Phenocopy: ask which systemic disease could be imitating this syndrome before accepting the psychiatric label, especially in a patient who already carries one. **R**ate and rhythm: use tempo and periodicity to narrow the system, then ask which class of treatment window is open. **O**rgan: name the axis, nutrient, solute, metal, organ of clearance or exposure accounting for the whole picture rather than one symptom. **B**ind the test to the question: choose the investigation that answers what you asked, get the sampling conditions right, and read the result against this patient. **E**xposure and escalation: your prescription is an exposure, so decide what will be monitored, who is responsible, and when this patient needs a physician rather than a psychiatric review.

Keep the boundaries visible while doing it. Delirium as a syndrome, and the persistent amnestic syndrome that may follow acute thiamine deficiency, belong to the Stroke, TBI, delirium and focal brain syndromes notes. The dementia syndrome and its workup belong to the Dementias and neurocognitive disorders notes. Administration and scoring of the cognitive instruments belong to the Psychotherapies, clinical assessment, MSE and nosology notes, so cognitive change is described here in clinical language. Hormone synthesis, receptor signalling and neuroendocrine measurement belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. Naming the interface and moving on shows the judgement being tested; re-teaching it shows the opposite.

Work backwards from the psychiatric syndrome to the systems that produce it, let tempo narrow the list and set the urgency, choose the test that answers your question, decide attribution before changing treatment, and follow the patient long enough to learn which of the two illnesses you were treating.

PLACEHOLDER references. Authored after grounding from the actual sources _CLAIMS.json rests on.

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