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PAPER II · VOLUME TWO

MD and DNB psychiatry, theory revision

Clinical Psychiatry

The Mood Disorders and Their Treatment

Mood disorder defined and divided: the depressive and bipolar syndromes, their course and biology. Then the antidepressants, the mood stabilisers and lithium.

Dr. Wilfred D'souza · Dr. Niharika Reddy

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WEAVE SPRINT · PAPER II

Clinical Psychiatry

THE WEAVE SPRINT SERIES

TITLE

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WRITTEN BY

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EDITION

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

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

ACKNOWLEDGEMENT

A word of thanks

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

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

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

Dr. Wilfred D'souza

Foreword

This second volume is mood, taken as one subject in two halves. The first chapter defines the territory and divides it, and sets out the biology proposed beneath the division. The second is the prescribing: the antidepressants, the mood stabilisers, and lithium, which still asks more of the prescriber than almost any other drug in psychiatry.

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

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

HOW TO USE THIS BOOK

The colour memory code

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

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

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

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

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PART IV

IV

Mood Disorders: Classification, Depressive and Bipolar Syndromes, Neurobiology

Mood disorder defined and divided: the depressive and bipolar syndromes, their course, and the biology beneath them.

PAPER II

Mood disorders: classification, depressive and bipolar syndromes, neurobiology

Five sections · one complete notes document

This material opens the mood block, gathering into one document how the mood disorders are classified, the full set of depressive and bipolar clinical syndromes, the guideline-anchored management of each, and the neurobiology that underlies them. The first band is **classification and nosology**: the ICD-11 episode-based architecture and how it cross-maps to ICD-10 and DSM-5-TR, the unipolar-versus-bipolar distinction and the detailed Akiskal bipolar spectrum, the historical Kraepelinian dichotomy, and the epidemiology. The second band is **depressive disorders**: major depressive disorder and its criteria and specifiers, persistent depressive disorder, the melancholic, atypical, psychotic and catatonic subtypes, seasonal affective disorder, peripartum depression and premenstrual dysphoric disorder, and the guideline-anchored management of depression. The third band is **bipolar and related disorders**: bipolar I and the manic episode, bipolar II and hypomania, cyclothymia, mixed features and rapid cycling, course and prognosis and the special populations, the management of bipolar disorder across acute mania, bipolar depression and maintenance, and the interleaved differential that separates the mood syndromes. The fourth band is **neurobiology and aetiology**: the monoamine, HPA-axis, neurotrophic, glutamatergic, inflammatory and genetic hypotheses, each taught with its evidence and its limitation, the neuroimaging and limbic-cortical circuit model, and the psychological theories. The examinable skill is discrimination and reasoning: to place a mood presentation by episode type and polarity, to tell the syndromes and subtypes apart, to reach for the right guideline-recommended treatment, and to explain the mechanisms without overclaiming them.

HOW TO USE THESE NOTES

Read the five bands as one continuous account of mood disorder from its classification through the syndromes and their management to the underlying neurobiology. The **classification** band gives the episode-based map and the detailed Akiskal spectrum that orients everything after it. The **depressive** and **bipolar** bands teach each syndrome against its mimics, and every named syndrome and subtype ends with a **Good to remember** box giving what it is, the core criteria or the one discriminating feature, and the one number or eponym to hold; each of those two bands closes with a guideline-anchored **management** topic led by the CANMAT guidelines and stating the Indian Psychiatric Society and NICE positions, on the where-to-treat, target-by-phase, modes-of-treatment spine. The **neurobiology** band teaches each hypothesis with both its supporting evidence and its limitation, so no mechanism is overclaimed. Figures declare one axis and code it in colour: **petrol** marks structure and the neutral case, **coral** marks the trap or the danger, and **marigold** highlights the number or eponym to hold. Several boundaries are worth stating up front: the individual drug pharmacology, the treatment-resistant algorithms and the pharmacotherapy detail are taught in the Mood disorders: pharmacotherapy notes and are cross-referenced here rather than repeated; the HPA-axis mechanics, the monoamine pathway anatomy and the neuroimaging principles live in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes, applied here to mood; the mood-with-psychotic-features boundary against schizoaffective disorder and the catatonia entity live in the Other psychotic disorders, delusional syndromes and catatonia notes, which cross-refers back to the mood-episode criteria owned here; the technique of electroconvulsive therapy lives in the ECT and neurostimulation notes; clinical suicide risk assessment lives in the Somatic-symptom, sexual, impulse-control disorders and suicide notes; and the raw descriptive definitions of the mood symptoms live in the Psychometry, Assessment and Descriptive Psychopathology notes. This is doctor-facing revision, so the full technical vocabulary is used, and every criterion, threshold, dose-free guideline recommendation, and number is verified against a source.

Mood disorders: classification and nosology

1 · Orientation: classifying the mood disorders

Why this matters. The mood disorders are the largest single block in the affective syllabus, and they are also the block most vulnerable to a snapshot error: a clinician who diagnoses from how the patient looks today, without the longitudinal history, will call a bipolar depression "major depression" and start the wrong drug. The whole modern nosology is built to stop exactly that. It is **episode-based**: you name the mood **episode** first, then let the lifetime pattern of episodes name the disorder. This orienting topic builds the **classification of mood** disorders as one map, seeds the master mnemonic that chains the entire chapter, and hands the reader the two master axes, polarity and episode type, against which everything downstream is placed.

The governing idea, which the examiner rewards over and over: everything in this family is a disturbance of mood that persists over time, so you never separate the disorders by "is the mood low or high" at a single visit but by which episodes have occurred across the person's life and in what pattern. Nosology here is given ICD-11 primary (the current CDDR grouping "mood

disorders"), with the DSM-5 (the DSM-5-TR) labels cross-mapped, because the two systems split the family into different chapters and the difference is itself examinable; ICD-10 is flagged where the exams still lean on it. The raw descriptive definitions of the individual mood symptoms, and the rating scales, are owned by the Psychometry, Assessment and Descriptive Psychopathology notes and are cross-referenced here, not re-derived; this chapter is the canonical home of the depressive-episode and manic-episode diagnostic criteria themselves.

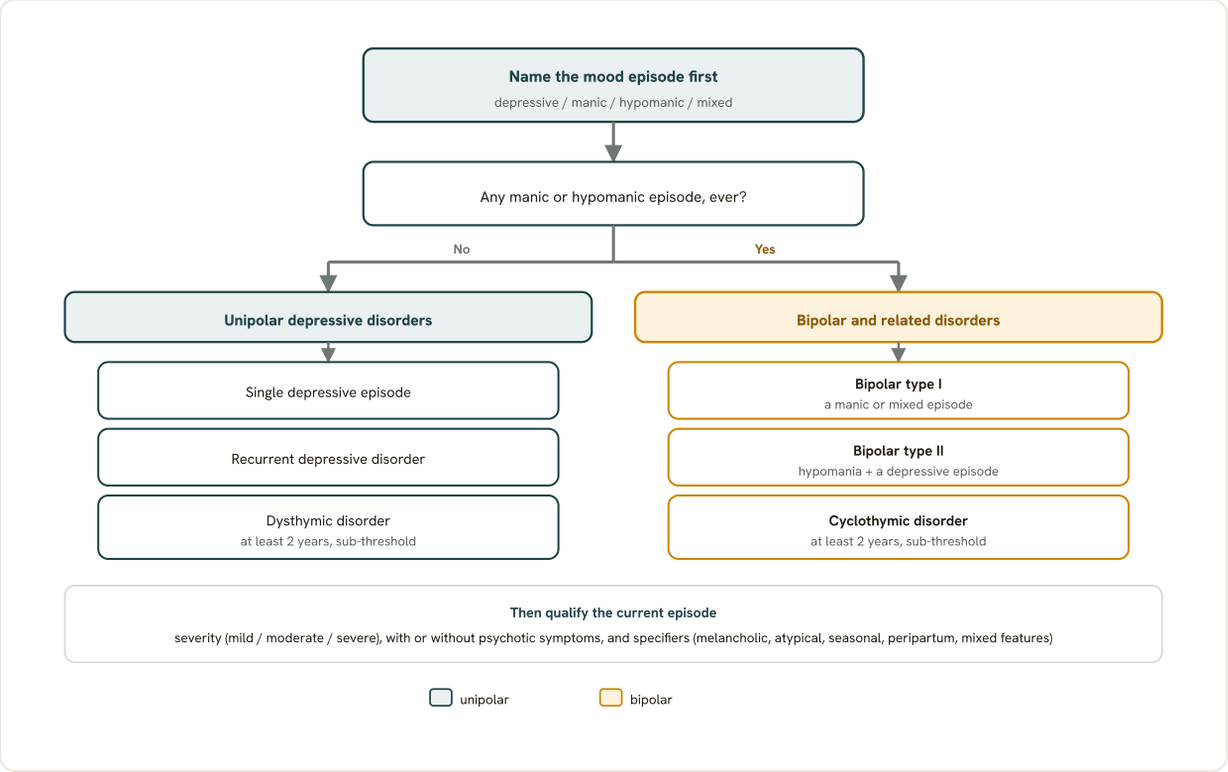

Fig 11.1 The ICD-11 episode-based mood-classification map. Name the current mood episode first, then split on polarity: any lifetime manic or hypomanic episode moves the patient into the bipolar column permanently, otherwise the illness is unipolar. The lifetime pattern of episodes then names the disorder, and a severity, psychotic-symptom and specifier layer is added to the current episode.

1.1 The episode is the atom: mood disorders are built on episodes

The single most important structural fact is that in ICD-11 the **mood episode** is the building block of the diagnosis, not a diagnosis in its own right. The ICD-11 CDDR states it plainly: "mood episodes are not independently diagnosable entities, and therefore do not have their own diagnostic codes"; rather, they are the components out of which the bipolar and depressive disorders are assembled (ICD-11 CDDR). There are four episode types the reader must hold: the depressive episode, the manic episode, the hypomanic episode and the mixed episode. A disorder is then defined by which of these episodes have occurred and how they pattern over time (ICD-11 CDDR; Kaplan & Sadock 2024). This is why the correct diagnostic move is always two-step: identify the episode in front of you, then interrogate the lifetime history for the episodes that reclassify it.

RULE **Name the episode first, then let the pattern of episodes name the disorder.** Depressive, manic, hypomanic or mixed is the atom; the lifetime pattern is the molecule.

TRAP **Do not diagnose a "disorder" from a cross-sectional snapshot.** A depressed patient today is a depressive episode; whether the disorder is unipolar or bipolar is decided only by the past history of a hypomanic or manic episode.

1.2 The four mood episodes and their duration thresholds

Before the disorders come the episodes, and the examiner tests the duration threshold of each as a reflex fact. A **depressive episode** requires the core mood or anhedonia change plus associated symptoms persisting for a period of **at least two weeks** (ICD-11 CDDR; DSM-5-TR major depressive episode). A **manic episode** is an extreme elevated, expansive or irritable mood with increased activity or energy lasting **at least one week** (or any duration if hospitalisation is needed), and by its severity it causes marked impairment, needs intensive treatment, or carries psychotic features (ICD-11 CDDR; DSM-5-TR). A **hypomanic episode** is the same symptom picture at lesser severity, without marked impairment, hospitalisation or psychosis; ICD-11 requires it "for at least several days", while DSM-5-TR sets a firm floor of **at least four consecutive days** (ICD-11 CDDR; DSM-5-TR). A **mixed episode** is prominent manic and depressive symptoms occurring simultaneously or alternating rapidly within the same episode (ICD-11 CDDR). The full criterion lists for the depressive and manic episodes are laid out in their own topics that follow; the point here is that the episode, with its threshold, is the unit of classification.

at least 2 wk	at least 1 wk	at least 4 days	several days
DEPRESSIVE EPISODE	MANIC EPISODE	HYPOMANIC (DSM-5-TR)	HYPOMANIC (ICD-11)

GOOD TO REMEMBER

- **Depressive episode:** low mood or anhedonia plus associated symptoms for **at least two weeks**; the depressive atom; criteria taught in full in this chapter.
- **Manic episode:** elevated, expansive or irritable mood with raised activity for **at least one week** (any duration if hospitalised), with marked impairment, need for intensive treatment, or psychosis; the defining episode of bipolar type I.
- **Hypomanic episode:** the manic symptom picture below the impairment or psychosis threshold; ICD-11 "several days", DSM-5-TR **at least four days**; the defining episode of bipolar type II.
- **Mixed episode:** prominent manic and depressive symptoms simultaneously or rapidly alternating within one episode; places the patient in bipolar type I.

1.3 Master axis one, polarity: the unipolar versus bipolar split

The first and most consequential axis is **polarity**: has the person ever crossed into the manic or hypomanic pole. On one side sit the unipolar depressive disorders, where the lifetime course contains depressive episodes only. On the other sit the **bipolar spectrum** disorders, where at least one manic or hypomanic episode has occurred (Kaplan & Sadock 2024). This single question splits the entire block, because it decides the treatment logic: an antidepressant is a reasonable first move in unipolar depression but is the classic error in a bipolar depression, where it risks a switch and is not the anchor of care. ICD-11 encodes the split at the top level of its grouping, dividing "mood disorders" into **bipolar and related disorders** and **depressive disorders** (ICD-11 CDDR). The detailed soft-bipolar gradation between the two poles, the Akiskal spectrum, is

developed in the unipolar-versus-bipolar-spectrum topic that follows; here it is enough to hold that polarity is the master cut.

TRAP **Never close a depression assessment without screening for a past hypomanic or manic episode.** An unscreened past hypomania is what silently reclassifies a "unipolar" depression as bipolar type II.

1.4 Master axis two, episode type and pattern: how the pattern names the disorder

Given polarity, the second axis reads the **episode type and its pattern over time**, and this is what actually assigns the diagnostic label. Within the unipolar depressive disorders, a first and only depressive episode is single episode depressive disorder, whereas a history of at least two depressive episodes separated by several months of relative euthymia is recurrent depressive disorder (ICD-11 CDDR). Within the bipolar disorders, one lifetime manic or mixed episode is sufficient for bipolar type I disorder (a depressive episode is not required), while bipolar type II disorder requires at least one hypomanic and at least one depressive episode with no history of a manic or mixed episode (ICD-11 CDDR; DSM-5-TR). Two chronic, sub-threshold patterns close the family: cyclothymic disorder, a persistent instability of hypomanic and depressive periods over **two years or more** that never meets full episode criteria and never includes a manic or mixed episode, and dysthymic disorder (persistent depressive disorder), a persistent depressed mood lasting **two years or more** that stays below the full depressive-episode threshold for most of that time (ICD-11 CDDR).

RULE **One manic or mixed episode is bipolar type I, full stop.** Bipolar type II needs a hypomania plus a depression and no manic or mixed episode ever; a manic episode anywhere in the history overrides the type II label.

GOOD TO REMEMBER

- **Single episode depressive disorder (6A70):** one lifetime depressive episode, no manic or hypomanic history; becomes recurrent on the second episode.
- **Recurrent depressive disorder (6A71):** **at least two** depressive episodes separated by several months of relative euthymia; the unipolar recurrent form (DSM-5-TR: major depressive disorder, recurrent).
- **Bipolar type I disorder (6A60):** at least one lifetime **manic or mixed** episode; a depressive episode is not required for the diagnosis; the discriminator is the full manic episode.
- **Bipolar type II disorder (6A61):** at least one **hypomanic** and at least one **depressive** episode, with **no** manic or mixed episode ever; the discriminator is a hypomania in a patient who has never been fully manic.
- **Cyclothymic disorder (6A62):** mood instability of hypomanic and depressive periods over **two years or more**, never meeting full episode criteria, no manic or mixed episode; the sub-threshold bipolar pattern.
- **Dysthymic disorder (6A72):** persistent depressed mood for **two years or more** below the full depressive-episode threshold; the sub-threshold unipolar pattern (DSM-5-TR: persistent depressive disorder).

1.5 Master axis three and four, severity and the psychotic and other specifiers

Once polarity and episode pattern have named the disorder, two further axes describe the current episode. **Severity** grades the current depressive episode as mild, moderate or severe on the number and intensity of symptoms and the impact on functioning, with the rule that a mild depressive episode by definition carries no psychotic symptoms (ICD-11 CDDR). The **psychotic specifier** then marks a moderate or severe episode as "with" or "without psychotic symptoms" (delusions or hallucinations), the mood-congruent guilt, poverty, nihilistic and persecutory delusions of depression being the classic examples (ICD-11 CDDR). Other examinable specifiers layered on top include the melancholic, atypical, seasonal, peripartum, mixed-features and rapid-cycling patterns, each of which steers prognosis and treatment. The full handling of mood with psychotic features, and the boundary with schizoaffective disorder, is cross-referenced to the Other psychotic disorders, delusional syndromes and catatonia notes.

PEARL

ICD-11 and DSM-5-TR both let an antidepressant-emergent (or ECT-, light- or rTMS-emergent) manic or hypomanic syndrome that **persists beyond the physiological effect of the treatment** count as a true manic or hypomanic episode, and therefore reclassify the patient as bipolar. A switch that resolves the moment the drug is stopped does not (ICD-11 CDDR; DSM-5-TR).

1.6 The three frameworks cross-mapped: ICD-11, DSM-5-TR and ICD-10

The reader needs to hold all three systems (the icd-11, the dsm-5 and the icd-10) because Indian examinations still cite ICD-10 alongside the newer manuals. ICD-11 gathers everything under a single superordinate "mood disorders" grouping split into bipolar-and-related and depressive disorders. DSM-5-TR, by contrast, breaks the same content into **two separate chapters**, "Bipolar and Related Disorders" and "Depressive Disorders", and deliberately places the bipolar chapter as a bridge between schizophrenia and depression (Kaplan & Sadock 2024; DSM-5-TR). ICD-10 used the older label "mood [affective] disorders" (F30 to F39) with "bipolar affective disorder" as a single unified category and no separate bipolar type II code, and it grouped the recurrent depressive and persistent (dysthymia, cyclothymia) forms alongside. The map below is the object to memorise: read each row across the three columns and note where the systems diverge.

ENTITY (CONCEPT)	ICD-11	DSM-5-TR	ICD-10 (STILL EXAMINED)
Superordinate grouping	**Mood disorders (one grouping, two sub-blocks)**	Two chapters: Bipolar and Related; Depressive	Mood [affective] disorders (F30 to F39)
Single depressive episode	Single episode depressive disorder (6A70)	Major depressive disorder, single episode	**Depressive episode (F32)**
Recurrent unipolar depression	Recurrent depressive disorder (6A71)	Major depressive disorder, recurrent	Recurrent depressive disorder (F33)
Chronic low-grade depression	Dysthymic disorder (6A72)	**Persistent depressive disorder (dysthymia)**	Dysthymia (F34.1)

ENTITY (CONCEPT)	ICD-11	DSM-5-TR	ICD-10 (STILL EXAMINED)
Manic-pole disorder, full mania	Bipolar type I disorder (6A60)	Bipolar I disorder	**Bipolar affective disorder (F31); no separate type**
Hypomania plus depression	Bipolar type II disorder (6A61)	Bipolar II disorder	**No distinct code (subsumed under F31)**
Chronic mood instability	Cyclothymic disorder (6A62)	Cyclothymic disorder	Cyclothymia (F34.0)

The mood-classification cross-map: the same clinical entities as they are coded across the three frameworks; the highlighted cell flags where a system diverges most from the others.

1.7 Two entities the DSM parks with depression: DMDD and PMDD

Two categories sit in the DSM-5-TR Depressive Disorders chapter that the reader should place now and expand later. Disruptive mood dysregulation disorder is a childhood-onset presentation of chronic, severe persistent irritability with frequent temper outbursts, placed among the depressive disorders to capture children who would otherwise be over-diagnosed as bipolar; it is a differential guard rather than a bipolar entity (DSM-5-TR). Premenstrual dysphoric disorder is a luteal-phase mood disturbance recurring across most menstrual cycles and remitting after menses; DSM-5-TR lists it as a depressive disorder, while ICD-11 codes it in the genitourinary chapter and cross-lists it under mood disorders for reference (ICD-11 CDDR; DSM-5-TR). Both are named here only to fix their place on the map; their criteria are developed in their own topics.

1.8 The classification map assembled: reading a stem in order

The axes chain into an ordered walk, and reading them in this order is the fastest route through any placement stem. First, characterise the current **episode** and confirm it meets threshold (depressive at two weeks, manic at one week, hypomanic at four days or several days, or mixed). Second, ask the **polarity** question: has there ever been a manic or hypomanic episode, which pulls the patient off the unipolar track and onto the bipolar spectrum. Third, read the **pattern**: one versus recurrent for the depressive disorders; manic-or-mixed (type I) versus hypomanic-plus-depressive (type II) for the bipolar disorders; and the two-year sub-threshold patterns (cyclothymia, dysthymia) for the chronic low-grade presentations. Fourth, layer the **severity and specifiers** (psychotic, melancholic, atypical, seasonal, peripartum, mixed-features, rapid-cycling) onto the named disorder. This ordered map is the concept figure for the whole chapter, Fig 11.1, the ICD-11 episode-based mood-classification tree.

WORKED EXAMPLE

A 26-year-old woman presents with a three-week depressive episode: low mood, anhedonia, poor sleep, hopelessness. Walk the map. The episode meets threshold (over two weeks). Now the polarity question: on careful history she describes a five-day period last year of reduced need for sleep, overactivity, rapid speech and uncharacteristic confidence that friends noticed but that caused no hospitalisation, no psychosis and no marked impairment, a hypomanic episode. She has therefore had a hypomanic plus a depressive episode and no manic or mixed episode: the diagnosis is bipolar type II disorder, currently in a depressive episode, not major depressive disorder. Miss the hypomania on the snapshot and you would start an antidepressant alone, the classic bipolar-depression error.

MNEMONIC

"EPISODE first, then POLARITY; CLASSIFY, DEPRESS, then BIPOLAR; MANAGE by phase; MECHANISM with its limit."

The master chain for the whole chapter. Start from the mood EPISODE and its threshold, then split on POLARITY (unipolar versus bipolar spectrum). Then work the chapter in order: CLASSIFY the family on this map, then the DEPRESSive syndromes (single, recurrent, dysthymia, the specifiers), then the BIPOLAR syndromes (type I, type II, cyclothymia and the Akiskal spectrum). Then MANAGE by phase, guideline-anchored (acute, continuation, maintenance for depression; acute mania, bipolar depression, maintenance for bipolar). Finish on the neurobiology, where every MECHANISM is held together with its LIMITation (monoamine, HPA, neurotrophic, gene-environment). Episode, then polarity, is the two-beat core the examiner rewards.

1.9 Management and neurobiology: where they live in the chapter

Management in this chapter is taught guideline-first, led by the CANMAT recommendations with the Indian Psychiatric Society (the IPS guidelines) and NICE positions stated alongside, and organised on a LOCUS (where to treat), FOCUS (the phase target) and MODUS (the modes of treatment) spine (CANMAT 2016; CANMAT 2018). Those recommendations are developed in the two management topics; the guideline-level headline to carry from the outset is that unipolar depression is treated by phase (acute, continuation, maintenance) with a second-generation antidepressant plus evidence-based psychotherapy first-line, while bipolar disorder is treated by presentation (acute mania, bipolar depression, maintenance) around lithium and the atypical antipsychotics and anticonvulsant mood stabilisers, with antidepressant monotherapy avoided (CANMAT 2016; CANMAT 2018). The deep drug pharmacology, the full dosing, the adverse-effect profiles and the treatment-resistant algorithms are owned by the Mood disorders: pharmacotherapy notes and are cross-referenced, not duplicated here. The neurobiology band teaches each hypothesis with its supporting evidence and its limitation; the HPA-axis mechanics, the monoamine pathway anatomy and the neuroimaging principles are grounded in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes, with the mood application taught here.

INDIA

Mood disorders are among the commonest presentations in Indian outpatient psychiatry, and the National Mental Health Survey of India 2015 to 2016 (Gururaj et al. 2016) remains the anchor epidemiological source cited in the exams; depressive disorders were among the most prevalent categories it identified. For severe, psychotic or treatment-resistant depression and for acute mania, ECT is widely available and heavily used across Indian teaching hospitals, a point returned to in the management and the ECT and neurostimulation notes. This chapter is largely generic; where any brand is named it leads with the Indian brand, but drug branding belongs to the Mood disorders: pharmacotherapy notes.

GOOD TO REMEMBER

- **Classification of mood disorders:** ICD-11 superordinate "mood disorders" split into bipolar-and-related and depressive disorders; DSM-5-TR splits the same content into two separate chapters; ICD-10 uses F30 to F39.
- **Episode-based architecture:** the mood episode (depressive, manic, hypomanic, mixed) is the atom; it has no code of its own; the lifetime pattern of episodes names the disorder.
- **Polarity:** the master split; depressive episodes only is unipolar, any manic or hypomanic episode places the patient on the bipolar spectrum.
- **Diagnostic order:** episode and threshold, then polarity, then pattern, then severity and specifiers; the map is Fig 11.1.

HOLD THIS

Name the mood episode first (depressive, manic, hypomanic or mixed), split on polarity (unipolar versus bipolar spectrum), and only then let the lifetime pattern of episodes name the disorder: the modern nosology is episode-based, never a snapshot.

2 · ICD-11 changes in mood disorders

Nosology is examined every sitting, and the mood chapter is where the classifications diverge most usefully. The **icd-11 changes** in mood disorders are not cosmetic: they reorganise the whole block around the mood episode as the unit of definition, they re-tool how a mixed presentation is coded, and they tighten the severity and psychotic-symptom qualifiers. This topic teaches what actually moved from ICD-10 to ICD-11, cross-maps to DSM-5-TR, and flags where Indian exams and clinics still sit on the older categorical structure.

One warning up front. A common revision error is to import the DSM change into ICD-11. DSM-5 deleted its old mixed episode and turned mixed states into a specifier; ICD-11 did something different. Read the two systems as distinct so you do not answer an ICD-11 stem with a DSM-5 fact. The raw descriptive definitions of the individual mood symptoms and the rating scales are carried in the Psychometry, Assessment and Descriptive Psychopathology notes; here we teach the classification and the discrimination.

2.1 The episode-based architecture: the mood episode as the building block

The core move. ICD-11 defines the mood disorders from a small set of **mood episode** descriptions and then builds the disorders on top of them, an **episode-based architecture** (ICD-

11 CDDR 2024). There are four episode types: the depressive episode, the manic episode, the mixed episode and the hypomanic episode. A disorder is then a pattern of these episodes over time: a single depressive episode, recurrent depressive disorder, bipolar type I (defined by at least one manic or mixed episode) or bipolar type II (a hypomanic episode plus a depressive episode). DSM-5-TR made the same architectural shift, folding the episode definitions into the disorder criteria to streamline bedside use (DSM-5-TR 2022).

RULE **Episode first, disorder second.** In ICD-11 you diagnose the current mood episode, then name the disorder from the lifetime episode pattern.

2.2 The mixed presentation: ICD-11 keeps a mixed episode, DSM-5 does not

The pivot fact. ICD-11 retains a standalone mixed episode as one of its four episode types (ICD-11 CDDR 2024). A mixed episode is diagnosed when several prominent manic and several prominent depressive symptoms occur simultaneously, or alternate rapidly, for most of the day nearly every day for at least about two weeks; it qualifies bipolar type I disorder (code 6A60 current episode mixed) and cross-walks to ICD-10 F31.6, bipolar affective disorder current episode mixed. DSM-5-TR, by contrast, deleted the old DSM-IV mixed episode and replaced it with a **mixed features** specifier that is applied to a depressive, manic or hypomanic episode when at least three symptoms of the opposite pole are present through most of the episode (DSM-5-TR 2022). So the two systems reach a similar clinical idea by opposite routes: ICD-11 by a dedicated episode, DSM-5 by a specifier.

COMMON TRAP

Do not say ICD-11 abolished the mixed episode. That is the DSM-5 change. ICD-11 kept a mixed episode; what disappears is the ICD-10 idea of a separate residual mixed affective category divorced from the bipolar course.

2.3 Mixed features as a qualifier, not a separate category

How to hold both systems. The exam-safe formulation is that a **mixed features** presentation is a qualifier on an episode, not a free-standing mixed disorder. In DSM-5-TR it is literally the "with mixed features" specifier on a manic, hypomanic or major depressive episode. In ICD-11 the same clinical reality is captured either as a mixed episode within a bipolar disorder or, for subthreshold contrapolar symptoms, through the symptomatic specifiers attached to the current episode. Either way the mixed state is coded onto the episode, never as an orphan diagnosis floating outside the mood-episode framework.

RULE **Mixed = a qualifier on an episode.** In ICD-11 a mixed presentation attaches to the episode within a bipolar disorder; it is not a separate "mixed disorder".

TRAP **ICD-10 logic under ICD-11.** Applying the old ICD-10 mixed-episode reasoning as if it were an independent category, rather than treating the mixed state as an episode-level qualifier, is the classic error.

2.4 The depressive episode: prominence and persistence

The threshold. An ICD-11 depressive episode requires a cluster of characteristic symptoms present nearly every day for **at least two weeks**, drawn from an affective cluster (depressed mood, or markedly reduced interest or pleasure), a cognitive-behavioural cluster (reduced concentration, worthlessness or guilt, hopelessness, recurrent thoughts of death or suicidality) and a neurovegetative cluster (disrupted sleep, appetite or weight change, psychomotor change, reduced energy) (ICD-11 CDDR 2024). The chronic depressive forms are coded separately: ICD-11 dysthymic disorder is a sub-threshold condition (persistent depressed mood for at least two years with additional, usually milder, symptoms and no full depressive episode during the first two years), whereas a full-threshold depressive episode that itself persists for two years or more is flagged by the "with persistent depressive episode" specifier; the two are opposites, and dysthymia is developed in the persistent depressive disorder topic. The prominence-and-persistence framing, symptoms both prominent enough and present nearly every day across the two-week window, is what distinguishes an episode from a normal reaction to adversity.

at least two weeks	at least 1 week	at least several days
DEPRESSIVE EPISODE DURATION	MANIC EPISODE DURATION	HYPOMANIC EPISODE DURATION

2.5 Severity grading and the psychotic-symptoms qualifier

The two axes. ICD-11 grades the current depressive episode as mild, moderate or severe on the number and severity of symptoms and the functional impact. Superimposed on that, moderate and severe episodes are further qualified as **without psychotic symptoms** or with psychotic symptoms, meaning the presence or absence of delusions or hallucinations (ICD-11 CDDR 2024). By definition a mild depressive episode carries no psychotic symptoms. This decouples severity from psychosis and is a genuine change from ICD-10, where the presence of psychotic symptoms in a depressive episode automatically forced the episode to be rated as severe. The mood-congruent versus mood-incongruent quality of those psychotic symptoms, and the schizoaffective boundary, belong to the Other psychotic disorders, delusional syndromes and catatonia notes.

> **PEARL**
> In ICD-11 you can have a moderate depressive episode with psychotic symptoms; in ICD-10 that combination did not exist, because psychosis pushed the episode straight to severe. This is a favourite single-best-answer discriminator.

2.6 The manic and hypomanic episodes, and the bipolar backbone

The bipolar definers. The manic episode requires euphoric, irritable or expansive mood with increased activity or energy, most of the day nearly every day, for **at least 1 week** (or any duration if hospitalisation is needed, or shortened by effective treatment), plus several additional symptoms; one manic or mixed episode is sufficient to define bipolar type I disorder. The hypomanic episode is the milder, non-impairing, non-psychotic form lasting **at least several days**, and a hypomanic episode with a depressive episode defines bipolar type II disorder (ICD-11 CDDR 2024). A useful ICD-11 detail: if a patient has had past manic or mixed episodes, the

one-week duration is not required to call a current manic episode. The detailed Akiskal soft-bipolar spectrum that sits behind these categories is developed in the unipolar-versus-bipolar-spectrum topic.

TRAP **Calling a hypomania a mania.** Impairment, psychosis or a need for hospitalisation moves the episode out of hypomania; without them, a several-day elevation is hypomanic, and the disorder is bipolar II, not bipolar I.

2.7 Cross-map to DSM-5-TR and the ICD-10 flag

Three-system literacy. DSM-5-TR keeps mixed features as a specifier (at least three opposite-pole symptoms on a manic, hypomanic or major depressive episode) and adds its own changes: the bereavement exclusion was removed from major depressive disorder, and premenstrual dysphoric disorder and disruptive mood dysregulation disorder sit within the depressive disorders (DSM-5-TR 2022). ICD-10, still the working system in many Indian settings and in a good share of exam material, retains the older categorical structure, with the mixed affective state coded F31.6 within bipolar affective disorder and psychosis forcing a severe rating. Knowing which system a stem is written in is half the answer.

FEATURE	ICD-10	ICD-11	DSM-5-TR
Organising unit	Episode plus disorder, loosely linked	**Mood episode as the building block, episode-based architecture**	Episode definitions folded into disorder criteria
Mixed presentation	F31.6 mixed affective episode within bipolar	**Retains a standalone mixed episode (qualifies bipolar I)**	**Mixed episode deleted; "with mixed features" specifier**
Depressive episode duration	At least two weeks	At least two weeks, nearly every day	At least two weeks (major depressive episode)
Severity and psychosis	**Psychosis forces a severe rating**	**Severity and the without psychotic symptoms / with psychotic symptoms qualifier are separate**	Severity and psychotic-features specifier separate
Bipolar II as a named type	Not a distinct category	Bipolar type II disorder present	Bipolar II disorder present
Exam relevance in India	**Still widely used clinically and in question banks**	Increasingly examined; the current WHO system	Cross-mapped; common in MCQ discriminators

The three-system grid: the hit cells are the discriminators most likely to be tested.

INDIA

Many Indian training programmes, case records and question banks still run on ICD-10, so a candidate must hold both the ICD-10 categorical structure and the ICD-11 episode-based architecture in parallel. When a stem quotes an F-code (for example F31.6 or F32), it is an ICD-10 item; when it talks about a mixed episode qualifying bipolar type I or a "moderate depressive episode with psychotic symptoms", it is ICD-11.

MNEMONIC

D-M-M-H

The four ICD-11 mood episodes, in the CDDR order: Depressive, Manic, Mixed, Hypomanic. Hold that the Mixed one survives in ICD-11 but not in DSM-5, and you will not swap the two systems.

GOOD TO REMEMBER

- **Episode-based architecture:** ICD-11 builds mood disorders from four mood episodes (depressive, manic, mixed, hypomanic); diagnose the episode, then the disorder from the lifetime pattern.
- **ICD-11 mixed episode:** retained as a distinct episode type; prominent manic and depressive symptoms together or rapidly alternating; qualifies bipolar type I (6A60 current episode mixed, cross-walks to ICD-10 F31.6).
- **DSM-5-TR mixed features:** the DSM-IV mixed episode was deleted; a "with mixed features" specifier now attaches to a manic, hypomanic or major depressive episode when at least three opposite-pole symptoms are present.
- **ICD-11 depressive episode:** characteristic symptoms nearly every day for at least two weeks across affective, cognitive-behavioural and neurovegetative clusters.
- **Severity and psychosis:** ICD-11 grades mild / moderate / severe and separately flags without psychotic symptoms or with psychotic symptoms; mild has no psychosis; unlike ICD-10, psychosis no longer forces a severe rating.
- **ICD-10 flag:** retains the older categorical structure (F31.6 mixed, psychosis forcing severe), still the working system in many Indian settings.

HOLD THIS

ICD-11 keeps a mixed episode and codes any mixed presentation as a qualifier on an episode within a bipolar disorder; DSM-5 deleted the mixed episode and made mixed features a specifier, so never answer an ICD-11 stem with the DSM-5 abolition.

3 · Unipolar versus bipolar and the Akiskal spectrum

The single most consequential act in assessing any depressed patient is deciding which of two illnesses you are looking at. **Unipolar** disorder has depressive episodes only; **bipolar** disorder has, somewhere in the history, a manic or hypomanic episode. That one fact reorganises the whole clinical picture, the family history, the expected course and, above all, the treatment, because the wrong answer means an antidepressant given alone to a patient who needed a mood stabiliser (Kaplan & Sadock 2024). The exam rewards the resident who can recite the point-by-point contrast and who reflexively screens every depression for a past hypomanic episode.

Beyond the clean unipolar/bipolar dichotomy lies a graded territory. Hagop Akiskal argued that bipolarity is not an on/off category but a continuum, the **bipolar spectrum**, whose milder end (the **soft bipolar** spectrum) shades imperceptibly into what looks like ordinary unipolar depression (Akiskal 2007). This topic lays that whole numbered spectrum out *before* you enter bipolar I proper, so you can see the terrain the diagnosis sits in. The raw descriptive definitions of the mood symptoms and the rating scales referenced here sit in the Psychometry, Assessment and Descriptive Psychopathology notes; the full manic and depressive episode criteria are taught in this chapter's own manic-episode and depressive-episode topics.

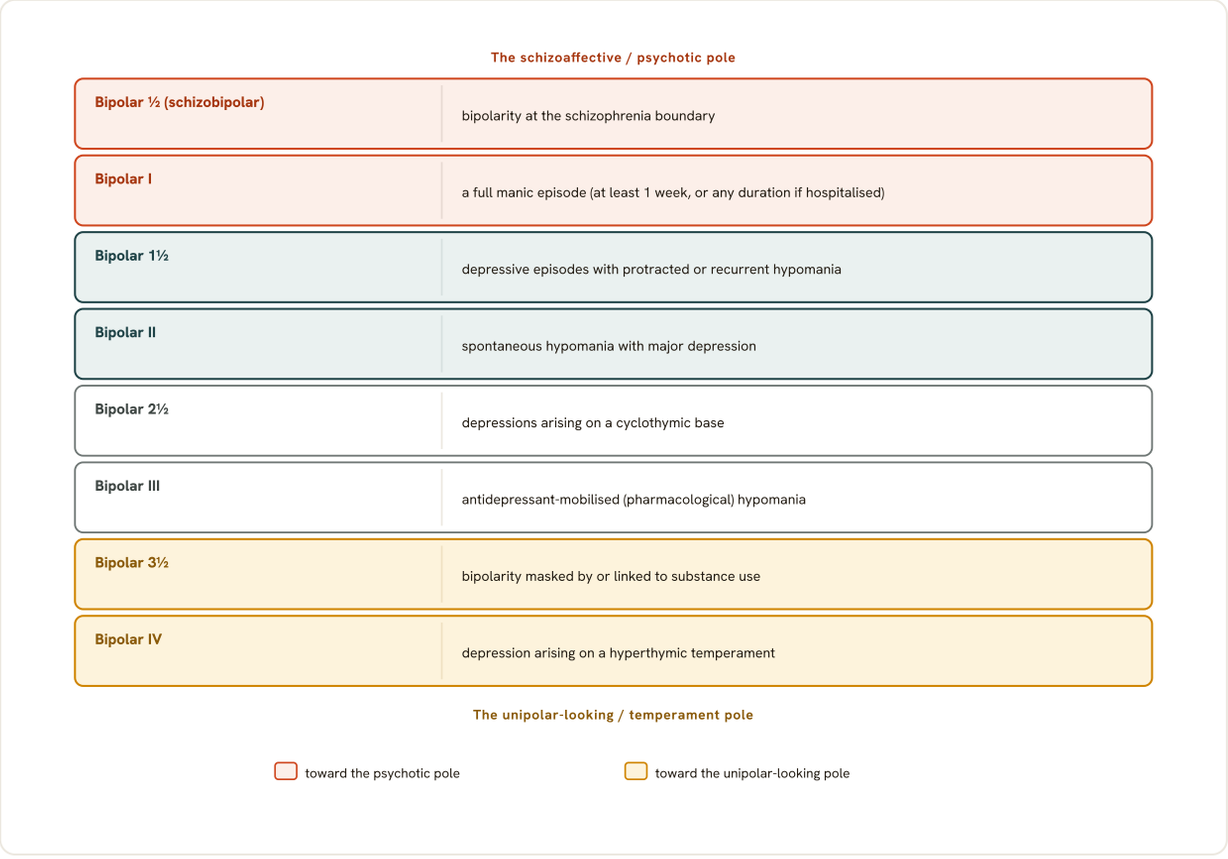

Fig 11.2 Akiskal's soft-bipolar spectrum, laid out before bipolar I proper. Read the fractions as rungs from the schizoaffective and psychotic pole at the top (bipolar one-half, then classic bipolar I) down through the temperament- and trigger-defined softer forms (protracted hypomania, spontaneous hypomania, cyclothymic depressions, antidepressant-mobilised and substance-linked bipolarity) to depression on a hyperthymic temperament, which looks unipolar on the surface. Only bipolar I, bipolar II and cyclothymia are formal ICD-11 categories; the numbered types are a lens for vigilance.

3.1 The definitional dividing line

One question decides it. The boundary is categorical and historical: has the patient *ever* had a manic or hypomanic episode? If yes, the disorder is bipolar and remains bipolar for life, even during a depressive presentation; if no, and only depressive episodes have ever occurred, it is unipolar (major depressive) disorder (Kaplan & Sadock 2024). A manic episode in ICD-11 lasts at least **1 week** (or any duration if hospitalisation is required) and defines bipolar type I disorder; a hypomanic episode is milder, without marked impairment or psychosis, and defines bipolar type II disorder when it occurs with major depression. ICD-11 requires a hypomanic episode to last **at least several days** and does not fix a day-count; DSM-5-TR requires **at least 4 consecutive**

days. The full criteria for both episodes are taught in this chapter's manic-episode and depressive-episode topics.

RULE **Ever high, then bipolar.** A single lifetime manic or hypomanic episode moves the patient into the bipolar column permanently, however depressed they look today.

3.2 Why the distinction is clinical, not academic

Bipolar and unipolar depressions differ across the board. They separate on temperament, sex ratio, age of onset, episode shape and drug response, and Kaplan & Sadock's Table 13.3-8 crystallises the contrast (Kaplan & Sadock 2024). Bipolar depression tends to be earlier in onset, more recurrent with shorter episodes, more often retarded and hypersomnic, and it carries the risk that an antidepressant will flip the mood; unipolar depression tends to be later, less recurrent with longer episodes, more often agitated and insomnic. Hold the discriminators below.

AXIS	BIPOLAR DEPRESSION	UNIPOLAR DEPRESSION
History of mania/hypomania (definitional)	**Yes**	**No**
Temperament and personality	Cyclothymic and extroverted	Dysthymic and introverted
Sex ratio	**Roughly equal**	**More women than men**
Age of onset	Teens, 20s and 30s	30s, 40s and 50s
Postpartum episodes	More common	Less common
Onset of episode	Often abrupt	More insidious
Number of episodes	**Numerous**	**Fewer**
Duration of episode	3 to 6 months	3 to 12 months
Psychomotor activity	**Retardation over agitation**	**Agitation over retardation**
Sleep	Hypersomnia over insomnia	Insomnia over hypersomnia
Response to most antidepressants	**Can induce hypomania or mania**	**Antidepressant effect, low switch risk**
Lithium carbonate	Prophylactic	Adjunctive at best

Kaplan & Sadock Table 13.3-8, differentiating bipolar from unipolar depressions. The italicised discriminators are the ones examiners test; the switch risk in the last two rows is why the unipolar/bipolar call changes management.

TRAP **Never diagnose bipolar II without a hypomanic episode.** Recurrent, early, retarded, hypersomnic depression *suggests* bipolarity, but the diagnosis needs a documented hypomanic episode, not a temperament or a hunch.

3.3 Every depression must be screened for past hypomania

Hypomania hides. Patients rarely volunteer hypomania. It is ego-syntonic, experienced as a welcome rebound from depression or as a pleasant, short-lived good spell, and many bipolar patients recoil from the word ("I am not a manic-depressive") (Kaplan & Sadock 2024). Benazzi and Akiskal advised asking first about *behavioural activation*: distinct sustained periods of

unusual energy, reduced sleep need, racing vivid thinking, over-talkativeness or disinhibition that others noticed, and only then anchoring the mood change to those periods. Collateral history from family is often decisive. Because hypomania is missed, apparent unipolar depression is frequently misclassified bipolar depression, and the screen is the safeguard.

WORKED EXAMPLE

A 26-year-old woman presents with her third episode of low mood since age 19: each time she sleeps 11 hours, feels leaden and slowed, and craves carbohydrate. She denies ever being "manic". On careful screening for behavioural activation she recalls two week-long spells of needing only 4 hours of sleep, redecorating the flat overnight and talking so fast that friends teased her, with no impairment. That is a hypomanic episode. The diagnosis is bipolar type II disorder, and an antidepressant alone would have been the wrong first move.

3.4 The bipolar spectrum and Akiskal's soft bipolar concept

A continuum, not a switch. From 1987, Akiskal propagated the idea of a soft bipolar spectrum, heavily dependent on temperament and managed with mood stabilisers rather than conventional antidepressants (Kaplan & Sadock 2024). The core intuition is that hypomania comes in three empirically recognised patterns, each defining a place on the spectrum: hypomania that *heralds the termination* of a retarded depression (bipolar II), hypomania that *alternates with mini-depressions* (cyclothymic disorder), and hypomania as an *elevated habitual baseline* (hyperthymic temperament) (Kaplan & Sadock 2024). Around these, Akiskal arranged a numbered spectrum of intermediate forms that bridge from schizoaffective territory at one pole to depression on a sunny temperament at the other. Lay the whole thing out before bipolar I so the softer forms are visible as variants, not exceptions.

SPECTRUM TYPE	DEFINING FEATURE	TEMPERAMENT OR TRIGGER
Bipolar one-half (schizobipolar)	**Bipolarity at the schizophrenia boundary; the schizobipolar pole of the affective-to-psychotic continuum**	Overlap with schizoaffective territory (Companion to Psychiatric Studies)
Bipolar I	**Full manic episode (at least 1 week, or any duration if hospitalised)**	Manic diathesis; classic manic-depressive illness
Bipolar one-and-a-half	**Depressive episodes with protracted or recurrent hypomania**	Prolonged hypomanic states
Bipolar II	**Spontaneous hypomania with major depression**	Hypomania heralding the end of a retarded depression
Bipolar two-and-a-half	**Depressions arising on a cyclothymic base (cyclothymic depressions)**	Cyclothymic temperament

SPECTRUM TYPE	DEFINING FEATURE	TEMPERAMENT OR TRIGGER
Bipolar III	**Antidepressant-associated or pharmacological hypomania (hypomania only ever mobilised by treatment)**	Antidepressant, or other somatic antidepressant treatment, as trigger
Bipolar three-and-a-half	**Bipolarity masked by, or associated with, substance use**	Stimulants, alcohol or other substances
Bipolar IV	**Depression arising on a hyperthymic temperament**	Hyperthymic (habitually cheerful, energetic) temperament

Akiskal's numbered soft bipolar spectrum, ordered before bipolar I proper. Read top to bottom as a slide from the schizophrenia boundary, through the classic manic pole, into progressively softer temperament- and trigger-defined forms that look unipolar on the surface (Akiskal 2007; Kaplan & Sadock 2024).

RULE **The spectrum is a screening mandate.** Because bipolarity shades continuously into apparent unipolar depression, every depression is screened for past hypomania, for a bipolar family history and for a hyperthymic or cyclothymic temperament.

3.5 Bipolar III and the temperaments that underwrite the soft forms

Trigger and temperament, not just episodes. Two Akiskal types are pure "reveal" phenomena: bipolar III is bipolarity that surfaces only as hypomania mobilised by an antidepressant (or other antidepressant treatment), and bipolar three-and-a-half is bipolarity tangled with substance use, where stimulants or alcohol both mask and mimic the mood swing (Kaplan & Sadock 2024). The softest end rests on affective temperaments. The cyclothymic temperament swings between cheerful and sad moods and occurs in roughly **4% to 6%** of young adults; the hyperthymic temperament, in which the person is habitually cheerful, energetic and confident, occurs in perhaps **2% to 5%** of young adults and is the base on which bipolar IV depressions arise (Kaplan & Sadock 2024). A depressed patient on a lifelong sunny, driven baseline is bipolar IV, not simply unipolar.

at least several days ICD-11 HYPOMANIC EPISODE	**at least 4 days** DSM-5-TR HYPOMANIC EPISODE	**4% to 6%** CYCLOTHYMIC TEMPERAMENT (YOUNG ADULTS)	**2% to 5%** HYPERTHYMIC TEMPERAMENT (YOUNG ADULTS)

3.6 Clinical use and the controversy of over-inclusiveness

Powerful lens, blunt instrument. The spectrum's clinical value is precisely that it teaches you to look for softer bipolarity behind an apparent unipolar depression: the recurrent early-onset retarded depression with a cyclothymic temperament, a bipolar family history, atypical (hypersomnic, hyperphagic, leaden) features, and antidepressant-mobilised highs are all soft-bipolar signals (Kaplan & Sadock 2024). Atypical features are so common in bipolar, especially bipolar II, that some treat them as markers of soft bipolar disorder, and it is clinically wise to exclude bipolar II before settling on major depressive disorder where hostile-labile features predominate (Kaplan & Sadock 2024). The controversy is over-inclusiveness: a spectrum with fuzzy edges risks re-labelling ordinary unipolar depression, temperament or personality variation as bipolarity, over-diagnosing the condition and exposing patients to mood stabilisers they may

not need. Neither DSM-5-TR nor ICD-11 adopts Akiskal's numbered types as formal categories; the operational nosology recognises only bipolar I, bipolar II and cyclothymic disorder, with the rest captured under "other specified" bipolar and related disorder. The spectrum is a heuristic for vigilance, not a licence to diagnose bipolarity from temperament alone.

COMMON TRAP

Treating an apparent unipolar depression that is really soft bipolar with an antidepressant alone. In bipolar depression, an antidepressant can induce hypomania, mania, mixed states or increased cycling; the deep pharmacology and the bipolar-depression treatment sit in the Mood disorders: pharmacotherapy notes, but the screening reflex belongs here.

PEARL

Hypomania "tends to recur (happiness does not)." A recurrent, distinct, ego-syntonic high, especially one that ends a retarded depression or is mobilised by an antidepressant, is the soft-bipolar signal that reclassifies the depression (Kaplan & Sadock 2024).

MNEMONIC

HALF-STEPS UP THE SPECTRUM

Read the fractions as rungs: bipolar one-half (schizobipolar) sits below bipolar I (mania); one-and-a-half is protracted hypomania; II is spontaneous hypomania with depression; two-and-a-half is cyclothymic depressions; III is antidepressant-mobilised hypomania; three-and-a-half is substance-linked bipolarity; IV is depression on a hyperthymic temperament.

INDIA

In Indian practice the soft-bipolar signal that changes management most often is the missed antidepressant-mobilised hypomania (Akiskal's bipolar III): a "treatment-resistant" or repeatedly relapsing depression that briefly brightened, over-brightened, on each antidepressant trial. Careful behavioural-activation questioning and family collateral, rather than a new drug, is what reclassifies it. The formal categories used are the ICD-11 ones (bipolar type I, bipolar type II, cyclothymic disorder); the numbered Akiskal types are taught as a lens, not coded as diagnoses.

GOOD TO REMEMBER

- **Unipolar disorder:** depressive episodes only, no lifetime mania or hypomania; discriminator is the negative hypomania screen; hold "depression only."
- **Bipolar disorder:** at least one lifetime manic (bipolar I) or hypomanic (bipolar II) episode; discriminator is the ever-high history; hold that one manic/hypomanic episode fixes the diagnosis for life.
- **Bipolar type I:** full manic episode; discriminator is mania lasting at least 1 week (or any duration if hospitalised); hold the 1-week manic threshold.
- **Bipolar type II:** spontaneous hypomania plus major depression; discriminator is a documented hypomanic episode without a full manic episode; hold "hypomania at least 4 days (DSM-5-TR), at least several days (ICD-11)."
- **Bipolar spectrum:** the continuum from strict unipolar to bipolar I; discriminator is graded rather than categorical bipolarity; hold Akiskal as the eponym.
- **Soft bipolar spectrum (Akiskal):** the milder end, temperament-driven, mood-stabiliser-managed; discriminator is bipolarity behind apparent unipolar depression; hold the numbered types one-half through IV.
- **Bipolar III:** antidepressant-associated (pharmacological) hypomania; discriminator is hypomania only ever mobilised by treatment; hold "antidepressant as trigger."
- **Bipolar IV:** depression on a hyperthymic temperament; discriminator is a lifelong cheerful, energetic baseline; hold the hyperthymic-temperament prevalence 2% to 5% of young adults.

HOLD THIS

Unipolar means depressive episodes only; a single lifetime manic or hypomanic episode makes it bipolar for life, so screen every depression for past hypomania, a bipolar family history and a hyperthymic or cyclothymic temperament before you commit to a unipolar diagnosis or an antidepressant.

4 · The Kraepelinian dichotomy and historical concepts

Why this matters. The whole modern nosology of the functional psychoses rests on one nineteenth-century decision: that **manic-depressive insanity** and dementia praecox are two separate diseases. That decision, the **kraepelinian** dichotomy, is the founding **historical concept** of the field, and the examiner rewards two things about it: that it was drawn on **course and outcome**, not on the cross-sectional symptom picture, and that a century of genetics and phenomenology has since blurred the line it drew. Getting both halves right, the origin and the erosion, is the whole of this topic.

This is a history-and-concepts topic, so it is taught around the people and the ideas, but with the exam-relevant discriminator kept sharp throughout: what each contributor actually claimed, and the one fact to hold about each. It is placed as the opener of the mood block because it explains why the block is organised by longitudinal pattern at all. The raw descriptive definitions of the mood symptoms and the rating scales are owned by the Psychometry, Assessment and Descriptive Psychopathology notes; the mood-with-psychotic-features presentations and the schizoaffective boundary are developed in the Other psychotic disorders, delusional syndromes and catatonia notes and are only sketched here as the place where the dichotomy breaks down.

4.1 Kraepelin's move: dividing the functional psychoses by course, not cross-section

The central figure in the history of psychiatric nosology is Emil Kraepelin, professor of psychiatry in Heidelberg from 1891 and in Munich from 1903 (Kaplan & Sadock 2024). Kraepelin had little use for theory or morbid anatomy and placed the diagnostic interest of psychiatry at the bedside, above all on the **course and outcome** of the illness (Kaplan & Sadock 2024). On that basis he stated, in the sixth edition of his textbook in 1899, that the two great endogenous diseases were manic-depressive insanity, a mood disorder that ran an episodic course with recovery between episodes, and dementia praecox, a progressive deteriorating illness of young onset later renamed schizophrenia by Bleuler (Kaplan & Sadock 2024; Companion 2010). The decisive point, and the one the examiner tests, is that he separated them not by how they looked on any one day, since both could show psychosis, but by their **longitudinal trajectory**: episodic with inter-episode recovery on the one side, progressive downhill deterioration on the other (Tasman 2015).

RULE **Kraepelin divided the functional psychoses by course, not by cross-section.** Episodic illness with recovery between episodes became manic-depressive insanity; progressive deterioration became dementia praecox.

MNEMONIC

"COURSE, not the CROSS-SECTION."

Kraepelin's whole innovation in one line. Two patients can look identical on the day you meet them, both psychotic, both agitated; what tells the diseases apart is the shape of the illness over years. Recover and relapse means manic-depressive insanity; grind steadily downhill means dementia praecox. When a stem asks what Kraepelin used to draw the dichotomy, the answer is course and outcome.

4.2 Manic-depressive insanity: what Kraepelin actually meant by it

A common trap is to read Kraepelin's manic-depressive insanity as the modern "bipolar disorder". It is not. Kraepelin's concept was deliberately broad: it took in the whole domain of periodic and circular insanity, simple mania, hypomania and the greater part of what was then called melancholia, and crucially it grouped together all severe recurrent mood illness **regardless of polarity**, so that a person with recurrent severe depression and no mania at all still fell inside manic-depressive insanity (Kaplan & Sadock 2024). In other words, Kraepelin lumped what modern systems split into unipolar and bipolar into a single unified disease, unified by its episodic, recovering course. Holding this is what lets the reader see why the later unipolar-bipolar split (4.4) was a genuine division of Kraepelin's category, not a footnote to it.

TRAP **Kraepelin's manic-depressive insanity is not DSM "bipolar disorder".** His category included recurrent unipolar depression too; it was polarity-blind and unified all episodic mood illness under one course-based label.

GOOD TO REMEMBER

- **Emil Kraepelin (1856 to 1926):** the father of descriptive psychiatric nosology; the discriminating feature is that he classified by **course and outcome**; the one date to hold is **1899**, the edition in which he stated the dichotomy.
- **Manic-depressive insanity:** Kraepelin's episodic, recovering endogenous mood disease; the discriminating feature is an episodic course with inter-episode recovery; the trap is that it was **polarity-blind** and included recurrent unipolar depression, not only bipolar illness.
- **Dementia praecox:** the progressive, deteriorating psychosis of young onset; the discriminating feature is a downhill course to defect; renamed **schizophrenia** by Bleuler in 1908.

4.3 The earlier French contributors: Falret and Baillarger

Kraepelin synthesised, he did not invent from nothing, and the examiner likes the two French alienists whose descriptions of the alternating illness preceded him by decades. In 1854 Jean-Pierre Falret described folie circulaire, "circular insanity", the recurring cycle of mania and depression with lucid intervals between (Companion 2010). In the same year, and famously presented only about two weeks before Falret's account, Jules Baillarger described folie a double forme, "insanity in two forms", the occurrence of mania and depression as two faces of a single illness (Companion 2010). It is from these two descriptions that the contemporary concept of recurrent oscillation between mania and depression emerged, later given its more explicit and unifying definition by Kraepelin as manic-depressive psychosis (Companion 2010). For the exam, hold the pairing: Falret with folie circulaire, Baillarger with folie a double forme, both 1854, both French, both antecedents of the Kraepelinian synthesis.

GOOD TO REMEMBER

- **Jean-Pierre Falret, folie circulaire (1854):** "circular insanity", the cyclical recurrence of mania and depression with lucid intervals; the eponym to hold is **folie circulaire**.
- **Jules Baillarger, folie a double forme (1854):** "insanity in two forms", mania and depression as two forms of one illness, described about two weeks before Falret; the eponym to hold is **folie a double forme**.

4.4 Leonhard's unipolar-bipolar split: the seed of the modern distinction

The modern division of Kraepelin's unified category into two diseases came from Karl Leonhard, a pupil of Karl Kleist (Kaplan & Sadock 2024). In his 1948 textbook Leonhard proposed the term **bipolar** for illness that alternates between depression and mania, setting it apart from a **unipolar** depression that shows only the depressive pole; he developed the split in his 1957 book, The Classification of the Endogenous Psychoses, arguing that unipolar depression had a different psychopathology from the bipolar variety (Kaplan & Sadock 2024). Leonhard grounded the distinction phenomenologically and then corroborated it with family data: mania occurred more often in the relatives of manic-depressive (bipolar) patients than in the relatives of unipolar patients, an early example of validating a purely descriptive split with an external correlate (Tasman 2015). This unipolar-bipolar distinction, carried into the literature by investigators such as Angst, Perris, Winokur and others, is what DSM-III inherited in 1980 when it anchored "bipolar disorder" as a disease separate from "major depression" (Kaplan & Sadock 2024).

Leonhard is therefore the bridge from the single Kraepelinian category to the two-axis modern classification.

RULE **Kraepelin lumped, Leonhard split.** Leonhard (1948) added the unipolar-versus-bipolar axis inside Kraepelin's manic-depressive category, and that split, not the dichotomy itself, is what the modern bipolar-versus-unipolar distinction descends from.

GOOD TO REMEMBER

- **Karl Leonhard:** introduced the **unipolar versus bipolar** split of the mood disorders; the discriminating claim is that bipolar (alternating) illness is a different disease from unipolar (depression-only) illness; the date to hold is **1948** for the term "bipolar", with the fuller account in his 1957 Classification of the Endogenous Psychoses.

4.5 The erosion of the strict dichotomy: shared genetics and overlapping neurobiology

The examiner's second demand is that the dichotomy is no longer treated as absolute. The **kraepelinian dichotomy** holds well for classic cases but breaks down at the boundaries, and modern psychiatric genetics is the main reason (Tasman 2015). Family, twin and molecular studies show that schizophrenia and bipolar disorder **share a substantial portion of their genetic liability**, with overlapping susceptibility loci rather than two cleanly separate genetic architectures, so the two poles do not breed true as fully distinct diseases (Craddock & Owen 2005). The neurobiology tells the same story: overlapping findings across the two conditions rather than a clean biological border. This body of evidence is what led Craddock and Owen to their landmark paper title, "The beginning of the end for the Kraepelinian dichotomy" (Craddock & Owen 2005), the reference to cite in any answer on this theme. The practical reading is that the dichotomy is best held as a useful clinical approximation, valid at the extremes, rather than a statement of two biologically watertight categories.

PEARL

The single reference to name when a stem asks about the erosion of the dichotomy is Craddock and Owen's 2005 editorial in the British Journal of Psychiatry, "The beginning of the end for the Kraepelinian dichotomy" (Craddock & Owen 2005). It marshalled the shared-genetics evidence into the argument that the two Kraepelinian diseases are not genetically separate.

4.6 The intermediate presentations: schizoaffective and psychotic mood on a continuum

The clinical face of the erosion is the population of **boundary cases** that will not sort cleanly into either Kraepelinian box. Kraepelin himself acknowledged that some patients showed features of both, and Bleuler proposed that manic-depressive illness and schizophrenia lie on a **continuum with no sharp border**, with patients often exhibiting characteristics of both and running a course midway between (Tasman 2015). The category that formalises this middle ground is schizoaffective disorder, the recognised diagnostic home for presentations that carry both prominent mood and prominent schizophrenia-type psychotic features (Tasman 2015). Alongside it sit the mood episodes **with psychotic features**, where a severe depressive or manic episode carries delusions or hallucinations and so blurs the phenomenological line between a

mood disorder and a psychotic one. Together, the shared genetics, the overlapping neurobiology and these intermediate schizoaffective and psychotic-mood presentations place the two Kraepelinian poles on a continuum rather than in separate boxes. The detailed criteria and the schizoaffective boundary itself are developed in the Other psychotic disorders, delusional syndromes and catatonia notes.

TRAP **Do not treat the dichotomy as absolute.** Shared genetic liability, overlapping neurobiology and the intermediate schizoaffective and psychotic-mood presentations blur the line; the boundary cases are the rule, not an exception, and the dichotomy is now read as a continuum.

GOOD TO REMEMBER

- **Bleuler continuum:** the proposal that manic-depressive illness and schizophrenia lie on a single continuum with no sharp border; the discriminating idea is boundary cases running a course midway between the two.
- **Schizoaffective disorder:** the recognised diagnostic home for mixed mood-and-psychosis presentations; the discriminating feature is prominent mood and prominent schizophrenia-type psychotic features together; criteria owned by the Other psychotic disorders, delusional syndromes and catatonia notes.

HOLD THIS

Kraepelin (1899) split the functional psychoses by **course and outcome**, episodic manic-depressive insanity versus progressive dementia praecox; Leonhard (1948) then split that mood category into **unipolar and bipolar**; and shared genetics with the intermediate schizoaffective and psychotic-mood cases has since turned the strict dichotomy into a **continuum**.

INDIA

The Kraepelinian course-based logic is the backbone of the ICD system used across Indian teaching hospitals, and the emphasis on longitudinal course over the cross-sectional picture is exactly why a careful lifetime history, not a single mental-state snapshot, is the taught standard for separating a recurrent mood disorder from schizophrenia in Indian practice.

5 · Epidemiology of mood disorders

Why this matters. The **epidemiology of mood** disorders is high-yield precisely because the numbers separate the two illnesses. Major depressive disorder is common, skews female roughly two to one, and tends to begin in adult life; bipolar disorder is a good deal rarer, has a roughly equal sex ratio, and starts earlier. An examiner tests whether you can quote the right figure for the right disorder, and whether you resist the classic error of transplanting a Western prevalence onto an Indian population. This topic teaches the population picture: prevalence, the **sex ratio**, the **age of onset**, the burden, the comorbidity and mortality, and the Indian data from the National Mental Health Survey.

The raw descriptive definitions of the mood symptoms and the rating scales that generate these prevalence estimates sit in the Psychometry, Assessment and Descriptive Psychopathology notes; here the concern is the population-level distribution. Clinical suicide risk assessment and safety

planning are developed in the Somatic-symptom, sexual, impulse-control disorders and suicide notes; the mortality figures below are the epidemiological headline only.

5.1 Major depressive disorder: how common

Common, and commoner in women. Major depressive disorder is among the most prevalent psychiatric disorders. Kaplan & Sadock give a **lifetime prevalence** in the region of **5% to 17%** across community surveys, with a widely quoted point (current) prevalence of roughly **2% to 3%** in men and **5% to 9%** in women (Kaplan & Sadock 2024). The single most robust epidemiological fact is the sex difference: depression is about **twice** as common in women as in men, the classic 2:1 female-to-male ratio, a finding that holds across most countries and cultures and is thought to reflect a mix of hormonal, psychosocial and help-seeking factors (Kaplan & Sadock 2024). Hold the prevalence as a range rather than a single figure, because surveys differ by method and case definition.

RULE **Depression is commoner in women, about two to one.** The 2:1 female preponderance in major depressive disorder is the most reproducible single fact in mood epidemiology.

5.2 Major depressive disorder: when it starts

Adult onset, spread wide. The **age of onset** of major depressive disorder spans the whole adult lifespan, but the bulk of first episodes cluster in the twenties to thirties, and community data show first onset can occur from adolescence into later life (Kaplan & Sadock 2024). Older texts quote a mean age of onset around 40, but a large share of patients now present with a first episode in the twenties and thirties, and depression rising in younger cohorts is a recognised secular trend. The clinical point for the exam is that depression is not confined to any single decade: an adolescent first episode and a late-life first episode are both fully compatible with the diagnosis, and the peak of new onsets sits in early to middle adult life.

GOOD TO REMEMBER

- **Major depressive disorder:** the commonest mood disorder; the discriminating epidemiological feature is the 2:1 female preponderance; hold lifetime prevalence roughly 5% to 17% and onset clustering in the twenties to thirties.
- **Sex ratio in depression:** women to men about 2:1; the discriminator from bipolar is that bipolar is roughly equal; hold "twice as common in women."
- **Age of onset in depression:** spread across adult life, peak in the twenties to thirties; the discriminator from bipolar is that depression starts later on average; hold "adult onset, wide range."

5.3 Bipolar disorder: rarer, equal by sex, earlier

Less common, and different in shape. Bipolar disorder is substantially less prevalent than unipolar depression. Bipolar type I disorder has a lifetime prevalence of around **1%** in community surveys, and the figure rises when the wider **bipolar spectrum** (bipolar II and subthreshold forms) is counted, with combined spectrum estimates commonly cited in the region of a few percent (Kaplan & Sadock 2024). Two population features distinguish bipolar from unipolar disorder and are examined directly: the sex ratio in bipolar I is roughly **equal** between men and women, unlike the female excess of depression, and the age of onset is earlier, typically

in the **late teens to twenties**, with a frequently quoted mean around the early twenties (Kaplan & Sadock 2024). A first manic episode presenting for the first time in later life should prompt a search for a secondary (organic or substance-related) cause.

TRAP **Do not quote a Western prevalence as an Indian one.** The community surveys behind the 5% to 17% depression figure and the 1% bipolar I figure are largely Western; for India, cite the National Mental Health Survey, not a US or European number.

2:1	5% to 17%	about 1%	roughly equal
FEMALE-TO-MALE RATIO, DEPRESSION	LIFETIME PREVALENCE, MAJOR DEPRESSION	LIFETIME PREVALENCE, BIPOLAR I	SEX RATIO, BIPOLAR DISORDER

5.4 The unipolar versus bipolar epidemiological contrast

Three axes separate them. The population profiles of the two disorders diverge on prevalence, sex ratio and age of onset, and this triad is the crux of the topic (Kaplan & Sadock 2024). The clean contrast is worth holding as a grid, because a single swapped cell (calling the bipolar sex ratio female-predominant, or making depression the earlier-onset illness) is exactly the kind of error the exam punishes. The full clinical differentiation of bipolar from unipolar depression, temperament, episode shape and drug response, is taught in this chapter's unipolar-versus-bipolar-spectrum topic; here the axes are purely epidemiological.

AXIS	MAJOR DEPRESSIVE DISORDER (UNIPOLAR)	BIPOLAR DISORDER
Lifetime prevalence	**Higher, roughly 5% to 17%**	**Lower, about 1% for bipolar I; more for the spectrum**
Sex ratio	**Women to men about 2:1**	**Roughly equal**
Age of onset	Twenties to thirties, wide adult range	**Earlier: late teens to twenties**
Family history	Positive, but weaker loading than bipolar	Strong bipolar loading, highly heritable

The three epidemiological discriminators between unipolar and bipolar disorder. Read across the italicised cells: depression is commoner and female-skewed with later onset; bipolar is rarer, sex-equal and earlier (Kaplan & Sadock 2024).

5.5 Burden, comorbidity and mortality

A leading cause of disability, and a lethal illness. Mood disorders carry a burden out of proportion to their visibility. Depression is consistently ranked a **leading cause of years lived with disability** worldwide in the Global Burden of Disease analyses, and both depressive and bipolar disorders sit high on the disability tables because they are prevalent, recurrent and disabling during episodes (Kaplan & Sadock 2024). Comorbidity is the rule, not the exception: anxiety disorders and substance use disorders co-occur heavily with both depression and bipolar disorder, worsening course and outcome. Mortality has two strands the exam expects. The first is suicide: mood disorders, especially with mixed features or comorbid substance use, carry a markedly raised suicide risk, and a substantial share of completed suicides occur in people with a mood disorder. The second is cardiovascular and other physical mortality, so that people with

severe mood disorders, and bipolar disorder in particular, have a shortened life expectancy driven partly by cardiovascular and metabolic disease. The clinical assessment of suicide risk itself is developed in the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

PEARL

The mortality of a mood disorder is not only from suicide. The excess deaths in bipolar disorder are driven substantially by cardiovascular and metabolic disease, which is why physical-health monitoring is part of long-term care, not an afterthought (Kaplan & Sadock 2024).

5.6 The Indian picture and the treatment gap

Cite the National Mental Health Survey, and flag the gap. For Indian data the anchor source is the National Mental Health Survey of India 2015 to 2016 (Gururaj et al. 2016), conducted across twelve states by NIMHANS. It reported an overall **lifetime prevalence** of mental disorders of **13.7%** and a current (point) prevalence of **10.6%** (Kaplan & Sadock 2024). Depressive disorders were among the most prevalent categories identified, and bipolar disorder was found at a lower prevalence, consistent with the global unipolar-over-bipolar pattern. The survey's headline public-health finding is the enormous **treatment gap**: for mental disorders overall the gap runs in the region of **70% to 92%**, meaning the great majority of people with a diagnosable disorder receive no treatment (Kaplan & Sadock 2024). India also has fewer than the desirable number of psychiatrists, well short of the target of three per 100,000 population, which frames the service context in which mood disorders go untreated.

INDIA

Quote the National Mental Health Survey 2015 to 2016 (Gururaj et al. 2016) as the Indian anchor: overall lifetime prevalence of mental disorders 13.7%, current prevalence 10.6%, and a treatment gap of roughly 70% to 92% for mental disorders overall. Depressive disorders were among the most prevalent categories, and bipolar disorder was less prevalent, mirroring the global picture. The exact NMHS point estimates specific to depressive disorders and to bipolar affective disorder (the disorder-specific prevalence percentages, rather than the all-disorder totals) could not be verified from the parsed sources and are flagged under gaps; describe them as "depression among the commonest, bipolar less common" rather than quoting an unverified percentage. For severe, psychotic or treatment-resistant depression and for acute mania, electroconvulsive therapy is widely available and heavily used across Indian teaching hospitals, a point returned to in the management topics and the ECT and neurostimulation notes.

TRAP **Never present a US or European mood-disorder prevalence as the Indian figure.** For India the number to give is the National Mental Health Survey estimate and its treatment gap, not the Western 5% to 17% or 1% quoted for depression and bipolar I.

MNEMONIC

DEPRESSION IS FEMALE AND LATER, BIPOLAR IS EQUAL AND EARLIER

Depression: commoner (5% to 17%), Female-skewed (2:1), Later onset (twenties to thirties). Bipolar: rarer (about 1% for bipolar I), Equal sex ratio, Earlier onset (late teens to twenties). Two illnesses, opposite on sex and onset.

HOLD THIS

Major depression is common (lifetime roughly 5% to 17%), twice as common in women, and starts in the twenties to thirties; bipolar disorder is rarer (about 1% for bipolar I), has a roughly equal sex ratio, and starts earlier in the late teens to twenties, and for India you quote the National Mental Health Survey with its 70% to 92% treatment gap, never a Western number.

Depressive disorders: clinical syndromes

6 · Major depressive disorder

Why this matters. **Major depressive disorder** is the commonest severe mood diagnosis in the syllabus and the canonical home of the depressive-episode criteria: the psychotic-disorders notes cross-refer here for the depressive pole of schizoaffective disorder, so the criteria are taught here in full. The examiner tests three reflexes on **mdd**: the exact criterion set for a **depressive episode**, the specifier that reshapes prognosis and treatment, and the single move that keeps the diagnosis honest, screening every depression for a past hypomanic episode before the label is applied. Miss that screen and a bipolar depression is mislabelled unipolar and mistreated from the outset.

The structure to hold is a nesting: the **depressive episode** is the atom of criteria; **major depressive disorder** (ICD-11: single episode depressive disorder or recurrent depressive disorder) is the disorder built from one or more such episodes with no lifetime manic or hypomanic episode. Nosology is given ICD-11 primary with the DSM-5 (the DSM-5-TR) criteria cross-mapped, because the two manuals word the same episode slightly differently and that difference is itself examinable. The raw descriptive definitions of the individual mood symptoms and the rating scales are owned by the Psychometry, Assessment and Descriptive Psychopathology notes and cross-referenced here, not re-derived.

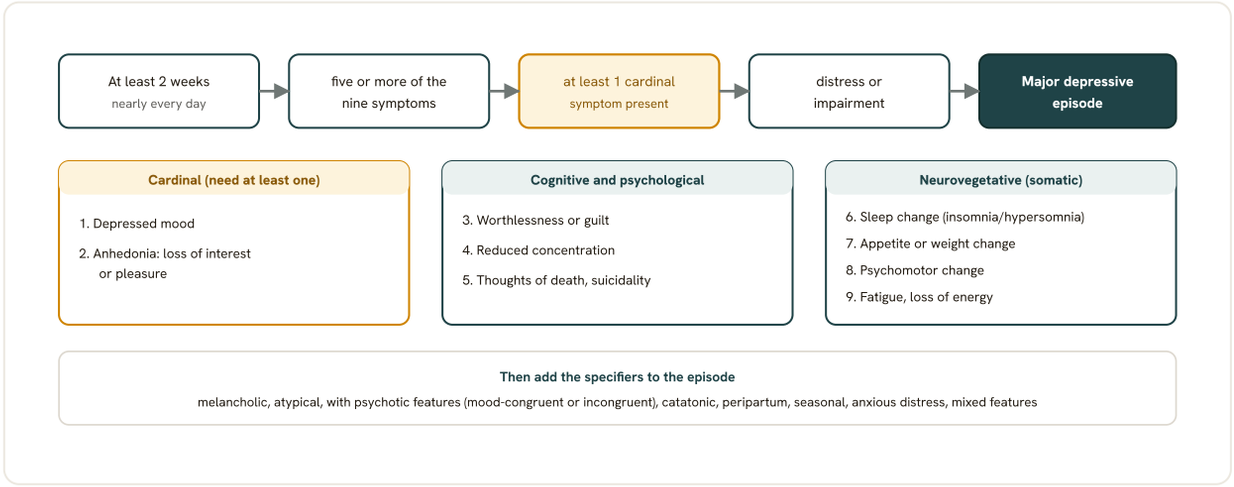

Fig 11.3 Major depressive disorder: the criteria gate and the specifier set. The episode needs at least two weeks, five or more of the nine symptoms including at least one cardinal symptom (depressed mood or anhedonia), and distress or impairment. The nine symptoms fall into a cardinal, a cognitive and psychological, and a neurovegetative cluster, and the diagnosed episode is then qualified with the specifiers.

6.1 The depressive episode: the two-week floor and the two cardinal symptoms

Every diagnosis in this family begins with a depressive episode, and the episode has a fixed duration floor. Both manuals require the symptom cluster to persist over the same period of **at least two weeks**, most of the day and nearly every day, representing a change from previous functioning (DSM-5-TR; ICD-11 CDDR). Within that window the episode is anchored on two **cardinal symptoms**: **depressed mood** (subjective sadness, emptiness or hopelessness, or observed tearfulness; in children and adolescents this may be irritability) and anhedonia, a markedly diminished interest or pleasure in all or almost all activities. DSM-5-TR requires that at least one of the five counted symptoms be one of these two cardinals; ICD-11 requires at least one symptom from its affective cluster, which carries the same two cardinals (DSM-5-TR; ICD-11 CDDR). This is the non-negotiable spine: two weeks, and at least one cardinal symptom present.

RULE **A major depressive episode needs at least two weeks and five of nine symptoms including one cardinal symptom.** No cardinal (depressed mood or anhedonia), no episode, however many other symptoms are counted.

6.2 The five of nine rule: the DSM-5-TR nine-symptom set

DSM-5-TR builds the episode from a count: the **five of nine** rule. Five or more of the following nine symptoms must have been present during the same two-week period, at least one being depressed mood or anhedonia (DSM-5-TR major depressive episode). The nine, verbatim in substance, are: (1) depressed mood; (2) markedly diminished interest or pleasure (anhedonia); (3) significant weight or appetite change (a change of more than **5% of body weight** in a month, or decreased or increased appetite); (4) insomnia or hypersomnia; (5) psychomotor agitation or retardation, observable by others; (6) fatigue or loss of energy; (7) feelings of worthlessness or excessive or inappropriate guilt, which may be delusional; (8) diminished ability to think, concentrate or decide; and (9) recurrent thoughts of death, recurrent suicidal ideation, or a suicide attempt or specific plan. The episode also requires clinically significant distress or impairment (criterion B) and is not attributable to a substance or another medical condition

(criterion C). The classic grouping the examiner rewards: two cardinal (mood, anhedonia), four neurovegetative (sleep, appetite or weight, energy, psychomotor), and three cognitive (worthlessness or guilt, concentration or indecision, and thoughts of death or suicidality).

at least 2 wk	5 of 9	1 cardinal	2:1
DEPRESSIVE EPISODE	DSM-5-TR SYMPTOM COUNT	MOOD OR ANHEDONIA REQUIRED	FEMALE-TO-MALE RATIO

WORKED EXAMPLE

A 34-year-old man reports three weeks of low mood and loss of interest in everything he used to enjoy, with early-morning waking, a 4 kg weight loss, fatigue, poor concentration and recurrent thoughts that his family would be better off without him. Count it: depressed mood and anhedonia (both cardinals), plus insomnia, weight loss, fatigue, concentration loss and death thoughts, which is seven of nine over more than two weeks, with impairment and no medical cause. This meets a major depressive episode. Now the mandatory next step, before the label major depressive disorder is written: screen the lifetime history for any past hypomanic or manic episode.

6.2b The ICD-11 wording and its small differences from DSM-5-TR

ICD-11 describes the same episode through **three symptom clusters** rather than a flat list of nine, and the reader should be able to name them (ICD-11 CDDR). The **affective cluster** carries depressed mood and anhedonia (the two cardinals) and, additionally, hopelessness about the future. The **cognitive-behavioural cluster** carries reduced concentration and indecisiveness, beliefs of low self-worth or excessive guilt (which may be delusional), and recurrent thoughts of death or suicidal ideation. The **neurovegetative cluster** carries disrupted or excessive sleep, appetite or weight change, psychomotor agitation or retardation, and reduced energy or fatigue. ICD-11 requires several symptoms present most of the day, nearly every day, for at least two weeks, with at least one from the affective cluster. The small differences that get examined: DSM-5-TR fixes a hard count of five of nine, whereas ICD-11 speaks of "several" symptoms across the clusters rather than a rigid arithmetic threshold; ICD-11 adds hopelessness as an explicit affective item; and both share the same two-week floor and the same cardinal anchoring. ICD-10 (F32, still cited in Indian exams) used a slightly different structure of core plus additional symptoms with a somatic syndrome specifier, and is flagged here.

TRAP **Do not diagnose major depressive disorder without excluding a past hypomanic episode.** A single unscreened hypomania in the history reclassifies the patient as bipolar type II, and the missed bipolarity changes first-line treatment entirely.

6.3 Severity grading and the with-psychotic-features distinction

Once an episode is confirmed, severity is graded as **mild, moderate or severe** on the number and intensity of symptoms and the impact on functioning (ICD-11 CDDR; DSM-5-TR). ICD-11 fixes a clean rule the examiner likes: a mild depressive episode by definition carries **no** psychotic symptoms, so psychosis can occur only in a moderate or severe episode (ICD-11 CDDR). The **with-psychotic-features** distinction then marks a moderate or severe episode as "with" or "without psychotic symptoms" (delusions or hallucinations). The classic depressive delusions are

mood-congruent and self-referential: guilt (falsely blaming oneself for wrongdoing), poverty or ruin, nihilistic delusions (Cotard-type beliefs that body organs or the self do not exist), and delusions of deserved punishment or impending disaster (ICD-11 CDDR; Kaplan & Sadock 2024). Perhaps 10% to 20% of depressed adults have psychotic symptoms, and psychotic depression carries a differential treatment response and a higher risk of progression to bipolar illness (Kaplan & Sadock 2024). The full handling of mood with psychotic features and the boundary with schizoaffective disorder is cross-referenced to the Other psychotic disorders, delusional syndromes and catatonia notes.

GOOD TO REMEMBER

- **Depressive episode:** low mood or anhedonia plus associated symptoms, most of the day nearly every day, for **at least two weeks**; DSM-5-TR requires **five of nine** including one cardinal.
- **Mild severity:** few symptoms above threshold, limited functional impact; by definition **no psychotic symptoms** (ICD-11).
- **Moderate severity:** intermediate symptom count and impairment; may be with or without psychotic symptoms.
- **Severe severity:** most symptoms present with marked impairment; may carry psychotic features; the number to hold is the psychotic-depression prevalence of roughly **10% to 20%** of depressed adults.

6.4 The specifiers: melancholic, atypical and mixed features

The specifiers refine a confirmed episode and steer prognosis and treatment; each is defined briefly here, with the fuller subtype detail owned by the next topic. Melancholic features require loss of pleasure or loss of reactivity to pleasurable stimuli, plus at least three of: depressed mood with a distinct quality of despair, mood worse in the morning, early-morning awakening, marked psychomotor change, significant anorexia or weight loss, and excessive guilt (DSM-5-TR; Kaplan & Sadock 2024). Atypical features are the mirror image, defined by **mood reactivity** plus at least two of: increased appetite or weight gain, hypersomnia, leaden paralysis, and a long-standing pattern of interpersonal rejection sensitivity; these reverse-vegetative signs carry an affinity with bipolar II, so atypicality should prompt a careful bipolar screen (DSM-5-TR; Akiskal 2007). Mixed features mark a depressive episode carrying at least three concurrent manic or hypomanic symptoms that do not themselves meet an episode threshold; it blurs the unipolar-bipolar boundary and flags heightened bipolar risk (DSM-5-TR; Kaplan & Sadock 2024).

6.5 The specifiers continued: psychotic, catatonic, peripartum, seasonal and anxious distress

The remaining specifiers complete the set. The **psychotic** specifier is split into **mood-congruent** psychotic features (delusions or hallucinations whose content fits the depressed mood, the guilt, poverty and nihilistic themes) and **mood-incongruent** features (content not consonant with depression, e.g. persecutory or thought-insertion themes), the incongruent pattern carrying a worse prognosis (DSM-5-TR; Kaplan & Sadock 2024). Catatonic features mark an episode dominated by the catatonic syndrome (stupor, mutism, negativism, posturing, waxy flexibility), with the catatonia entity itself owned by the Other psychotic disorders, delusional syndromes and catatonia notes. Peripartum onset applies when the episode begins during pregnancy or within four weeks of delivery in DSM-5-TR, with the wider perinatal frame cross-referenced to

the Perinatal/women's mental health and emergency psychiatry notes. Seasonal pattern marks a regular temporal relationship of episodes to a time of year (classically autumn-winter onset with spring remission). Anxious distress requires at least two of tension, restlessness, difficulty concentrating from worry, fear that something awful may happen, and fear of loss of control, and it predicts a worse course and higher suicide risk (DSM-5-TR).

SPECIFIER	DEFINING FEATURE	THE ONE DISCRIMINATOR TO HOLD
Melancholic	Loss of pleasure or reactivity plus 3 or more of despair, AM-worse mood, early waking, psychomotor change, anorexia or weight loss, guilt	**Non-reactive mood plus early-morning awakening and diurnal (AM-worse) variation**
Atypical	Mood reactivity plus 2 or more of hyperphagia or weight gain, hypersomnia, leaden paralysis, rejection sensitivity	**Reactive mood and reverse-vegetative signs; a bipolar-II red flag**
Mixed features	Depressive episode with 3 or more concurrent subthreshold manic or hypomanic symptoms	**Manic symptoms inside the depression; blurs into the bipolar spectrum**
Psychotic, mood-congruent	Delusions or hallucinations consonant with depression (guilt, poverty, nihilism)	Content fits the depressed mood
Psychotic, mood-incongruent	Delusions or hallucinations not consonant with depression (e.g. persecution, passivity)	**Incongruent content; worse prognosis**
Catatonic	Episode dominated by the catatonic syndrome (stupor, mutism, negativism, posturing)	Catatonia overlaid on the mood episode
Peripartum onset	Onset in pregnancy or within 4 weeks of delivery (DSM-5-TR)	**The four-week postpartum window (DSM-5-TR)**
Seasonal pattern	Regular seasonal timing of episodes (classically autumn-winter)	Temporal, not symptomatic, definition
Anxious distress	2 or more of tension, restlessness, worry-driven poor concentration, fear of something awful, fear of loss of control	**Predicts worse course and higher suicide risk**

The MDD specifier map: each specifier with its defining feature and the single discriminator to hold; the highlighted cell is the fact the examiner tests.

GOOD TO REMEMBER

- **Melancholic:** loss of pleasure or reactivity plus 3 or more classic features; the eponymic marker is non-reactive mood with early-morning awakening and AM-worse diurnal variation.
- **Atypical:** mood reactivity plus 2 or more reverse-vegetative signs (hyperphagia, hypersomnia, leaden paralysis, rejection sensitivity); the number to hold is 2 features, and it is a bipolar-II red flag.
- **Mixed features:** depressive episode with 3 or more concurrent subthreshold manic or hypomanic symptoms; flags bipolar risk.
- **Psychotic (mood-congruent vs incongruent):** congruent content fits the mood (guilt, poverty, nihilism); incongruent content carries a worse prognosis.
- **Catatonic:** episode dominated by the catatonic syndrome; the entity is owned by the psychotic-disorders and catatonia notes.
- **Peripartum:** onset in pregnancy or within **4 weeks** of delivery (DSM-5-TR).
- **Seasonal:** regular seasonal timing of episodes, classically autumn-winter onset with spring remission.
- **Anxious distress:** 2 or more anxiety items; predicts worse course and higher suicide risk.

6.6 Course concepts: single versus recurrent, relapse versus recurrence

Major depressive disorder is defined longitudinally as well as cross-sectionally. A first and only lifetime episode is single episode depressive disorder (DSM-5-TR: major depressive disorder, single episode); a history of at least two depressive episodes separated by several months of relative euthymia is recurrent depressive disorder (DSM-5-TR: recurrent). Two course words are examined and are not interchangeable: **relapse** is the return of symptoms of the same, still-active episode during the continuation window before full recovery, whereas **recurrence** is a genuinely new episode arising after a period of full recovery (Kaplan & Sadock 2024). This distinction drives the management phases: continuation treatment targets relapse of the index episode, while maintenance treatment targets recurrence of a new one. Recurrence is common: the majority of patients with a first major depressive episode will experience further episodes over a lifetime, and each additional episode raises the risk of the next.

6.7 Treatment-resistant depression as a course concept

Treatment-resistant depression is best held at this stage as a course concept, not a management algorithm. The working definition the examiner expects is failure to achieve adequate response after at least two antidepressant trials of adequate dose and duration within the current episode (Kaplan & Sadock 2024). It matters here because it reshapes prognosis and prompts a re-examination of the diagnosis itself (missed bipolarity, an unaddressed psychotic feature, a comorbidity, or non-adherence are the commonest reasons a depression appears resistant). The staged pharmacological approach to treatment-resistant depression, the augmentation and switching strategies, and the deep drug detail are owned by, and cross-referenced to, the Mood disorders: pharmacotherapy notes and are not duplicated here.

COMMON TRAP

Before labelling a depression "treatment-resistant", re-screen for a past hypomanic episode and for undetected psychotic features. A bipolar depression treated with antidepressant monotherapy, or a psychotic depression treated without an antipsychotic or ECT, will look resistant when the real error is a missed specifier or missed polarity, not true pharmacological resistance.

6.8 Suicide: the key risk, and the neuroendocrine correlate

Suicide is the dominant risk of major depressive disorder and the reason severity, psychotic features and anxious distress all matter clinically; recurrent thoughts of death and suicidality are one of the nine episode symptoms, and active suicidal ideation is common in a depressive episode where it is rare in normal grief (Kaplan & Sadock 2024). The structured clinical assessment of suicide risk and safety planning is owned by the Somatic-symptom, sexual, impulse-control disorders and suicide notes and cross-referenced here. One laboratory correlate is examined as a biological marker of the depressive state: the dexamethasone suppression test (DST). One milligram of dexamethasone is given orally at 11 PM and plasma cortisol measured the next day; a plasma cortisol above **5 micrograms per decilitre** (nonsuppression) is the abnormal, positive result, reflecting HPA-axis overactivity (Kaplan & Sadock 2024). Its limitation, and the reason it is not a diagnostic test, is its poor specificity: nonsuppression occurs in many other conditions, so a positive DST supports but never confirms a depressive diagnosis. The HPA-axis mechanics behind the test are owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the mood application is held here.

INDIA

Depressive disorders are among the commonest presentations in Indian outpatient psychiatry, and the National Mental Health Survey of India 2015 to 2016 (Gururaj et al. 2016) remains the anchor epidemiological source cited in the exams, with depressive disorders among the most prevalent categories it identified. For severe, psychotic or treatment-resistant depression, ECT is widely available and heavily used across Indian teaching hospitals; the ECT technique is owned by the ECT and neurostimulation notes. This chapter is largely generic and names no brand for major depressive disorder itself; drug branding, Indian brand first, belongs to the Mood disorders: pharmacotherapy notes.

6.9 Management pointer and the criteria-and-specifiers map

Management of major depressive disorder is taught guideline-first, led by the CANMAT recommendations with the Indian Psychiatric Society (the IPS guidelines) and NICE positions stated alongside, and organised by phase (acute, continuation, maintenance); the guideline-level headline to carry from the outset is a second-generation antidepressant plus an evidence-based psychotherapy first-line, with the full detail developed in the depression-management topic and cross-referenced there (CANMAT 2016). The whole diagnostic object of this topic assembles into a single map: the two-week floor and the two cardinal symptoms at the centre, the five of nine count around them, the three symptom groups (cognitive, neurovegetative and the worthlessness-guilt and suicidality items), the severity grading with the psychotic split, and the

ring of specifiers. That map is the concept figure for this topic, Fig 11.3, the MDD criteria and specifiers map.

MNEMONIC

SIG E CAPS (plus the two cardinals)

The eight neurovegetative and cognitive counters that sit around the two cardinal symptoms (depressed mood, anhedonia): **S**leep change, loss of **I**nterest (anhedonia, a cardinal), **G**uilt or worthlessness, **E**nergy loss or fatigue, **C**oncentration loss, **A**ppetite or weight change, **P**sychomotor change, and **S**uicidality. Count five or more over two weeks, with at least one cardinal, and the depressive episode is met.

HOLD THIS

A depressive episode is at least two weeks, five of nine symptoms, and at least one cardinal symptom (depressed mood or anhedonia); and no major depressive disorder is diagnosed until a past hypomanic or manic episode has been excluded.

7 · Persistent depressive disorder and double depression

Why this matters. **Persistent depressive disorder** is the low-intensity, high-chronicity end of the depressive spectrum, and the examiner tests it precisely because it is so easy to under-read. Where major depressive disorder is a break from the premorbid self that the patient can date to a month or a season, **dysthymia** is a chronically low mood that has become the background weather of the person's life, present most of the time for years and often mistaken for temperament rather than illness (Kaplan & Sadock 2024). The single reflex to build here is that the diagnostic principle is **chronicity, not severity**: a milder syndrome that is defined by its duration, carried by a fixed two-year floor.

Two named entities live in this topic and each ends with a good-to-remember line: **persistent depressive disorder** (the DSM-5 merger of chronic major depression and dysthymia, ICD-11 dysthymic disorder) and **double depression**, a major depressive episode breaking out on top of underlying dysthymia. Nosology is given ICD-11 primary with the DSM-5 (the DSM-5-TR) cross-mapped and ICD-10 flagged where Indian exams still use it. The raw descriptive definitions of the individual mood symptoms are owned by the Psychometry, Assessment and Descriptive Psychopathology notes and cross-referenced here, not re-derived; the deep pharmacology and treatment-resistance algorithms belong to the Mood disorders: pharmacotherapy notes.

7.1 The core criterion: chronic low mood for two years

The defining criterion of persistent depressive disorder is a chronic, low-grade depressed mood, present for most of the day, on more days than not, for a period of at least **two years** (in children and adolescents the mood may be irritable and the duration threshold falls to at least **one year**) (DSM-5-TR; ICD-11 CDDR). During that depressed period the patient must carry **two or more** associated depressive symptoms from a short list, and, crucially, must never have been symptom-free for more than **two months** at a time across the whole two-year span (DSM-5-TR). It is this "never free for more than two months" clause that makes the disorder persistent rather than

recurrent: the low mood is a near-continuous state, not a series of discrete episodes with clean euthymia between them.

RULE **Persistent depressive disorder is chronicity at lower intensity.** The diagnostic hallmark is duration, low mood for at least two years, never symptom-free for more than two months, not the depth of any one day.

7.2 The two-or-more symptoms and the associated features

Once the chronic low mood over two years is established, the diagnosis needs **two or more** of the associated symptoms present during the depressed period (DSM-5-TR; ICD-11 CDDR). The list is a compact, mostly neurovegetative and cognitive set: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions, and feelings of hopelessness. The syndrome must cause clinically significant distress or functional impairment, and the usual exclusions apply: it cannot be diagnosed if there has ever been a manic, hypomanic or mixed episode (which would move the patient to the bipolar side), and it is not better explained by a psychotic disorder, a substance, or another medical condition (DSM-5-TR; Kaplan & Sadock 2024).

Depressed mood

Low mood most of the day, more days than not, for at least two years; the anchoring criterion.

Two or more associated symptoms

Appetite change, sleep change, low energy, low self-esteem, poor concentration or indecision, hopelessness.

The two-month rule

Never symptom-free for longer than two months across the two-year span; this is what makes it persistent.

7.3 The DSM-5 merger and the ICD-11 dysthymic disorder

The nosological headline the examiner rewards is the **DSM-5 merger**: DSM-IV kept chronic major depressive disorder and dysthymic disorder as separate categories, and DSM-5 collapsed both into a single umbrella, persistent depressive disorder, on the reasoning that the two could not be reliably distinguished and predicted the same chronic course (DSM-5-TR; Kaplan & Sadock 2024). DSM-5-TR then re-captures the old distinctions through course specifiers, most importantly "with pure dysthymic syndrome" (full major-depressive criteria not met in the last two years) versus "with persistent major depressive episode" (full criteria met throughout the whole two-year period) and the two "intermittent major depressive episode" variants. ICD-11 does **not** merge: it keeps a discrete dysthymic disorder, defined as a persistent depressed mood lasting at least two years with additional depressive symptoms that do not meet the threshold for a depressive episode, and it stipulates that a depressive episode must not have been present during the first two years of the disturbance (ICD-11 CDDR). ICD-10 used the label dysthymia (F34.1) in the same spirit, and is flagged here because Indian exams still cite it.

SYSTEM	LABEL	STRUCTURAL STANCE
DSM-5-TR	Persistent depressive disorder	**Merges chronic MDD and dysthymia into one umbrella; old distinctions live on as course specifiers**
ICD-11	Dysthymic disorder	**Keeps it discrete; no depressive episode in the first two years**
ICD-10	Dysthymia (F34.1)	Persistent mild depression below episode threshold; still cited in Indian exams

The nosology map for persistent depressive disorder: DSM-5 merges, ICD-11 keeps dysthymic disorder discrete, and the highlighted cells are the discriminators the examiner tests.

at least 2 years	2 or more	at most 2 months
CHRONIC LOW MOOD FLOOR	ASSOCIATED SYMPTOMS	LONGEST SYMPTOM-FREE GAP

GOOD TO REMEMBER

- **Persistent depressive disorder:** chronic low-grade depressed mood for at least **two years** (one year in children and adolescents) with **two or more** depressive symptoms, never symptom-free for more than **two months**; the DSM-5 merger of chronic MDD and dysthymia, ICD-11 dysthymic disorder.
- **Dysthymia:** the older name for the same chronic sub-threshold depression; the one number to hold is the two-year floor, and ICD-11 requires no depressive episode in the first two years.

7.4 Double depression: a major depressive episode on underlying dysthymia

Double depression is the term for a **major depressive episode superimposed on underlying dysthymia** (or persistent depressive disorder), so that an acute episode erupts on a chronically depressed baseline and, on remitting, the patient returns not to euthymia but to the antecedent dysthymic floor (Kaplan & Sadock 2024). Kaplan & Sadock illustrate exactly this as one of the graphic courses of depression: recurrent major depression overlapping an underlying dysthymic disorder, with a return to that dysthymia between episodes. The clinical importance is the **incomplete inter-episode recovery**: because baseline is never normal mood, "recovery" from the acute episode still leaves residual depressive symptoms, and this is the mechanism behind its poorer prognosis. In the Collaborative Depression Study follow-up, patients with double depression had depressive symptoms roughly **three-quarters** of the time over follow-up (Judd et al. 1998, cited in Tasman), and double depression is listed as a marker of treatment resistance and of recurrence or relapse (Kaplan & Sadock 2024).

WORKED EXAMPLE

A 41-year-old woman describes feeling flat, tired and hopeless "for as long as I can remember, at least the last four years", never really well but coping. Over the past six weeks she has slid further: pervasive anhedonia, early-morning waking, a 5 kg weight loss, poor concentration and passive death wishes, now meeting full major-depressive-episode criteria. This is double depression: a major depressive episode on top of established dysthymia. The trap is to treat only the acute episode and, when the florid symptoms lift, to call her recovered, when in fact she has merely returned to her dysthymic baseline and remains at high risk of the next episode.

TRAP **Do not dismiss persistent depressive disorder as "just personality" and under-treat it.** The chronic low mood is a treatable illness, not a fixed trait; missing it, or stopping at partial recovery in double depression, leaves the patient chronically symptomatic and at high relapse risk.

GOOD TO REMEMBER

- **Double depression:** a major depressive episode superimposed on underlying dysthymia; the discriminating feature is incomplete inter-episode recovery (return to the dysthymic floor, not to euthymia), and the number to hold is symptoms roughly **three-quarters** of follow-up time, marking a poorer prognosis (Judd et al. 1998).

7.5 Clinical significance: high burden despite lower severity, and the management pointer

The paradox of persistent depressive disorder is a **high cumulative burden despite lower per-day severity**. Because the illness is chronic, its total load of impairment, its comorbidity (with anxiety disorders, substance use, and personality pathology) and its association with disability accrue over years even though no one day looks dramatic (Kaplan & Sadock 2024). Chronicity, not intensity, is the burden. On management, the one-line pointer is that persistent depressive disorder is treated with the same broad tools as major depression, combining pharmacotherapy with structured psychotherapy, with specifically chronic-depression-oriented psychotherapy (of the CBASP type) and antidepressants both used, and combined treatment often outperforming either alone; the detailed drug selection, dosing and treatment-resistance algorithms are owned by the Mood disorders: pharmacotherapy notes and are cross-referenced, not duplicated here (Kaplan & Sadock 2024).

PEARL

The single most useful discriminator at the bedside is the course shape: major depression is an *episode* the patient can date to a month or a season and from which they return to their usual self; dysthymia is a *trait-like* chronic low mood that has become their normal, and double depression is the episode breaking out on that chronic floor and sinking back into it.

HOLD THIS

Persistent depressive disorder is depression defined by duration, not depth: low mood for at least two years, never symptom-free for more than two months; a major depressive episode on that dysthymic baseline is double depression, and its chronicity, incomplete recovery and comorbidity are the burden.

8 · The depressive subtypes

Why this matters. Once a **depressive episode** is confirmed, the examiner tests whether the reader can read its **clinical shape**: the same five-of-nine episode splits into recognisable subtypes that carry different biology, different prognosis and, downstream, different treatment. This topic is the keyed grid of those subtypes. Four earn their own line and their own keyword: **melancholic** depression, **atypical depression**, **psychotic depression** and **catatonic depression**. Each is a DSM-5-TR specifier applied to an episode whose core criteria are owned by the major depressive disorder topic and cross-referenced here, not re-derived; the raw descriptive definitions of the individual mood symptoms are owned by the Psychometry, Assessment and Descriptive Psychopathology notes.

The single organising axis to carry through the whole grid is **mood reactivity**. Melancholic depression loses it; atypical depression keeps it. That one contrast, non-reactive versus reactive mood, is the pivot the examiner returns to, and it maps onto the older endogenous-versus-neurotic split and onto the more biological versus more bipolar-spectrum poles of the depressive syndrome (Kaplan & Sadock 2024; Akiskal 2007). Psychotic and catatonic depression then layer a second dimension on top, the presence of psychosis or of the catatonic syndrome, marking the most severe end of the range.

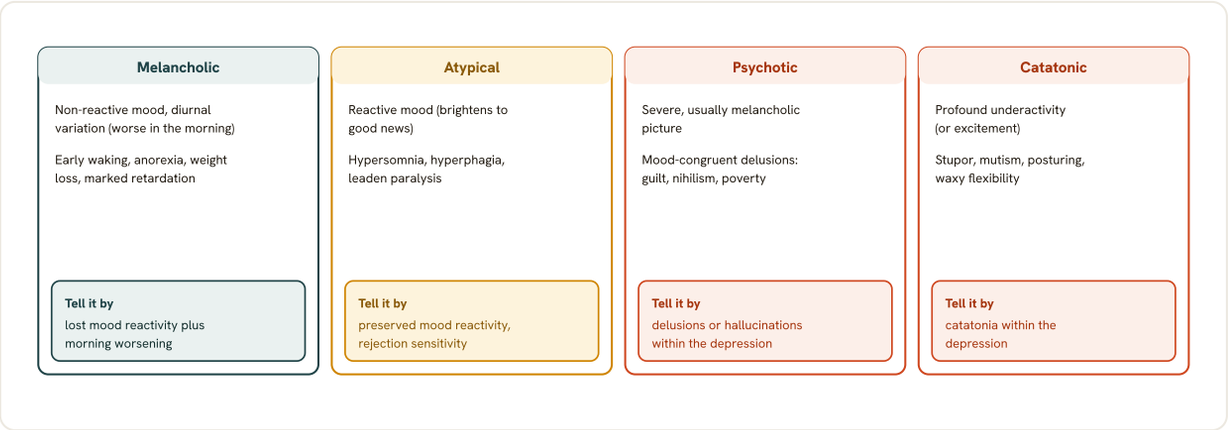

Fig 11.4 The depressive subtypes, keyed on the one feature that tells each apart. The pivotal contrast is mood reactivity: melancholic depression loses it (with morning worsening and early waking), atypical depression keeps it (with reversed vegetative signs and rejection sensitivity). Psychotic depression adds mood-congruent delusions, and catatonic depression adds catatonic signs within the episode. The catatonia entity itself is developed in the Other psychotic disorders, delusional syndromes and catatonia notes.

8.1 Melancholic depression: the non-reactive, more biological picture

Melancholic depression (DSM-5-TR: **with melancholic features**; the older term is endogenous depression) is the classic severe, biological presentation. The DSM-5-TR specifier has a two-part structure the reader should be able to reproduce (DSM-5-TR; Kaplan & Sadock 2024). Criterion A requires **one** of: loss of pleasure in all or almost all activities, or a lack of reactivity to usually pleasurable stimuli (mood does not brighten even temporarily when something good happens). Criterion B then requires **three or more** of six features: a distinct quality of depressed mood (profound despondency, despair, moroseness, or an empty mood, experienced as qualitatively different from ordinary sadness); depression regularly worse in the morning, the diurnal variation; early-morning awakening at least **2 hours** before the usual time; marked psychomotor

agitation or retardation observable by others; significant anorexia or weight loss; and excessive or inappropriate guilt. The signature to hold is the cluster: non-reactive mood plus a distinct quality of mood, plus the AM-worse diurnal variation and early-morning waking, plus marked psychomotor change, anorexia and weight loss and excessive guilt. Melancholia is more frequent in inpatients than outpatients, in more severe rather than milder episodes, and in episodes carrying psychotic features (DSM-5-TR).

RULE **Melancholic loses mood reactivity; atypical keeps it. Reactivity is the pivot.** A non-reactive mood with a distinct quality, morning worsening and early waking points melancholic; a mood that still brightens to good events points away from it.

GOOD TO REMEMBER

- **Melancholic depression:** the non-reactive, more biological depression; DSM-5-TR needs loss of pleasure or loss of reactivity plus **3 or more** of distinct-quality mood, AM-worse diurnal variation, early-morning awakening, marked psychomotor change, anorexia or weight loss, and excessive guilt; the one discriminating feature to hold is **non-reactive mood** with early-morning awakening.

8.2 Atypical depression: reactive mood and the reverse-vegetative signs

Atypical depression (DSM-5-TR: **with atypical features**) is the mirror image, and its name is historical rather than a claim of rarity: it is atypical only in contrast to the classical agitated, endogenous presentations that were the norm when depression was rarely diagnosed in outpatients (DSM-5-TR). Criterion A is the defining feature, **mood reactivity**, the capacity for mood to brighten in response to actual or potential positive events, sometimes to euthymia for extended periods if circumstances stay favourable. Criterion B then requires **two or more** of four features: significant weight gain or increased appetite (hyperphagia); hypersomnia (an extended night sleep or daytime napping totalling at least 10 hours a day, or at least 2 hours more than when well); leaden paralysis, a heavy, leaden or weighted-down feeling usually in the arms or legs; and a long-standing pattern of interpersonal rejection sensitivity that is present whether or not the person is depressed and causes real social or occupational impairment (DSM-5-TR). This last feature is a trait with early onset that persists through adult life, which is why it is long-standing rather than episode-bound. Criterion C requires that the episode not meet criteria for melancholic features or catatonia in the same episode: the two are defined as mutually exclusive.

Two downstream facts are examinable. First, atypical features carry an affinity with the **bipolar spectrum**: the reverse-vegetative signs of hypersomnia and hyperphagia are overrepresented in bipolar II depression, so an atypical picture should prompt a careful screen for a past hypomanic episode (DSM-5-TR bipolar II text; Akiskal 2007). Second, the historical anchor: atypical depression was defined by the Columbia group precisely because these patients responded to MAOIs where they responded poorly to tricyclics, phenelzine outperforming imipramine and placebo in their trials (Kaplan & Sadock 2024). The drug detail is cross-referred forward to the Mood disorders: pharmacotherapy notes; here only the responsiveness pattern is held.

TRAP **Do not dismiss reversed vegetative signs as "not real depression".** Hypersomnia and hyperphagia are the core of a defined subtype (atypical depression), not evidence against a mood disorder; reading them as trivial misses a bipolar-spectrum red flag.

GOOD TO REMEMBER

- **Atypical depression:** depression with **preserved mood reactivity** plus **2 or more** of hyperphagia or weight gain, hypersomnia, leaden paralysis, and long-standing rejection sensitivity; associated with the bipolar spectrum; the eponymic anchor to hold is the historical **MAOI** responsiveness (Columbia group).

8.3 Psychotic depression: a depressive episode with delusions or hallucinations

Psychotic depression (DSM-5-TR: **with psychotic features**) is a major depressive episode in which delusions or hallucinations are present at any time during the episode. It is a marker of severity, not a separate disorder, and it can occur in the context of both unipolar and bipolar depression (Maudsley 2021). The psychotic content is usually **mood-congruent**: the delusions and hallucinations track typical depressive themes of personal inadequacy, guilt, disease, death, nihilism (the Cotard-type belief that organs or the self do not exist, or that one is dead), poverty or ruin, and deserved punishment or impending disaster (DSM-5-TR; Kaplan & Sadock 2024). Sometimes the content is **mood-incongruent**, not consonant with depression (for example persecutory or passivity themes, or a mixture); the incongruent pattern carries a worse prognosis. Psychotic depression has a lifetime prevalence of roughly **1%**, is frequently under-diagnosed, and carries greater illness severity, longer episodes, poorer long-term outcome and a substantially higher suicide risk than non-psychotic depression (Maudsley 2021).

The boundary that must be drawn cleanly is against schizoaffective disorder and the wider mood-with-psychosis territory: when psychotic and mood symptoms are present the rule is whether the psychosis is confined to the mood episode (mood disorder with psychotic features) or extends beyond it. That whole mood-with-psychotic-features boundary and the schizoaffective decision are owned by the Other psychotic disorders, delusional syndromes and catatonia notes and cross-referred there. The management, which differs from non-psychotic depression, is an antidepressant plus an antipsychotic, or electroconvulsive therapy; the guideline-level detail is a pointer to the Mood disorders: pharmacotherapy notes and the ECT technique to the ECT and neurostimulation notes.

PEARL

Psychotic depression needs a different treatment from non-psychotic depression and is commonly missed because clinicians do not ask about mood-congruent delusions of guilt, poverty or nihilism. An antidepressant alone under-treats it; the evidence-based options are an antidepressant plus an antipsychotic, or ECT, developed in the Mood disorders: pharmacotherapy notes.

GOOD TO REMEMBER

- **Psychotic depression:** a major depressive episode **with delusions or hallucinations**, usually mood-congruent (guilt, nihilism, poverty, deserved punishment), sometimes incongruent (worse prognosis); the number to hold is a lifetime prevalence near **1%**, and it is treated with an antidepressant plus an antipsychotic or with ECT.

8.4 Catatonic depression: a depressive episode with catatonia

Catatonic depression (DSM-5-TR: **with catatonia**) is a depressive episode dominated by the catatonic syndrome, coded in DSM-5-TR with an additional catatonia code. Clinically it presents with the catatonic signs overlaid on the mood episode: stupor, mutism, negativism, posturing, waxy flexibility, and in the extreme a depressive stupor. It sits at the severe, biological end of the depressive range alongside melancholia and psychosis. The catatonia entity itself, its full sign list, its differential across mood, psychotic and organic causes, and its management (the benzodiazepine challenge and ECT), is owned by the Other psychotic disorders, delusional syndromes and catatonia notes and is cross-referred there; the catatonic-depression subtype, catatonia arising specifically within a depressive episode, is owned here.

GOOD TO REMEMBER

- **Catatonic depression:** a depressive episode **with catatonia** (stupor, mutism, negativism, posturing, waxy flexibility), the most severe motor pole of depression; the catatonia entity is cross-referred to the psychotic-disorders and catatonia notes, the subtype is owned here.

8.5 The keyed subtypes grid

The four named subtypes assemble into a single keyed grid, each row carrying its defining feature and the one discriminator the examiner tests. Read down the reactivity axis first (melancholic non-reactive, atypical reactive), then the psychosis and catatonia layer on top.

SUBTYPE	DEFINING FEATURE	THE ONE DISCRIMINATOR TO HOLD
Melancholic depression	Loss of pleasure or loss of reactivity, plus 3 or more of distinct-quality mood, AM-worse variation, early-morning awakening, marked psychomotor change, anorexia or weight loss, excessive guilt	**Non-reactive mood with early-morning awakening and AM-worse diurnal variation; the more biological picture**
Atypical depression	Mood reactivity preserved, plus 2 or more of hyperphagia or weight gain, hypersomnia, leaden paralysis, long-standing rejection sensitivity	**Reactive mood plus reverse-vegetative signs; bipolar-spectrum affinity; historical MAOI responsiveness**
Psychotic depression	Major depressive episode with delusions or hallucinations, usually mood-congruent (guilt, poverty, nihilism, deserved punishment)	**Presence of psychosis; needs antidepressant plus antipsychotic, or ECT; lifetime prevalence near 1%**

SUBTYPE	DEFINING FEATURE	THE ONE DISCRIMINATOR TO HOLD
Catatonic depression	Depressive episode dominated by the catatonic syndrome (stupor, mutism, negativism, posturing, waxy flexibility)	**Catatonia overlaid on the mood episode; entity cross-referred, subtype owned here**

The depressive-subtypes grid: each named subtype with its defining feature and the single discriminator to hold; the highlighted cell is the fact the examiner tests. This is the concept figure for this topic, Fig 11.4.

3 of 6 MELANCHOLIC B-FEATURES	**2 of 4** ATYPICAL B-FEATURES	**about 1%** PSYCHOTIC DEPRESSION LIFETIME	**2 hours** EARLY-MORNING AWAKENING

WORKED EXAMPLE

A 52-year-old woman has three weeks of severe low mood that does not lift even when her grandchildren visit, wakes at 4 AM (about 2 hours early), feels worst in the mornings, is visibly slowed, has lost 5 kg and voices intense guilt about being a burden. The non-reactive mood, early-morning awakening, AM-worse diurnal variation, psychomotor retardation, weight loss and guilt read as melancholic depression. Contrast a 28-year-old man whose mood still brightens when friends call, who sleeps 11 hours, eats more than usual, describes his legs as leaden, and has a lifelong hypersensitivity to rejection: preserved reactivity plus two reverse-vegetative features read as atypical depression, and prompt a screen for a past hypomanic episode.

MNEMONIC

Melancholic goes DOWN, Atypical goes UP

Melancholic runs the vegetative signs **down**: appetite and weight down (anorexia), sleep down (early-morning awakening), mood down and non-reactive. Atypical runs them **up**: appetite up (hyperphagia), sleep up (hypersomnia), and mood still able to lift (reactive). The reverse-vegetative direction, plus preserved reactivity, is the whole of the atypical picture.

HOLD THIS

Melancholic depression loses mood reactivity (with a distinct-quality mood, AM-worse variation, early-morning awakening at least 2 hours early); atypical depression keeps mood reactivity (with hyperphagia, hypersomnia, leaden paralysis, rejection sensitivity); psychotic depression adds mood-congruent delusions and catatonic depression adds the catatonic syndrome.

9 · Seasonal affective disorder and chronobiology

Why this matters. **Seasonal affective disorder** is a small-print but reliably examined corner of the mood block, and it is examined for a precise reason: it is not a separate disorder but a course specifier, and the discriminator is temporal, not symptomatic. The reflex the examiner rewards is that a **seasonal pattern** requires a regular relationship between mood episodes and a time of year across several years, not a single bad winter. Around it sits the **chronobiology** of mood, the clearest worked example in psychiatry of a circadian mechanism translated into a diagnosis and a physical treatment.

The mechanics of the master clock, the suprachiasmatic nucleus and the molecular clock genes are owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the raw descriptive definitions of the mood symptoms are owned by the Psychometry, Assessment and Descriptive Psychopathology notes. Held here is the mood application: how disrupted **circadian** and sleep-wake rhythms feed seasonal and non-seasonal relapse, and how **light therapy** exploits that biology. The deep drug detail and chronotherapy pharmacology are cross-referred to the Mood disorders: pharmacotherapy notes.

9.1 Seasonal affective disorder and the seasonal pattern specifier

Seasonal affective disorder (SAD), the term introduced by Rosenthal and colleagues, describes recurrent depressive episodes with a regular seasonal onset and remission, classically an autumn-winter onset with spring-summer recovery (Kaplan & Sadock 2024; Companion 2010). Both manuals code it not as a distinct entity but as a course specifier on a recurrent mood disorder: DSM-5-TR calls it **with seasonal pattern**, ICD-11 codes it as with seasonal pattern of mood episode onset (6A80.4), and each can attach to recurrent depressive disorder or to bipolar disorder (DSM-5-TR; ICD-11 CDDR). The DSM-5-TR requirement is the crux and is worth holding precisely: a regular temporal relationship between the onset of episodes and a particular time of year, full remission (or a switch to the opposite pole) also at a characteristic time of year, this pattern present for at least the last **two years** with no non-seasonal episodes in that period, and seasonal episodes substantially outnumbering any non-seasonal episodes over the lifetime (DSM-5-TR). The winter episodes carry a characteristic symptom skew toward **atypical features**: hypersomnia, hyperphagia with carbohydrate craving, weight gain, leaden fatigue and low mood, rather than the insomnia and anorexia of melancholia (Kaplan & Sadock 2024; Companion 2010). Prevalence rises with latitude, a correlation used as circumstantial evidence for a light-dependent mechanism (New Oxford 2020).

RULE **A seasonal pattern is defined by a regular temporal relationship across years, not by symptoms in one winter.** DSM-5-TR needs the pattern over at least the last two years with no intervening non-seasonal episodes, and seasonal episodes outnumbering non-seasonal ones lifetime.

TRAP **Do not label any winter low mood as SAD.** A single dark-month dip, or a depression that merely happens to fall in winter once, is not a seasonal pattern; the specifier is refused unless the temporal regularity is documented across years and non-seasonal episodes are effectively absent.

9.2 The summer pattern and the differential

The autumn-winter form dominates, but a less common **summer pattern** exists, with episodes beginning in spring or summer and remitting in autumn or winter; it tends to carry the reverse profile of insomnia, reduced appetite, weight loss and agitation rather than the atypical reverse-vegetative signs of winter SAD (DSM-5-TR; Kaplan & Sadock 2024). Two differentials keep the diagnosis honest. First, a mood disturbance that recurs each year because of a recurring psychosocial stressor tied to a season, for example a predictable seasonal workload or an anniversary reaction, is explicitly excluded: the specifier does not apply where the seasonality

reflects a season-linked stressor rather than an endogenous pattern (DSM-5-TR; Shorter Oxford 2018). Second, the very status of SAD as a discrete syndrome has been questioned, since some community studies fail to confirm a specific winter-depression syndrome and instead find a milder general seasonality of mood in the population; the specifier remains, but the reader should know the construct is not uncontested (Companion 2010).

9.3 Chronobiology and the circadian theories of mood

Chronobiology is the study of biological rhythms, and circadian rhythms, with a period of about a day, are entrained to the light-dark cycle by the suprachiasmatic nucleus acting on time cues (zeitgebers), the most powerful of which is light (Kaplan & Sadock 2024). Two overlapping hypotheses connect this to seasonal depression. The **reduced-light hypothesis** holds that the shorter photoperiod of winter, less light reaching the retina and the suprachiasmatic nucleus, drives the winter episode, which fits the latitude gradient and the response to added bright light (New Oxford 2020; Kaplan & Sadock 2024). The **phase-shift hypothesis** (Lewy and colleagues) is more specific: it proposes that in winter SAD the internal circadian clock, and in particular the timing of nocturnal melatonin secretion, drifts into a phase delay relative to the sleep-wake cycle, and that correctly timed morning bright light works by **phase-advancing** the clock back into alignment (Kaplan & Sadock 2024). Melatonin, synthesised from serotonin and secreted at night by the pineal under suprachiasmatic control, is the central rhythm signal, and its mistimed secretion is the mechanistic hinge of the phase-shift account (New Oxford 2020).

> **PEARL**
>
> The phase-shift hypothesis predicts the clinical instruction. If winter SAD is a phase-delayed clock, then light must be given in the **morning** to phase-advance it; morning bright light is more effective than evening light in most trials, and this timing logic, not the raw brightness alone, is the examinable point (Kaplan & Sadock 2024).

9.4 Social rhythm disruption and circadian relapse in both poles

Beyond the seasonal case, disrupted rhythms feed relapse across the mood disorders, and the framework the examiner names is the social rhythm disruption model of Ehlers, Frank and colleagues. The claim is that regular daily **social zeitgebers**, consistent bedtimes, mealtimes and first daily social contact, stabilise the underlying circadian and sleep-wake rhythm, and that a life event which disrupts these social rhythms (bereavement, shift work, a transmeridian flight, a new infant) destabilises the biological rhythm and can precipitate a mood episode (Kaplan & Sadock 2024). In bipolar disorder the link is sharpest at the manic pole: sleep loss and circadian disruption can trigger the rapid onset of mania, which is why protecting sleep and regularising routine is central to relapse prevention (New Oxford 2020). This is the rationale for interpersonal and social rhythm therapy (IPSRT), which combines interpersonal psychotherapy with behavioural stabilisation of the daily schedule to smooth social rhythms and lengthen time to relapse; the psychotherapy detail itself sits with management, but the mechanism belongs here (Frank et al.; Kaplan & Sadock 2024).

HOLD THIS

Seasonal affective disorder is a course specifier, not a separate disorder: a regular seasonal onset and remission across at least two years, a winter form skewed to atypical features, explained by a phase-delayed circadian clock, and treated first-line with morning bright light.

9.5 Light therapy: the first-line pointer for seasonal depression

Light therapy (phototherapy) is the established first-line treatment for winter seasonal depression: daily exposure to **bright light, typically in the morning**, using a light box delivering of the order of **10,000 lux** for about 30 minutes, or lower intensities such as 5,000 lux for longer, timed to phase-advance the delayed clock (Kaplan & Sadock 2024; Shorter Oxford 2018). It is best evidenced in SAD with atypical winter features and has also shown benefit in non-seasonal depression (Tasman 2015). It is generally well tolerated; the main cautions are theoretical switch risk in bipolar patients and eye considerations, and its overall specificity over dim-light control has at times been hard to disentangle from placebo, so the reader should present it as first-line but not miraculous (Companion 2010; New Oxford 2020). The comparative drug choice for seasonal depression, notably the SSRI and agomelatine options and the use of chronotherapeutic techniques such as sleep-phase advance and adjunctive melatonin, is cross-referred to the Mood disorders: pharmacotherapy notes and given at guideline level only there.

at least 2 yr	10,000 lux	morning
DSM-5-TR SEASONAL PATTERN	STANDARD LIGHT-BOX DOSE	TIMING TO PHASE-ADVANCE

INDIA

Classic winter seasonal affective disorder is far less prominent in Indian practice than in high-latitude countries, consistent with the latitude gradient: most of India lies in low latitudes with a small seasonal photoperiod swing, so the syndrome is uncommon and light therapy is a niche rather than a routine tool in Indian psychiatry. This chapter names no brand for it; drug branding, Indian brand first, belongs to the Mood disorders: pharmacotherapy notes.

GOOD TO REMEMBER

- **Seasonal affective disorder:** recurrent depression with regular seasonal onset and remission; it is a **course specifier** (DSM-5-TR: with seasonal pattern; ICD-11 6A80.4), not a separate disorder; the number to hold is the DSM-5-TR requirement of the pattern over at least the last **two years** with no non-seasonal episodes.
- **Winter (autumn-winter) pattern:** the common form; the discriminating feature is **atypical** symptoms, hypersomnia, hyperphagia and carbohydrate craving; the eponym to hold is Rosenthal.
- **Summer pattern:** the uncommon form; spring or summer onset with the reverse profile of insomnia, poor appetite, weight loss and agitation.
- **Phase-shift hypothesis:** winter SAD as a phase-**delayed** circadian clock with mistimed melatonin; the eponym is Lewy, and it predicts that **morning** light corrects it.
- **Social rhythm disruption model:** loss of regular social zeitgebers destabilises the circadian rhythm and precipitates episodes; the names are Ehlers and Frank, and the therapy is IPSRT.
- **Light therapy:** first-line for winter SAD; bright light, morning, of the order of **10,000 lux**; well tolerated but of debated specificity over dim-light control.

10 · Peripartum and postpartum depression

Why this matters. A depressive episode arising around childbirth is one of the highest-yield mood-syndrome vignettes in the exam, because it packages three separable things the examiner wants you to keep apart: a genuine mood disorder carrying a course specifier, a benign self-limited adjustment (the blues), and a psychiatric emergency (postpartum psychosis). The single reflex being tested is that **peripartum** is a *specifier on a mood episode*, not a free-standing diagnosis, and that behind the soft label "postnatal depression" may hide a bipolar depression or an evolving psychosis that changes management completely.

Hold the terminology first. **Peripartum** (use "peripartum") is the DSM-5-TR onset window; **postpartum depression** (use "postpartum depression"), also called **postnatal depression** (use "postnatal depression"), is the clinical entity of a depressive episode after delivery. This topic owns the perinatal *mood* syndrome and its screening and management pointer; the wider perinatal frame (perimenopause, perinatal anxiety, the obstetric liaison picture) is cross-referenced to the Perinatal/women's mental health and emergency psychiatry notes, and postpartum psychosis proper is owned by the Other psychotic disorders, delusional syndromes and catatonia notes. The raw descriptive definitions of the depressive symptoms and the rating scales are owned by the Psychometry, Assessment and Descriptive Psychopathology notes.

10.1 The entity: a depressive episode with a peripartum-onset specifier

There is no separate criterion set for "postpartum depression": the depressive episode is diagnosed by the standard criteria (taught in full in the major depressive disorder topic), and childbirth is captured by a peripartum-onset specifier. In DSM-5-TR the specifier "with peripartum onset" applies when the onset of mood symptoms occurs during pregnancy or in the **4 weeks** following delivery (DSM-5-TR). The manual deliberately uses "peripartum" rather than "postpartum" because about **50%** of postpartum major depressive episodes actually begin before delivery, so pregnancy-onset and delivery-onset episodes are grouped together (DSM-5-TR). Clinically the episode often declares itself within the first months rather than the first four weeks, which is why the strict specifier window and the looser clinical reality are both examinable.

RULE **Peripartum is a specifier, not a diagnosis.** Diagnose the depressive episode on standard criteria, then add "with peripartum onset" if it began in pregnancy or within four weeks of delivery (DSM-5-TR).

10.2 ICD-11 nosology and the ICD-10 flag

ICD-11 handles the perinatal picture differently: it does not use an onset specifier but provides a grouping, **6E20** mental and behavioural disorders associated with pregnancy, childbirth or the puerperium **without psychotic symptoms**, and **6E21** the same **with psychotic symptoms**, applied when a mood (or other mental) syndrome arises during pregnancy or within about **6 weeks** after delivery and cannot be better classified elsewhere (ICD-11 CDDR). Note the small discriminator the examiner likes: the DSM-5-TR window is **4 weeks** postpartum, whereas the ICD-11 puerperal window is roughly **6 weeks**. ICD-10 (F53, mental and behavioural disorders

associated with the puerperium not elsewhere classified, still cited in Indian exams) is flagged here. Nosology is given ICD-11 primary with DSM-5-TR cross-mapped.

SYSTEM	HOW CHILDBIRTH IS CODED	THE ONSET WINDOW TO HOLD
DSM-5-TR	Course specifier "with peripartum onset" on the mood episode	**Pregnancy or within 4 weeks of delivery**
ICD-11	6E20 (without psychotic symptoms) / 6E21 (with psychotic symptoms)	**Pregnancy or about 6 weeks after delivery (puerperium)**
ICD-10	F53 puerperal mental disorders not elsewhere classified (exam legacy)	Puerperium (flagged for older exams)

How each system codes a peripartum mood episode; the highlighted cells are the two onset windows the examiner contrasts.

10.3 The three-way distinction: blues versus depression versus psychosis

The core discrimination of this topic is a three-way one, and getting it right is the whole exam point. The postpartum blues (maternity blues, "baby blues") is **not a mental disorder**: sudden mood changes, tearfulness in the absence of true depression, mild sleep disturbance and even transient confusion, with **no functional impairment**, appearing in the first days after delivery and self-limiting, typically improving within a week without treatment (DSM-5-TR). It is common, affecting a large proportion of new mothers. **Postpartum depression** is a full depressive episode with the standard duration and symptom threshold, causing impairment and needing treatment. Postpartum psychosis is a separate psychiatric emergency, typically resembling a manic or mixed episode with psychotic features, strongly associated with bipolar I disorder, of sudden onset in the first days to weeks, carrying a rare but real risk of infanticide when driven by command hallucinations to harm the infant or delusions that the infant is possessed (DSM-5-TR). The entity itself is owned by the Other psychotic disorders, delusional syndromes and catatonia notes; it is contrasted here because the whole safety of the topic turns on not mistaking one for another.

FEATURE	POSTPARTUM BLUES	POSTPARTUM DEPRESSION	POSTPARTUM PSYCHOSIS
Status	Not a disorder; physiological	Mood disorder (depressive episode)	**Psychiatric emergency**
Typical onset	First few days postpartum	Within weeks to first months (peripartum window)	**First few days to 2 weeks, abrupt**
Duration	Self-limited, resolves within a week	Persistent, meets episode threshold	Rapidly progressive without treatment
Impairment	None	Present	Severe
Psychosis	Absent	Absent (unless severe with psychotic features)	**Defining; command hallucinations, delusions about the infant**

FEATURE	POSTPARTUM BLUES	POSTPARTUM DEPRESSION	POSTPARTUM PSYCHOSIS
Core association	Physiological postpartum change	Past depression, poor support	**Bipolar I disorder**
Action	Reassurance, watchful waiting	Screen, treat, safeguard	Urgent admission, treat as emergency

The three-way peripartum differential; the highlighted cells carry the discriminators that separate an emergency from an illness from a normal adjustment.

TRAP **Do not let "postnatal depression" hide a bipolar depression or an evolving postpartum psychosis.** An abrupt, fluctuating, psychotic or manic-tinged postpartum presentation is an emergency, not a low mood; always ask about past hypomania before you reach for an antidepressant.

10.4 Epidemiology and the prevalence numbers to hold

Perinatal depression is common, not rare. Postpartum depression occurs in approximately **15%** of women (Tasman 2015). DSM-5-TR frames the risk temporally: about **9%** of women will experience a major depressive episode between conception and birth, and the best estimate for a major depressive episode between birth and 12 months postpartum is just below **7%** (DSM-5-TR). Postpartum psychosis is far rarer, occurring in roughly **1 in 500 to 1 in 1,000** deliveries and more common in primiparous women (DSM-5-TR).

~15%	4 weeks	~50%	1 in 500 to 1,000
POSTPARTUM DEPRESSION PREVALENCE	DSM-5-TR PERIPARTUM WINDOW	OF POSTPARTUM MDES BEGIN BEFORE DELIVERY	POSTPARTUM PSYCHOSIS (DELIVERIES)

10.5 Risk factors and the recurrence figures

The risk factors cluster into psychiatric history, social support and obstetric or psychosocial stress. The strongest is a **past depressive or bipolar illness**: women with a history of major depression carry a **10% to 25%** risk of an episode of postpartum depression (Tasman 2015). A prior postpartum depression is the single most predictive marker, carrying about a **50%** risk of another episode with subsequent births, which makes eliciting that history essential (Tasman 2015). The other established risks are **poor social support** (an unsupportive partner, isolation), and **obstetric and psychosocial stressors** (a difficult delivery, an unwell or unwanted infant, poverty, marital conflict, and life events around the birth). For postpartum psychosis specifically, once a woman has had a psychotic postpartum episode the recurrence risk with each subsequent delivery is between **30% and 50%**, and a personal or family history of bipolar I disorder markedly raises the risk (DSM-5-TR).

RULE **Ask about the last delivery.** A prior postpartum depression carries roughly a 50% recurrence risk with the next birth, and a prior postpartum psychosis carries a 30% to 50% recurrence risk; the obstetric psychiatric history is the highest-yield question you can ask.

10.6 Impact on mother-infant bonding and child development

The reason perinatal depression is prioritised in public health is that it does not affect the mother alone. Untreated maternal depression impairs **mother-infant bonding** and the quality of early interaction, and is associated with poorer **child developmental outcomes**, including effects on the infant's emotional, cognitive and behavioural development, mediated through reduced responsive caregiving and disturbed early attachment (Tasman 2015; New Oxford Textbook 2020). This dyadic impact is the argument for universal screening and for treating the mother as the route to protecting the child, and it is why the topic is examined as a maternal-and-infant problem rather than a maternal one.

10.7 Screening: the Edinburgh Postnatal Depression Scale

Because a new mother is sleep-deprived and preoccupied, and may not distinguish a drift from the blues into a mood disorder, active **screening** (use "screening") is standard rather than waiting for spontaneous complaint. The instrument to name is the Edinburgh Postnatal Depression Scale (EPDS), a 10-item self-report questionnaire developed for detecting postnatal depression (Cox et al. 1987), deliberately weighted away from the somatic symptoms (sleep, appetite, fatigue) that are confounded by normal new motherhood and towards the mood and cognitive items (New Oxford Textbook 2020; Companion to Psychiatric Studies 2010). It is a screen, not a diagnostic test: a positive EPDS flags a woman for a full clinical assessment, and any endorsement of the self-harm item is acted on directly. The structured suicide risk assessment and safety planning are owned by the Somatic-symptom, sexual, impulse-control disorders and suicide notes; the descriptive detail of the scales is owned by the Psychometry, Assessment and Descriptive Psychopathology notes.

RULE **Screen every perinatal woman, and always ask about past hypomania before an antidepressant.** Use the EPDS to screen; a prior hypomanic episode reclassifies the depression as bipolar and changes first-line treatment.

10.8 Management principles as a guideline pointer

Management is given here at guideline level only; the drug detail (mechanisms, dosing, adverse effects, interactions and treatment-resistant algorithms) is owned by the Mood disorders: pharmacotherapy notes, and the ECT technique by the ECT and neurostimulation notes. Three principles carry the exam answer. First, for **mild to moderate** postpartum depression, a **psychological therapy is first-line**: CANMAT recommends offering CBT or interpersonal therapy, individual or group, as first-line treatment for mild to moderate postpartum depression in breastfeeding women (CANMAT 2016). Second, when an antidepressant is needed in a **breastfeeding** woman, sertraline is the preferred agent: CANMAT lists citalopram, escitalopram or sertraline as the preferred antidepressants for postpartum depression in breastfeeding women, and the British Association for Psychopharmacology similarly prefers sertraline because of its low transfer into breast milk and low rate of reported adverse effects (CANMAT 2016; BAP 2015). Third, for **severe, psychotic or treatment-resistant** perinatal depression, ECT is considered, and breastfeeding can continue during ECT (CANMAT 2016). NICE similarly places psychological interventions first for mild to moderate perinatal depression and reserves

antidepressants and ECT for more severe or refractory illness, weighing risks and benefits with the woman. The Indian Psychiatric Society (use "Indian Psychiatric Society") clinical practice guidelines for depression (Gautam et al. 2017, the IPS guidelines) endorse the same phase-based, therapy-first-for-milder-illness framework; the specific perinatal breastfeeding-antidepressant recommendation could not be separately confirmed in the IPS text available here and is therefore named without a specific IPS agent claim rather than invented. The wider perinatal management frame is cross-referenced to the Perinatal/women's mental health and emergency psychiatry notes.

SITUATION	GUIDELINE RECOMMENDATION (FIRST-LINE)	SOURCE
Mild to moderate postpartum depression	**CBT or interpersonal therapy (individual or group), first-line**	CANMAT 2016; NICE
Antidepressant needed, breastfeeding	**Sertraline preferred (also citalopram, escitalopram); low breast-milk transfer**	CANMAT 2016; BAP 2015
Severe, psychotic or treatment-resistant	**Consider ECT; breastfeeding may continue during ECT**	CANMAT 2016
Any perinatal depression, before starting a drug	Screen for past hypomania; safeguard mother and infant	General principle

The guideline-anchored management pointer for peripartum depression; the highlighted cells are the three first-line moves the examiner rewards.

INDIA

Perinatal depression is a substantial and under-recognised problem in Indian settings, where the disorder is often expressed somatically and detected late, and where limited social support and obstetric or psychosocial stress are common; community screening with the Edinburgh Postnatal Depression Scale is used in Indian research and district mental health work, and comparative data have historically suggested perinatal mood disturbance is at least as common in lower-resource settings as in higher-resource ones (Shorter Oxford Textbook 2018). For severe, psychotic or treatment-resistant perinatal depression, ECT is widely available across Indian teaching hospitals and is a practical option, with breastfeeding continued. This chapter is generic and names no brand; drug branding, Indian brand first, belongs to the Mood disorders: pharmacotherapy notes. A verified India-specific perinatal prevalence figure from the National Mental Health Survey could not be confirmed in the sources available here and is not asserted.

WORKED EXAMPLE

A 27-year-old woman is brought at three weeks postpartum with two weeks of low mood, anhedonia, guilt about being a "bad mother", poor sleep beyond the infant's demands, and thoughts that the baby would be better off without her. She is fully oriented with no fluctuation of awareness and no delusions or hallucinations. Count the episode: this meets a depressive episode, and because onset is within four weeks of delivery it is major depressive disorder, with peripartum onset (DSM-5-TR). Now the two mandatory moves before treatment: screen the lifetime history for any past hypomanic episode (to catch a bipolar depression), and act on the passive death wish with a formal risk assessment. Because she is breastfeeding and this is moderate, offer a psychological therapy first-line, and if an antidepressant is needed prefer sertraline (CANMAT 2016). Had she instead been abruptly perplexed, elated at times, and convinced the infant was possessed, the answer would pivot to a suspected postpartum psychosis and urgent admission.

GOOD TO REMEMBER

- **Peripartum-onset specifier (DSM-5-TR):** a depressive episode with onset in pregnancy or within **4 weeks** of delivery; a specifier, not a separate diagnosis; about **50%** of postpartum episodes begin before delivery.
- **Postpartum (postnatal) depression:** a full depressive episode after childbirth, prevalence approximately **15%**; needs treatment; the number to hold is the roughly **50%** recurrence with the next birth.
- **Postpartum blues:** not a disorder; tearful mood swings in the first days, self-limiting within a week, no impairment, no treatment.
- **Postpartum psychosis:** a psychiatric emergency, abrupt, manic or mixed with psychotic features, strongly tied to bipolar I, **1 in 500 to 1,000** deliveries; owned by the psychotic-disorders notes.
- **ICD-11:** 6E20 (without psychotic symptoms) / 6E21 (with psychotic symptoms), puerperal window about **6 weeks**.
- **Screening scale:** the Edinburgh Postnatal Depression Scale (EPDS), a 10-item self-report screen (Cox et al. 1987).
- **Management (guideline):** psychological therapy first-line for mild to moderate; sertraline the preferred antidepressant in breastfeeding; ECT for severe or psychotic cases (CANMAT 2016).

MNEMONIC

BLUES vs BLUE MOOD vs BREAK

Three B's for the three-way split: **BLUES** is benign and brief (self-limits within a week, no impairment); **BLUE MOOD** is the depression proper (a true episode, screen and treat); **BREAK** is the psychotic break (postpartum psychosis, an emergency, bipolar-linked). If the mother is breaking with reality, it is the third B and it is urgent.

PEARL

The word "peripartum" is itself the teaching point: DSM-5-TR chose it over "postpartum" precisely because half of these episodes start in pregnancy. If the vignette gives you low mood that began in the third trimester and worsened after delivery, that is still "with peripartum onset", not a new postnatal illness.

HOLD THIS

Peripartum is a specifier on a depressive episode (pregnancy or within 4 weeks of delivery, DSM-5-TR): screen every perinatal woman with the EPDS, ask about past hypomania before any antidepressant, prefer sertraline in breastfeeding, and never let "postnatal depression" mask a bipolar depression or an evolving postpartum psychosis.

11 · Premenstrual dysphoric disorder

Why this matters. **Premenstrual dysphoric disorder** is the affective disorder the examiner tests to see whether the candidate understands that the diagnosis is made by **prospective timing**, not by a plausible history. It is a cluster of marked affective and physical symptoms, irritability, mood lability, depressed mood and anxiety alongside physical symptoms, that is confined to the **luteal phase** of the menstrual cycle and remits shortly after the onset of menses, returning the woman to a symptom-free follicular baseline (DSM-5-TR; Kaplan & Sadock 2024). The whole clinical identity of the entity rests on that cyclical on-off pattern locked to the cycle.

The board-relevant points are three: the luteal-phase confinement with post-menstrual remission, the requirement that the diagnosis be **confirmed by prospective daily rating** over at least two cycles rather than accepted from a single retrospective account, and the split nosological placement, DSM-5 filing it among the depressive disorders while ICD-11 places it in the gynaecological chapter with a cross-listing back into the mood grouping. The raw descriptive definitions of the individual mood symptoms and the rating scales are owned by the Psychometry, Assessment and Descriptive Psychopathology notes; the wider frame of women's reproductive-cycle mood disturbance sits with the Perinatal/women's mental health and emergency psychiatry notes; the detailed pharmacology of the SSRIs belongs to the Mood disorders: pharmacotherapy notes.

11.1 The entity: luteal-phase symptoms that remit after menses

Premenstrual dysphoric disorder (PMDD, abbreviated pmdd) is defined by a symptomatic cluster that appears in the final premenstrual (luteal) week for **most menstrual cycles of the preceding year**, begins to improve within a few days of the onset of menses, and becomes minimal or absent in the post-menstrual (follicular) week (DSM-5-TR; Kaplan & Sadock 2024). DSM-5-TR (Criterion A) requires at least **5 of 11** symptoms in that premenstrual week; Criterion B requires that at least **one** of them be from the affective core, marked affective lability, marked irritability or anger, marked depressed mood or hopelessness, or marked anxiety or tension; Criterion C supplies the remaining symptoms, decreased interest, poor concentration, lethargy, appetite change or food cravings, hypersomnia or insomnia, a sense of being overwhelmed, and physical symptoms such as breast tenderness or swelling, joint or muscle pain, bloating or weight gain (DSM-5-TR). Criterion D requires significant distress or functional interference, and Criterion E requires that the symptoms not be merely a premenstrual exacerbation of another disorder, though PMDD may co-occur with one.

RULE **PMDD is confirmed by prospective luteal-phase rating, not recall.** The symptoms must be timed to the luteal phase and shown, by daily charting across at least two cycles, to remit after menses; the pattern, not the symptom list, is the diagnosis.

11.2 Prospective daily rating over at least two cycles confirms it

The criterion that separates a rigorous diagnosis from a guess is DSM-5-TR Criterion F: the timing described in Criterion A must be **confirmed by prospective daily ratings** during at least two symptomatic cycles, because a provisional diagnosis made from history alone is unreliable and frequently overturned once the woman actually charts her symptoms against her cycle (DSM-5-TR; Kaplan & Sadock 2024). Retrospective report over-attributes ordinary premenstrual complaints to the luteal phase and cannot demonstrate the post-menstrual remission that defines the disorder; only prospective daily rating over at least two cycles establishes the luteal-phase confinement and the return to a symptom-free follicular baseline. This is why the prospective chart, not the presenting story, is the operative test.

TRAP **Diagnosing PMDD from a single retrospective history.** A convincing account of premenstrual irritability is not the diagnosis; without at least two cycles of prospective daily rating the timing is unconfirmed and the label is premature.

11.3 Placement (DSM-5 depressive, ICD-11 gynaecological with a cross-listing) and management pointer

The nosology is the classic split the examiner probes. DSM-5 (and DSM-5-TR) places premenstrual dysphoric disorder as a full diagnosis **within the depressive disorders** chapter, treating it as a mood disorder proper (DSM-5-TR; Shorter Oxford Textbook of Psychiatry). ICD-11 (GA34.41) does the opposite: it classifies PMDD primarily in the grouping of premenstrual disturbances in Chapter 16 on diseases of the genitourinary system, but **cross-lists** it (secondary-parents it) into the depressive disorders grouping so that clinicians reading the mood section still find it (ICD-11 CDDR). ICD-10 carried the older, looser "premenstrual tension syndrome" and did not require prospective confirmation, and is flagged because Indian exams still cite it. On management, the one-line pointer is that SSRIs are first-line, given either continuously or restricted to luteal-phase dosing, with roughly two-thirds of women responding; the detailed drug pharmacology, dosing and next-line options (including the GnRH agonists reserved for SSRI non-responders) are owned by, and cross-referenced to, the Mood disorders: pharmacotherapy notes (Kaplan & Sadock 2024).

SYSTEM	PLACEMENT	CONFIRMATION STANCE
DSM-5-TR	**Depressive disorders chapter (a mood disorder proper)**	Criterion F: prospective daily ratings over at least two cycles
ICD-11 (GA34.41)	**Chapter 16 genitourinary (premenstrual disturbances), cross-listed into depressive disorders**	Luteal-phase symptoms confirmed against the cycle
ICD-10	Premenstrual tension syndrome (gynaecological)	No prospective-charting requirement; still cited in Indian exams

Placement map for PMDD: DSM-5 files it among the depressive disorders, ICD-11 in the gynaecological chapter with a cross-listing back to mood, and only the modern systems demand prospective confirmation.

5 of 11	at least 2 cycles	about 5%
SYMPTOMS, LUTEAL WEEK	PROSPECTIVE DAILY RATING	SEVERE PREMENSTRUAL SYMPTOMS

GOOD TO REMEMBER

- **Premenstrual dysphoric disorder (PMDD):** a luteal-phase cluster of marked affective (irritability, mood lability, depressed mood, anxiety) and physical symptoms that remits shortly after menses onset; the one discriminating feature is confinement to the luteal phase confirmed by **prospective daily rating over at least two cycles** (DSM-5-TR Criterion F), and the numbers to hold are **5 of 11** symptoms with at least one from the affective core.
- **Placement:** DSM-5 among the depressive disorders; ICD-11 gynaecological (GA34.41, Chapter 16) with a cross-listing into depressive disorders; SSRIs (continuous or luteal-phase dosing) are first-line, cross-referred to the Mood disorders: pharmacotherapy notes.

INDIA

PMDD is under-recognised in Indian practice because it usually presents first to gynaecology as "premenstrual tension" rather than to psychiatry, and the ICD-10 gynaecological framing many Indian services still work from does not demand prospective charting; the practical teaching point is to hand the woman a simple daily symptom chart across at least two cycles before committing to the diagnosis or starting an SSRI (Kaplan & Sadock 2024).

HOLD THIS

PMDD is a luteal-phase affective disorder confirmed by prospective daily rating over at least two cycles (not by retrospective history), needing 5 of 11 symptoms with at least one affective-core symptom; DSM-5 files it under depressive disorders, ICD-11 files it in the gynaecological chapter with a cross-listing, and SSRIs continuous or luteal-phase are first-line.

12 · Andrade construct, masked and mixed anxiety-depression

Why this matters. This is the small-print corner where depression stops looking like the textbook picture. Three ideas cluster here: the academic reframing of depression as a **syndrome** rather than a single disease, the everyday clinical reality that depression often arrives dressed as physical complaints, and the diagnostic no-man's-land where anxiety and low mood sit together but neither reaches threshold. Each is separately examinable, and each carries the same practical lesson: the mood component is often present but unspoken, and it is found only if you ask.

The raw descriptive definitions of the mood symptoms and the rating scales are owned by the Psychometry, Assessment and Descriptive Psychopathology notes; the full depressive-episode criteria live earlier in this chapter. Held here is the atypical presentation: how depression hides behind somatic symptoms, what the **depressive equivalents** are, and where sub-threshold mixed anxiety-depression sits in the nosology.

12.1 The Andrade construct: depression as a syndrome of depression

The Andrade construct, an Indian academic reframing associated with the term **syndrome of depression**, treats depression not as a single unitary disease but as a heterogeneous syndrome, a

final common presentation reachable by many routes, so that the clinical entity is better understood as a cluster of overlapping subtypes than as one disorder. This is the same conceptual move made across the field when depression is called an affective **spectrum** rather than a discrete illness, and it underpins why masked forms and depressive equivalents belong in the same discussion. The exact wording, scope and primary attribution of the Andrade **syndrome of depression** construct could not be confirmed against the parsed reference library, so it is named here and flagged rather than elaborated with invented detail; the trainee should hold the label and the core idea (depression as a syndrome, not a single disease) and verify the primary source before quoting specifics.

RULE **Read depression as a syndrome, not a single disease.** A common depressive surface is reached by many routes, which is exactly why it can present masked, somatised or blended with anxiety.

12.2 Masked depression and the somatic presentation

Masked depression describes a depressive disorder in which the depressive mood is not readily apparent and is hidden behind a **somatic presentation**: the patient complains of physical symptoms, and low mood is elicited only on direct enquiry (Shorter Oxford 2018). Older writers called it *depressio sine depressione* (depression without depression) or a **depressive equivalent**, but the concept was never officially endorsed by the classifications and appears in DSM-5-TR only informally, listed among the varied presentations of a depressive episode (Kaplan & Sadock 2024). The somatic complaints span chronic pain, insomnia, atypical facial pain, paraesthesias, fatigue and multiple unexplained bodily symptoms, and the picture is described as especially common in the elderly, where facial expression, vocal inflection and overall appearance may reveal the underlying mood the patient does not report (Kaplan & Sadock 2024). The depressive core can also be obscured by concurrent alcohol or drug misuse.

The examinable counterpoint is that the reasoning must run both ways. Just as a depressive disorder can be missed in a patient who does not spontaneously complain of low mood, so a depression should not be diagnosed merely because depressive symptoms are prominent, since those may belong to another disorder; and unexplained aches and pains must not be assumed to be depressive equivalents without excluding treatable physical illness such as hypothyroidism or anaemia (Shorter Oxford 2018).

WORKED EXAMPLE

A woman in her sixties attends repeatedly with chronic backache, poor sleep and vague paraesthesias; investigations are unremarkable and analgesics do little. On direct enquiry she describes weeks of anhedonia, early-morning waking, guilt and hopelessness that she had never volunteered because she came about her body, not her mood. The physical complaints were the mask; the depressive episode was found only because mood was asked about directly.

RULE **When a patient somatises, ask directly about mood.** Masked depression is common, and the depressive core is elicited on direct enquiry, not volunteered.

TRAP **Do not keep treating recurrent unexplained somatic complaints without screening for depression.** Repeated analgesics and investigations for a masked depression miss the treatable disorder underneath.

GOOD TO REMEMBER

- **Masked depression:** a depressive disorder hidden behind physical or somatic complaints, with the mood elicited only on direct enquiry; the one discriminator is that low mood is present but not volunteered; the label to hold is *depressio sine depressione*, and it was never officially endorsed by the classifications.
- **Somatic presentation:** the dominant complaints are physical, chronic pain, insomnia, atypical facial pain, paraesthesias, fatigue; classically described as most common in the elderly.
- **Depressive equivalents:** conditions comparable to, or on the affective spectrum with, depression (for example chronic pain, panic, agoraphobia, alcoholism, eating disorders) that are not part of the core depressive syndrome; hold that many respond to antidepressants but the concept is not an official diagnosis.

12.3 Mixed anxiety and depressive disorder

Mixed anxiety and depressive disorder, also written **mixed anxiety-depressive** disorder, describes the co-occurrence of sub-threshold anxiety and depressive symptoms together, causing distress or disability, where neither symptom set meets the full criteria for a specific anxiety disorder nor for a depressive disorder (Shorter Oxford 2018). Anxiety and depressive symptoms overlap most when they are mild and least when they are severe enough to reach a categorical diagnosis, so this residual category captures the milder, blended presentations that are common in primary care and medical outpatient settings and frequently go untreated in the community (Shorter Oxford 2018). In the English Adult Psychiatric Morbidity Survey it was the most common psychiatric syndrome in the community, with about **9%** of adults meeting the symptomatic criteria in the week before interview, commoner in women and in low-income households (McManus et al. 2009, in Shorter Oxford 2018).

Classification. The nosological placement is itself the exam point. ICD-10 contains a category of mixed anxiety and depressive disorder (F41.2), placed among the other anxiety disorders, whereas DSM-5 and DSM-5-TR deliberately do **not** include it as a diagnosis (Shorter Oxford 2018). In ICD-11 the category is retained but reconceptualised and moved into the depressive-disorders grouping as mixed depressive and anxiety disorder, a genuine shift from its ICD-10 home under the anxiety disorders (ICD-11 CDDR); the exact ICD-11 code is flagged under gaps as it could not be confirmed against the parsed library. For examinations that still use ICD-10, the point to reproduce is that ICD-10 has the category and DSM-5 does not.

TRAP **Do not reach for mixed anxiety and depressive disorder in DSM-5.** DSM-5 and DSM-5-TR have no such category; it is an ICD construct, placed under anxiety in ICD-10 and moved to the depressive grouping in ICD-11.

Prognosis. The prognostic significance is the second high-yield point: despite being sub-threshold, the outcome of mixed anxiety and depressive disorder appears to be **worse** than that of a specific anxiety disorder (Tyrer et al. 2004, in Shorter Oxford 2018), so the label is not

simply a mild or trivial residual state. Persistent anxiety more often precedes the onset of secondary depression than the reverse, and the two share predisposing factors including childhood adversity and probable common genetic mechanisms with generalised anxiety disorder (Shorter Oxford 2018).

about 9%	F41.2	sub-threshold
COMMUNITY WEEK-PREVALENCE (APMS)	ICD-10 CATEGORY (ABSENT IN DSM-5)	NEITHER SET MEETS FULL CRITERIA

INDIA

Masked depression with a predominant somatic presentation, and sub-threshold mixed anxiety-depression, are both familiar in Indian practice, where distress is frequently expressed through bodily complaints and first presents to general and medical outpatient departments rather than to psychiatry. The practical implication is the same as the rule: screen for mood directly in the patient who somatises, because the depressive core is common and treatable but is not volunteered.

GOOD TO REMEMBER

- **Mixed anxiety and depressive disorder:** sub-threshold anxiety and depressive symptoms together with neither meeting full criteria; the discriminating feature is that it is a residual category defined by what it does *not* reach; the codes to hold are ICD-10 F41.2 (present) versus DSM-5 (absent), with ICD-11 moving it to the depressive grouping.
- **Prognostic significance:** the one fact examiners want is that its outcome is *worse* than a specific anxiety disorder (Tyrer 2004), so it is not a benign residual label.
- **Epidemiology:** the number to hold is about **9%** community week-prevalence in the English APMS, the most common community psychiatric syndrome there, commoner in women.

HOLD THIS

Depression is a syndrome that often hides: masked depression presents through somatic complaints with the mood found only on direct enquiry, and mixed anxiety and depressive disorder is a sub-threshold ICD category (F41.2 in ICD-10, absent in DSM-5) whose outcome is worse than a specific anxiety disorder.

13 . Management of depressive disorders: guidelines-first

Managing a depressive disorder is a decision about three things in order: **where** to treat the patient, **what phase** of illness you are targeting, and **which mode** of treatment each guideline recommends first. The board answer is not a drug list, it is this structured, guideline-anchored plan. This topic teaches the plan at **guideline level**; the individual drug pharmacology, the dosing tables, the adverse-effect profiles and the treatment-resistant-depression algorithm are owned by, and cross-referred to, the Mood disorders: pharmacotherapy notes.

Lead with the CANMAT guidelines (CANMAT 2016 and its updates), then state what the Indian Psychiatric Society and NICE recommend. Throughout, the spine is LOCUS (where), FOCUS (which phase), MODUS (which mode). The single organising principle that the exam rewards: **treat to remission, then continue.**

13.1 LOCUS: where to treat, and when to admit

Outpatient is the default. Most depressive episodes are managed in the outpatient or the day care centre setting from the outset. Admission is reserved for a defined set of high-risk situations: **high suicide risk**, depression **with psychotic features**, severe **self-neglect** (not eating or drinking, dehydration), and the need for inpatient-level treatment such as ECT. The clinical suicide risk assessment and safety planning that decide the admission threshold are owned by the Somatic-symptom, sexual, impulse-control disorders and suicide notes. Across every locus, care is delivered as **measurement-based care**: CANMAT specifies regular, frequent monitoring of clinical and functional outcomes with a validated scale, not clinical impression alone (CANMAT 2016).

RULE **Admit for suicide risk, psychosis, severe self-neglect, or the need for ECT.** Everything else is outpatient with measurement-based follow-up.

13.2 FOCUS: the acute phase, aim remission

The acute-phase target is **remission**, not merely response. Review early and often: CANMAT and BAP both advise reviewing the patient every **1 to 2 weeks** after starting an antidepressant (BAP 2015). Response is judged on a trajectory: **lack of significant improvement by 2 to 4 weeks** substantially reduces the chance of eventual sustained response, so for a non-improver at 2 to 4 weeks you increase the dose if tolerated, or switch if tolerability is the problem (CANMAT 2016). BAP frames the same checkpoint as assessing response at 4 weeks and again at 6 to 8 weeks, switching or stepping up if there is no improvement trajectory by 4 weeks or only minimal improvement by 6 to 8 weeks (BAP 2015).

TRAP **Do not combine two antidepressants at initiation.** CANMAT states this explicitly; start one first-line agent, monitor, then optimise or switch.

13.3 FOCUS: the continuation phase, protect the remission

Once remission is achieved, do not stop. The **continuation** phase continues the antidepressant at the **acute treatment dose** (not a reduced "maintenance" dose) for **6 to 9 months** after symptomatic remission (CANMAT 2016). BAP frames the lower bound as at least 1 year for anyone with an increased relapse risk (BAP 2015). This is the phase most often failed in practice: the patient feels well at week 8 and stops, and the relapse that follows is a continuation-phase relapse, not a new episode.

13.4 FOCUS: the maintenance phase, prevent recurrence

For recurrent or high-risk illness, the plan extends into a **maintenance** phase. CANMAT extends antidepressant treatment to **2 years or more** for patients with risk factors for recurrence (CANMAT 2016); BAP names the higher-risk group as, for example, more than five lifetime episodes or two episodes in recent years, and recommends at least 2 years and often long-term (BAP 2015). The maintenance-phase psychological options are CBT or mindfulness-based cognitive therapy (MBCT) to prevent relapse (CANMAT 2016). When treatment is eventually

stopped, taper slowly over several weeks to limit discontinuation symptoms, which CANMAT summarises with the mnemonic FINISH.

MNEMONIC

FINISH

Antidepressant discontinuation symptoms: **F**lu-like symptoms, **I**nsomnia, **N**ausea, **I**mbalance, **S**ensory disturbances, **H**yperarousal (CANMAT 2016). Taper over several weeks; taper short half-life drugs more slowly.

13.5 MODUS: CANMAT first-line pharmacotherapy

The **first-line** pharmacological treatment is a **second-generation antidepressant**, individualised to patient and medication factors with measurement-based monitoring (CANMAT 2016). The first-line class as a group covers the SSRIs, the SNRIs, bupropion, mirtazapine, vortioxetine and agomelatine (with liver-function monitoring for agomelatine). CANMAT's caution at initiation is explicit: two antidepressants are not combined at the initiation of treatment. The deep pharmacology, the full dosing and the adverse-effect detail live in the Mood disorders: pharmacotherapy notes.

RULE **First-line = a second-generation antidepressant, one agent, individualised.** SSRIs and other newer agents are preferred for tolerability and overdose safety (BAP 2015).

13.6 MODUS: CANMAT first-line psychological treatments

The first-line psychological treatments for acute major depressive disorder are cognitive behavioural therapy (CBT), interpersonal therapy (IPT) and behavioural activation (BA) (CANMAT 2016). CANMAT's headline for combination is that, where feasible, combining a psychological treatment (CBT or IPT) with an antidepressant is superior to either alone. Combined medication-plus-therapy is therefore the preferred option for many patients, not a fallback. The raw descriptive definitions of the mood symptoms and the rating scales used to measure them are cross-referred to the Psychometry, Assessment and Descriptive Psychopathology notes.

13.7 MODUS: augmentation and the next step (guideline pointer)

For an inadequate response after an optimised first-line trial, the first-line augmentation agents are the atypical antipsychotics aripiprazole (2 to 15 mg/day), quetiapine (150 to 300 mg/day) and risperidone (1 to 3 mg/day), or adjunctive lithium to therapeutic serum levels with monitoring (CANMAT 2016; BAP 2015). This is a guideline-level pointer only: the full treatment-resistant-depression algorithm, the sequencing, the switch-versus-augment logic and the drug detail are owned by the Mood disorders: pharmacotherapy notes.

13.8 MODUS: neurostimulation and the psychotic-depression rule

Neurostimulation appears at guideline level in two places. rTMS, including intermittent theta burst stimulation (iTBS), is a **first-line** option that CANMAT positions alongside pharmacotherapy for acute depression (CANMAT 2016). ECT is reserved for severe, psychotic or

treatment-resistant depression; the ECT technique itself is owned by the ECT and neurostimulation notes. The **psychotic-depression rule** is a fixed board point: treat with an **antidepressant plus an antipsychotic** from the outset, in preference to either alone, or use ECT (BAP 2015). The mood-with-psychotic-features entity and the schizoaffective boundary are owned by the Other psychotic disorders, delusional syndromes and catatonia notes.

TRAP **Do not treat psychotic depression with an antidepressant alone.** The rule is antidepressant plus antipsychotic from the outset, or ECT.

13.9 The Indian Psychiatric Society and NICE positions

Beyond CANMAT, two further guideline positions are examinable. The Indian Psychiatric Society Clinical Practice Guideline for depression has been updated: the 2025 IPS depression update (IPS 2025, Tripathi et al., Indian J Psychiatry 2026;68:68-93) supersedes the 2017 Gautam guideline and is the current standard Indian reference cited in postgraduate examinations. It names the **SSRIs** as the first-line antidepressants on grounds of tolerability and overdose safety, with the other second-generation agents including vilazodone, vortioxetine and agomelatine as alternatives; it selects the initial treatment by severity (psychotherapy preferred for mild low-risk depression, pharmacotherapy or psychotherapy for moderate, combined pharmacotherapy and psychotherapy for severe without psychosis, an antidepressant plus an antipsychotic for severe with psychosis, and ECT with admission for life-threatening presentations); it reappraises the regimen if there is under a quarter improvement by about four weeks (optimise the dose, switch within or between class, augment, or add ECT); and it sets the treatment phases as acute 8 to 16 weeks, continuation 4 to 9 months and maintenance 6 to 24 months (long-term for recurrent depression), reserving ECT for severe, psychotic, suicidal or treatment-resistant depression (IPS 2025, Tripathi et al.). NICE organises depression management as **stepped care**: for less severe depression it favours a psychological or psychosocial intervention first, and for more severe depression it recommends an antidepressant combined with a psychological therapy. CANMAT, the IPS position (at the level of principle) and NICE therefore converge on the same spine: a second-generation antidepressant or an evidence-based psychotherapy first, combination for the more severe, and continuation after remission.

2 to 4 wk	6 to 9 mo	2 years+	1 to 2 wk
ACUTE NON-IMPROVER REVIEW	CONTINUATION AFTER REMISSION	MAINTENANCE IF RECURRENT	EARLY REVIEW INTERVAL

PHASE	TARGET	DURATION / CHECKPOINT	GUIDELINE-FIRST MODES
Locus decision	Choose the safest adequate setting	**Admit for suicide risk, psychosis, severe self-neglect or the need for ECT**	Outpatient default; measurement-based care throughout

PHASE	TARGET	DURATION / CHECKPOINT	GUIDELINE-FIRST MODES
Acute	Remission	**Review every 1 to 2 weeks; judge response by 2 to 4 weeks and switch or step up if no trajectory**	Second-generation antidepressant (one agent) and/or CBT, IPT or BA; combination superior for many (CANMAT 2016)
Continuation	Protect the remission	**Continue at the acute dose for 6 to 9 months after remission**	Same acute-phase agent at the same dose; do not down-titrate (CANMAT 2016)
Maintenance	Prevent recurrence	**Extend to 2 years or longer for recurrent or high-risk patients**	Continue antidepressant; CBT or MBCT to prevent relapse; taper slowly (FINISH) at stop (CANMAT 2016)
Inadequate response	Optimise, then augment or switch	Optimise dose first; reassess	First-line augmentation aripiprazole, quetiapine, risperidone or lithium; details in the pharmacotherapy notes
Neurostimulation	Severe or resistant illness	By severity and resistance	**First-line rTMS/iTBS; ECT for severe, psychotic or treatment-resistant depression**
Psychotic depression	Remission with psychosis control	From the outset	**Antidepressant plus antipsychotic, or ECT (BAP 2015)**

The phase-by-phase, guideline-first plan on the LOCUS to FOCUS to MODUS spine; the highlighted cell in each row is the fact the examiner tests. Drug detail is cross-referred to the Mood disorders: pharmacotherapy notes.

INDIA

In Indian practice, the full range of second-generation antidepressants (SSRIs, SNRIs, bupropion, mirtazapine, vortioxetine, agomelatine) is widely available, and the SSRIs are the usual first-line pharmacotherapy for depressive disorders. This chapter is generic and names no brand; drug branding, Indian brand first, belongs to the Mood disorders: pharmacotherapy notes. For severe, psychotic or treatment-resistant depression, ECT is widely available and heavily used across Indian teaching hospitals, and it remains a mainstream option for inpatient-level depression rather than a last resort. The current Indian Psychiatric Society guideline for depression is the 2025 update (IPS 2025, Tripathi et al.), which supersedes the 2017 Gautam guideline and is the one most likely to be named in Indian postgraduate examinations for depression management.

GOOD TO REMEMBER

- **LOCUS:** outpatient default; admit for suicide risk, psychosis, severe self-neglect or the need for ECT; measurement-based care throughout.
- **Acute phase:** aim remission; review every **1 to 2 weeks**; switch or step up if no improvement trajectory by **2 to 4 weeks** (CANMAT 2016).
- **Continuation phase:** continue at the acute dose for **6 to 9 months** after remission; do not down-titrate.
- **Maintenance phase:** extend to **2 years or longer** for recurrent or high-risk patients; CBT or MBCT prevents relapse.
- **CANMAT first-line:** a second-generation antidepressant (one agent, individualised) or CBT / IPT / behavioural activation; combination superior for many.
- **Do-not-combine rule:** two antidepressants are not combined at initiation (CANMAT 2016).
- **Psychotic depression:** antidepressant plus antipsychotic from the outset, or ECT (BAP 2015).
- **Convergence:** CANMAT leads; the Indian Psychiatric Society and NICE agree on stepped care and continuation after remission.

WORKED EXAMPLE

A 42-year-old woman with a first moderate depressive episode, no psychosis and no active suicidal plan, is managed as an outpatient. She is started on a single second-generation antidepressant with a shared decision about which agent, and offered CBT alongside because combination is superior to either alone. She is reviewed at 2 weeks, then at 4 weeks: there is a partial improvement trajectory, so the dose is optimised rather than switched. She reaches remission by month 3. The antidepressant is continued at the same acute dose for 6 to 9 months, not reduced, because stopping at response is the classic route to relapse. Because this is a first episode with no high-risk features, an open-ended maintenance phase is not mandated, but the recurrence-risk conversation is documented for the future.

PEARL

"Remission then continuation" is a single instruction, not two. The dose that achieved remission is the dose that maintains it: the continuation phase is the acute-phase drug at the acute-phase dose for 6 to 9 months. Reducing the dose once the patient feels well is a common and avoidable cause of relapse.

RULE **Treat to remission and continue at the acute dose; do not stop at response.** Continuation is 6 to 9 months at the same dose after remission (CANMAT 2016).

TRAP **Stopping the antidepressant as soon as the patient feels better.** Response is not remission, and remission is not the end point; early cessation invites relapse.

HOLD THIS

First-line is a second-generation antidepressant or an evidence-based psychotherapy, combination is superior for many, continuation runs 6 to 9 months at the acute dose after remission, and CANMAT leads while the Indian Psychiatric Society and NICE agree on stepped care.

Bipolar and related disorders

14 · Bipolar I disorder

Having walked the whole soft-bipolar spectrum, you now step onto its classic pole. **Bipolar I disorder** (written bipolar 1 in some notations) is the modern name for manic-depressive illness, and its definition is deceptively simple: it is the disorder in which a single **manic episode** has ever occurred. Everything else about the illness, the depressions that dominate the timeline, the recurrences, the suicide burden, follows from that one anchoring fact but is not needed to make the diagnosis (DSM-5-TR 2022; Kaplan & Sadock 2024). The exam rewards the resident who states the definition crisply, who knows the illness is mostly a depressive one over a lifetime despite being named for mania, and who never demands a depressive episode before diagnosing.

This topic stays at the disorder level: the definitional frame, the lifetime pattern, the course and its kindling logic, the comorbidity and burden. The phenomenology of the manic episode itself, the Criterion A and B symptoms, is the next topic; the full manic-episode and depressive-episode criteria live in this chapter's own episode topics, and the raw descriptive definitions of the mood symptoms sit in the Psychometry, Assessment and Descriptive Psychopathology notes. Nosology is given ICD-11-primary, DSM-5-TR cross-mapped.

	Bipolar I	Bipolar II	Cyclothymia
Defining episode	a manic (or mixed) episode	a hypomanic plus a major depressive episode	sub-threshold highs and lows
High pole	full mania	hypomania only, never mania	hypomanic symptoms only
Duration threshold	mania at least 1 week	hypomania at least 4 days (several days, ICD-11)	at least 2 years
Psychosis or admission	may occur	excludes hypomania	no
Tell it by	**one manic episode, ever**	**hypomania plus depression, no mania**	**chronic, 2 years, sub-threshold**

Fig 11.5 Bipolar I versus bipolar II versus cyclothymia. A single manic episode, ever, defines bipolar I. A hypomanic episode plus a major depressive episode, with no manic episode ever, defines bipolar II, and any marked impairment, psychosis or hospitalisation would make the high a mania instead. Cyclothymia is at least two years of sub-threshold highs and lows that never reach episode criteria.

14.1 The definition: one manic episode makes the diagnosis

A single lifetime mania is sufficient, and necessary. DSM-5-TR Criterion A for bipolar I disorder reads that criteria have been met for at least one manic episode, and the text is explicit that "the occurrence of at least one manic episode is necessary for the diagnosis of bipolar I disorder" (DSM-5-TR 2022). A manic episode required is therefore the whole gate: no manic episode, no bipolar I. Hypomanic and major depressive episodes usually occur across the lifetime and are the reason most patients present, but DSM-5-TR states plainly that they are "not essential to a diagnosis of bipolar I disorder" (DSM-5-TR 2022). ICD-11 mirrors this: bipolar type I disorder is defined by a history of at least one manic or mixed episode, and a manic episode

lasting **at least 1 week** (or any duration if hospitalisation is required) is the definitional event. The full manic-episode criteria are taught in this chapter's manic-episode topic.

RULE **One manic episode is enough for bipolar I, ever.** A single lifetime manic episode makes and fixes the diagnosis, however the patient looks today, and no depressive episode is required.

TRAP **Do not require a depressive episode.** Demanding a past major depression before diagnosing bipolar I is the classic error; depression is usual but never a diagnostic requirement, and a first-episode mania with no prior depression is already bipolar I.

14.2 The lifetime pattern: a recurring, mostly depressive illness

Named for mania, lived as depression. Bipolar I disorder is, in DSM-5-TR's phrasing, "characterized by a clinical course of recurring mood episodes (manic, depressive, and hypomanic)" (DSM-5-TR 2022). Onset can take several shapes: some patients begin with weeks or months of depression that then switches into a manic episode; others open with a severely psychotic manic episode with schizophreniform features whose affective nature is clarified only when a more classic mania follows; in a third group several depressive episodes precede the first mania (Kaplan & Sadock 2024). A "single manic episode" simply describes a patient in a first episode of mania; most such patients eventually develop depressive episodes, and more than **90%** of individuals who have a single manic episode go on to have recurrent mood episodes (DSM-5-TR 2022). Approximately **60%** of manic episodes occur immediately before a major depressive episode (DSM-5-TR 2022).

PEARL

Chart the course in colour over time (Kraepelin's method, developed into systematic science by Robert Post at the NIMH): red for manic, blue for depressive, violet for mixed, with hypomanic and cyclothymic periods on a smaller scale, and arrows for life events, stressors and treatment. A life chart makes the predominant polarity and the cycle pattern visible at a glance (Kaplan & Sadock 2024).

14.3 The course of bipolar I: episodic with inter-episode recovery

Episodes come and go against a baseline of relative recovery. The course of bipolar I disorder is classically episodic: discrete manic, depressive, hypomanic and mixed episodes separated by periods of inter-episode recovery in which the patient returns toward, though often not fully to, euthymia (Kaplan & Sadock 2024). The course is highly heterogeneous. Polarity of the first episode tends to predict the predominant polarity of future episodes, so a depressive onset is associated with a greater density of depressive episodes and more suicidal behaviour (DSM-5-TR 2022). About half of patients show a predominant polarity (relapse tending to be either depressive or manic); one international bipolar I cohort found 31.3% with predominant mania, 21.4% with predominant depression and 47.3% without polarity predominance (DSM-5-TR 2022). Inter-episode recovery is the norm early, but subthreshold symptoms and functional deficits frequently persist between full episodes.

14.4 More time is spent depressed than manic

The depressive pole dominates the lifetime clock. Despite the manic naming, patients with bipolar I disorder spend far more of their symptomatic time depressed than manic. NIMH Collaborative Depression Study data, using prospective life-charting of bipolar I cohorts followed for an average of **12 years**, showed patients were symptomatic for nearly **50%** of the weeks across the entire follow-up, with depression, especially its subthreshold variants, predominating over mania (Kaplan & Sadock 2024). This asymmetry is why bipolar depression, not mania, is the harder and more time-consuming management problem, and why an antidepressant given alone to a patient later found to be bipolar is such a common and costly error.

RULE **More time depressed than manic.** Over a lifetime the bipolar I patient is symptomatically depressed for far longer than manic; mania names the illness, depression fills its calendar.

WORKED EXAMPLE

A 24-year-old man is admitted with his first episode: three days of no sleep, grandiose plans to buy a hotel, pressured speech and reckless spending, requiring involuntary admission. He has never had a depressive episode. This is already bipolar I disorder, because a single manic episode is sufficient and no depression is required. Over the next decade, if his course runs true to form, he will have several more episodes and will spend more of his symptomatic time depressed than manic; his management therefore looks past this admission to long-term relapse prevention, not just to settling the mania.

14.5 Recurrence risk and the kindling / cycle-acceleration concept

Episodes beget episodes. Recurrence is the rule, not the exception: with the single-manic-episode patient having a greater than **90%** chance of recurrent mood episodes and a lifetime mean of around **8 to 9** major episodes in bipolar disorder (against five to six in recurrent unipolar depression), bipolar I is fundamentally a recurrent illness (DSM-5-TR 2022; Kaplan & Sadock 2024). The **kindling** and **cycle-acceleration** model, associated with Robert Post, proposes that early episodes are often triggered by identifiable psychosocial stressors, whereas later episodes arise more autonomously and the cycle length (the interval between episodes) tends to shorten over time, as if episodes progressively sensitise the brain to recur (Kaplan & Sadock 2024). The evidence is the observed shortening of well intervals across successive episodes and the analogy to electrophysiological kindling. The limitation: the model is a heuristic, not a settled mechanism; the human data are largely retrospective and confounded by treatment, adherence and ascertainment, and prospective cohorts have not uniformly reproduced a lawful progressive shortening. It motivates early and continued prophylaxis without being an established pathophysiology.

TRAP **Do not present kindling as proven mechanism.** Cycle acceleration is a clinically useful model with real retrospective support, but it is confounded and not consistently replicated prospectively; state it as a hypothesis, not a fact.

at least 1 wk	>90%	~50% of weeks	8 to 9
MANIC EPISODE (DEFINES BIPOLAR I)	RECURRENCE AFTER ONE MANIC EPISODE	SYMPTOMATIC OVER 12 YR FOLLOW-UP	MEAN LIFETIME MAJOR EPISODES

14.6 Comorbidity: anxiety and substance use are the rule

Pure bipolar I is uncommon. Co-occurring disorders are so frequent that their absence is notable. Anxiety disorders are the commonest comorbidity and, when present, are associated with a worse course of illness across both bipolar I and bipolar II (DSM-5-TR 2022). Substance use is the other dominant partner: nearly **half** of individuals whose symptoms meet criteria for bipolar disorder have an alcohol use disorder, and those with both are at greater risk of suicide attempt and suicide death (DSM-5-TR 2022). Across bipolar I and II the commonest substance comorbidities are alcohol use (**42%**) and cannabis use (**20%**) disorders, and cannabis in particular is associated with exacerbation of manic symptoms and with first onset of mania in the general population (DSM-5-TR 2022). Childhood adversity predisposes to earlier onset and a worse picture including comorbidity, suicide and psychotic features.

14.7 Functional and suicide burden

A high-mortality, high-disability illness. Bipolar I disorder carries significant decrements in quality of life and well-being even between episodes, and the suicide burden is severe: the lifetime risk of suicide in bipolar disorder is estimated at **20 to 30 times** that of the general population, and an estimated **5% to 6%** die by suicide (DSM-5-TR 2022). Suicide attempts are more frequent in women, but lethal suicide is more common in men; a past suicide attempt and the proportion of days spent depressed in the past year predict greater risk of attempts and completions (DSM-5-TR 2022). Mixed features add risk: depressive symptoms occur in some 35% of manic episodes, and mixed presentations carry a poorer prognosis, poorer lithium response and increased suicide attempts (DSM-5-TR 2022). Clinical suicide risk assessment and safety planning are taught in the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

INDIA

In Indian practice the two comorbidity patterns that most change the bipolar I picture are alcohol use disorder (very common in men, and a driver of relapse, non-adherence and suicide) and cannabis use (a frequent precipitant and aggravator of manic episodes). Both are routinely screened at every review. Lithium, the long-standing prophylactic backbone, is widely available and affordable in India; the guideline-level management and its monitoring headline are covered in the bipolar-management topic below, and the deep pharmacology sits in the Mood disorders: pharmacotherapy notes.

14.8 One-line management pointer

Diagnosis reframes treatment from episode to lifetime. Because bipolar I is recurrent and mostly depressive over time, the management goal is not only to treat the presenting episode but to prevent the next one. Guideline-anchored management, led by CANMAT (with the Indian Psychiatric Society and NICE positions cross-mapped), is organised by phase (acute mania,

bipolar depression, maintenance) and leads with mood stabilisers, most classically lithium, rather than antidepressant monotherapy (CANMAT 2018; Kaplan & Sadock 2024). The full guideline plan is taught in the bipolar-management topic; the deep drug pharmacology, dosing and treatment-resistant algorithms are owned by the Mood disorders: pharmacotherapy notes.

MNEMONIC

ONE HIGH

ONE manic episode, ever, and it is bipolar I. Read it as the whole definition: you need exactly one lifetime "high" that reaches manic threshold, and you need nothing else, no depression, to diagnose.

HOLD THIS

One manic episode ever, lasting at least 1 week (or any duration if hospitalised), makes bipolar I; no depressive episode is required, yet the patient spends more lifetime time depressed than manic.

GOOD TO REMEMBER

- **Bipolar I disorder:** the disorder in which at least one lifetime manic episode has occurred; the one discriminator is a full manic episode (at least 1 week, or any duration if hospitalised); hold "one manic episode required."
- **Course of bipolar I:** episodic with inter-episode recovery but more time spent depressed than manic; the one discriminator is the depressive-predominant lifetime clock; hold "symptomatic ~50% of weeks over 12-year follow-up."
- **Recurrence:** the rule, not the exception; the one discriminator is that a single manic episode carries a greater than 90% chance of further mood episodes; hold ">90% recur; mean 8 to 9 lifetime episodes."
- **Kindling / cycle acceleration:** a hypothesis that cycles shorten and become more autonomous over time; the one discriminator is the retrospective narrowing of well intervals; hold "Post; heuristic, not proven, motivates early prophylaxis."
- **Comorbidity:** anxiety (commonest, worsens course) and substance use (nearly half have alcohol use disorder); the one discriminator is that pure bipolar I is uncommon; hold "alcohol 42%, cannabis 20%."
- **Suicide burden:** a high-mortality illness; the one discriminator is a lifetime suicide risk 20 to 30 times the general population; hold "5% to 6% die by suicide."

15 · The manic episode

Why this matters. The **manic episode** is the diagnostic keystone of bipolar type I disorder: a single lifetime manic episode is sufficient for the diagnosis, no depressive episode being required. This chapter is the canonical home of the manic-episode criteria, so they are taught here in full; the Other psychotic disorders, delusional syndromes and catatonia notes cross-refer here for the manic pole of schizoaffective disorder. The examiner tests three reflexes on **mania**: the exact criterion set (the mood-and-energy anchor, the duration floor, and the symptom count), the point at which the episode acquires **psychotic features**, and the discrimination from hypomania on which the whole bipolar-I-versus-bipolar-II split turns.

The structure to hold is a nesting mirrored from the depressive side: the manic episode is the atom of criteria; bipolar type I disorder is the disorder built from at least one such episode. Nosology is given ICD-11 primary with the DSM-5 (the DSM-5-TR) criteria cross-mapped, and ICD-10 (F30) flagged where Indian exams still cite it. The raw descriptive definitions of the individual manic symptoms, pressured speech and flight of ideas among them, are owned by the Psychometry, Assessment and Descriptive Psychopathology notes and cross-referenced here, not re-derived. The full drug pharmacology of the antimanic agents is owned by the Mood disorders: pharmacotherapy notes.

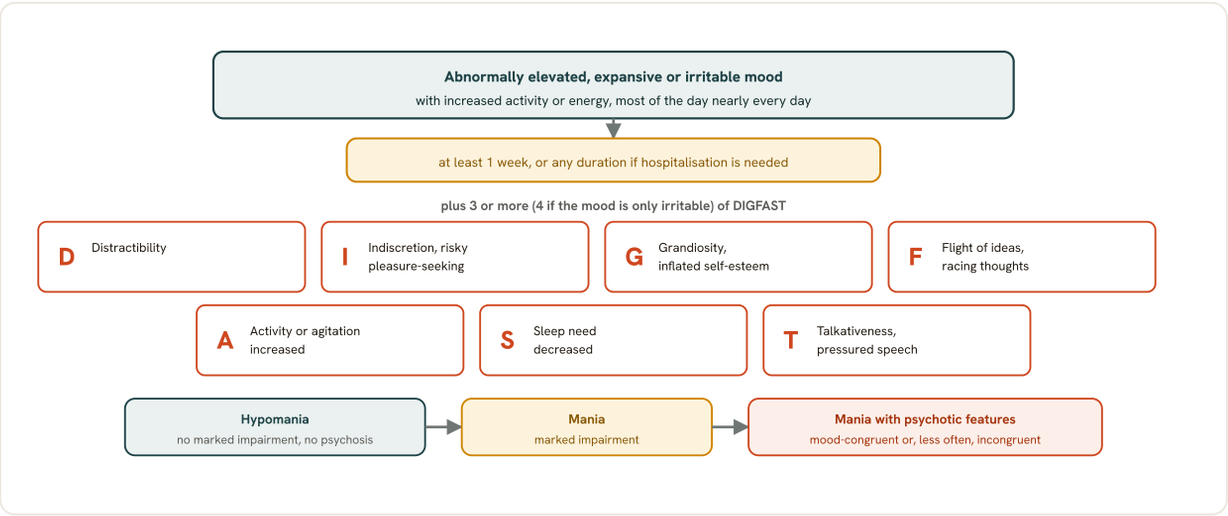

Fig 11.6 The manic episode. A distinct period of abnormally elevated, expansive or irritable mood with increased activity or energy, lasting at least one week (or any duration if hospitalisation is needed), plus three or more of the DIGFAST symptoms (four if the mood is only irritable), causing marked impairment. Severity runs from hypomania, which has no marked impairment and no psychosis, up to mania and mania with psychotic features.

15.1 The mood-and-energy anchor: the two-part gate criterion A

Every manic diagnosis opens on a two-part anchor, and the modern point is that both parts are mandatory. DSM-5-TR criterion A requires a distinct period of abnormally and persistently **elevated, expansive, or irritable mood** *and* abnormally and persistently increased activity or energy (DSM-5-TR). The steer for this topic uses **elevated or irritable** as the shorthand for the mood limb: mood may be euphoric and expansive or, especially when wishes are thwarted, purely irritable. The change from DSM-IV that the examiner rewards is that **increased activity or energy is now a required part of the gate, not merely an associated symptom**: euphoria alone, without the rise in goal-directed activity or energy, does not open the gate. ICD-11 phrases the same anchor as an extreme mood state of euphoria, irritability or expansiveness together with increased activity or a subjective experience of increased energy, both representing a significant change from the individual's typical state (ICD-11 CDDR).

RULE **Mania needs mood and energy together.** Abnormally elevated or irritable mood plus abnormally increased activity or energy is the two-part gate; euphoria without the energy rise does not qualify.

15.2 The duration floor: one week or hospitalisation

The anchor must hold for a fixed minimum. The mood-and-energy disturbance must last at least **one week** and be present most of the day, nearly every day, *or any duration if hospitalisation is necessary* (DSM-5-TR; ICD-11 CDDR). Two riders complete the duration rule. First, an episode that meets the full symptom requirements but is cut short below one week **because a treatment intervention truncated it** still counts as a manic episode (ICD-11 CDDR). Second, a fully syndromal manic episode that emerges during antidepressant treatment (medication, ECT, light therapy) and **persists beyond the physiological effect of the inducing agent** is sufficient for a manic episode and hence for bipolar I disorder (DSM-5-TR, criterion D). The **one week** floor is the single number that most cleanly separates mania from hypomania, whose floor is four days.

at least 1 wk	any duration	3 (or 4)	4 days
MANIC EPISODE	IF HOSPITALISATION NEEDED	DIGFAST SYMPTOMS REQUIRED	HYPOMANIA FLOOR (CONTRAST)

15.3 The symptom count and the DIGFAST set

Within the anchored window, DSM-5-TR criterion B requires **three or more** of a seven-symptom set to be present to a significant degree, rising to **four or more if the mood is only irritable** rather than elevated or expansive (DSM-5-TR). The seven, verbatim in substance, are: (1) inflated self-esteem or **grandiosity**; (2) decreased need for sleep (feeling rested after only about three hours); (3) more talkative than usual or pressure to keep talking; (4) flight of ideas or the subjective experience that thoughts are racing; (5) distractibility, attention too easily drawn to unimportant external stimuli; (6) increase in goal-directed activity or psychomotor agitation; and (7) excessive involvement in activities with a high potential for painful consequences (unrestrained buying, sexual indiscretions, foolish investments). The examiner's memory hook is **digfast**: **D**istractibility, **I**ndiscretion/impulsivity (irresponsibility), **G**randiosity, **F**light of ideas, **A**ctivity increase, **S**leep decrease (decreased need), **T**alkativeness/pressured speech. ICD-11 carries the same symptoms as a list from which "several" must be present, without DSM-5-TR's rigid arithmetic (ICD-11 CDDR).

MNEMONIC

DIGFAST

Distractibility, Indiscretion/impulsivity (irresponsibility), Grandiosity, Flight of ideas, Activity increase, Sleep decrease (decreased need for sleep), Talkativeness/pressured speech. Count three of these to a significant degree, or four if the mood is only irritable, over one week (or any duration if hospitalised), with the mood-and-energy anchor present.

TRAP **Do not read decreased need for sleep as insomnia.** In mania the person sleeps little yet feels rested and energised; insomnia is wanting to sleep but being unable to. Only the former counts toward DIGFAST.

15.4 Criterion C: marked impairment, hospitalisation, or psychosis

The final required criterion sets the severity floor that distinguishes mania from hypomania. DSM-5-TR criterion C is satisfied by **any one** of three conditions: the mood disturbance is severe enough to cause **marked impairment** in social or occupational functioning; it **necessitates hospitalisation** to prevent harm to self or others; or there are **psychotic features** (DSM-5-TR). By definition, the presence of psychotic features during the episode makes it manic, never hypomanic. ICD-11 phrases the same threshold as significant impairment, or the need for intensive treatment such as hospitalisation to prevent harm, or the presence of delusions or hallucinations (ICD-11 CDDR). Any one of these three, on its own, lifts a candidate episode above the hypomania line.

WORKED EXAMPLE

A 26-year-old man is brought in after nine days of barely sleeping, talking non-stop, spending his savings on a business he cannot explain, and telling relatives he has been chosen to reform the country. Count it: the mood is expansive with grandiosity, and there is a clear rise in goal-directed activity (the two-part anchor); over more than one week he shows grandiosity, decreased need for sleep, pressured speech, and reckless spending, which is four DIGFAST symptoms; and the financial ruin plus the need for admission satisfy criterion C. This is a manic episode. Because the grandiosity has reached the belief of a special mission, screen for psychotic features: if it is held with delusional conviction, the episode is manic with psychotic features.

15.5 Severity and the psychotic features of mania

Mania is graded from a syndrome that just clears threshold to a life-threatening state. When present, **psychotic features** are most often **mood-congruent**: grandiose delusions consonant with the elevated mood, such as beliefs of special powers, a divine mission, exceptional wealth or a special relationship to a famous person (ICD-11 CDDR; Kaplan & Sadock 2024). Less often the psychosis is **mood-incongruent**, carrying persecutory, self-referential, or passivity and thought-interference phenomena (thought insertion, withdrawal or broadcast) whose content does not fit the elevated mood; the incongruent pattern is the harder one and points toward the schizoaffective boundary (ICD-11 CDDR). Hallucinations are less frequent than delusions and usually accompany the delusional theme. The fuller handling of mood with psychotic features and the schizoaffective boundary is cross-referenced to the Other psychotic disorders, delusional syndromes and catatonia notes.

RULE **Manic psychosis is grandiose until proven otherwise.** The default psychotic feature of mania is a mood-congruent grandiose delusion; mood-incongruent or first-rank content should prompt a look toward the schizoaffective boundary.

15.6 Delirious (Bell's) mania: the extreme

At the severe extreme sits delirious mania, also called Bell's mania after Luther Bell, who described it in 1849 (Kaplan & Sadock 2024). It is a rapidly escalating triad of manic excitement, psychosis and a clouded, delirium-like disturbance of consciousness with disorientation, and it frequently overlaps with catatonic features. It is a psychiatric emergency: exhaustion,

hyperthermia and dehydration threaten life, and it is classically responsive to ECT. The catatonia entity itself and the ECT technique are cross-referenced to the Other psychotic disorders, delusional syndromes and catatonia notes and the ECT and neurostimulation notes respectively; what to hold here is that the most severe manic presentation carries clouding of consciousness and demands urgent treatment.

INDIA

Severe and psychotic manic and delirious-mania presentations are a recognised indication for ECT in Indian practice, where ECT is widely available in teaching hospitals and is used for treatment-refractory, catatonic or life-threatening mania; the technique itself is owned by the ECT and neurostimulation notes.

15.7 The differential from hypomania, and a management pointer

The single most examined discrimination is manic episode versus hypomanic episode, and it turns on four axes: **duration** (one week versus four days), **severity/impairment** (marked impairment in mania, no marked impairment in hypomania), **psychosis** (its presence defines the episode as manic and excludes hypomania), and **hospitalisation** (needing admission defines mania). Hypomania is, in essence, the same symptom picture at a shorter duration and a lower severity that stops short of marked impairment, psychosis or admission; the detailed hypomania criteria are the subject of the next topic (DSM-5-TR; ICD-11 CDDR). For management, the one-line pointer: a confirmed manic episode is treated with a mood stabiliser or an atypical antipsychotic first-line (lithium, quetiapine, divalproex, aripiprazole and others), any antidepressant is discontinued, and the acute and maintenance detail is owned by the bipolar-management topic and the Mood disorders: pharmacotherapy notes (CANMAT 2018).

AXIS	MANIC EPISODE	HYPOMANIC EPISODE
Minimum duration	**At least one week (or any duration if hospitalised)**	At least four consecutive days
Impairment	**Marked impairment in social or occupational functioning**	Observable change, but no marked impairment
Psychotic features	**May be present; if present, the episode is by definition manic**	Absent (any psychosis makes it manic)
Hospitalisation	**May require admission; need for admission defines mania**	Does not require admission
Symptom count	3 or more DIGFAST (4 if mood only irritable)	Same set, same count

The manic-versus-hypomanic grid: the four discriminators (duration, impairment, psychosis, hospitalisation) that lift an episode from hypomania to mania; the highlighted cells are the mania-defining features.

TRAP **Do not call an impairing, psychotic or hospitalised episode "hypomania".** Marked impairment, any psychotic feature, or the need for admission each independently makes the episode manic; hypomania has none of these.

PEARL

Think of the four "mania makers", each sufficient on its own to exclude hypomania: a full week's duration, marked impairment, psychosis, and hospitalisation. If any one is present, the episode is manic, and a single lifetime manic episode is enough to diagnose bipolar type I disorder.

GOOD TO REMEMBER

- **Manic episode:** abnormally elevated or irritable mood plus increased activity/energy (the two-part gate), lasting at least **one week** (or any duration if hospitalisation is needed), with three or more DIGFAST symptoms (four if mood only irritable) and marked impairment, hospitalisation, or psychosis; one lifetime episode diagnoses bipolar type I.
- **DIGFAST:** Distractibility, Indiscretion/impulsivity, Grandiosity, Flight of ideas, Activity increase, Sleep decrease, Talkativeness; the count to hold is 3, or 4 if irritable-only.
- **Psychotic features of mania:** most often mood-congruent grandiose delusions; less often mood-incongruent; their presence makes the episode manic, never hypomanic.
- **Delirious (Bell's) mania:** manic excitement plus psychosis plus clouded consciousness/delirium, often with catatonia; the eponym is Luther Bell (1849), and it is an ECT-responsive emergency.

HOLD THIS

One week (or hospitalisation), the two-part mood-and-energy gate, three DIGFAST symptoms (four if irritable-only), and marked impairment or psychosis: any one of impairment, psychosis or admission makes it mania, not hypomania.

16 · Bipolar II and hypomania

Why this matters. **bipolar ii** disorder is the diagnosis the exam loves because it is the one most easily missed at the bedside and most easily faked on paper. The patient almost always arrives depressed, the highs are quiet and ego-syntonic, and the whole diagnosis rests on documenting a single genuine **hypomanic episode** that the patient and often the last three clinicians never noticed. Two reflexes are tested: the precise definition of the disorder (at least one hypomanic episode and at least one major depressive episode, and never a manic episode), and the exact **hypomania** threshold, the same symptom set as mania but at a shorter duration and, decisively, under the impairment, psychosis and hospitalisation ceilings that separate it from mania.

Fig 11.7 Longitudinal course distinguishes recurrent unipolar depression from bipolar I, with full manic peaks, and bipolar II, with hypomanic peaks plus major depressive episodes.

Fig 11.8 Mania, hypomania and depression differ in activation, symptom intensity, duration and functional consequence; hypomania is not merely a milder visual version of mania but lacks marked impairment or psychosis.

This topic teaches the disorder-level definition and the hypomanic-episode criteria in full, since the manic-episode and depressive-episode criteria are taught in this chapter's own episode topics and the raw descriptive definitions of the individual mood symptoms sit in the Psychometry, Assessment and Descriptive Psychopathology notes. Nosology is given ICD-11 primary, DSM-5-TR cross-mapped, with ICD-10 (F31) flagged where the exams still cite it. The deep drug pharmacology of bipolar depression is owned by the Mood disorders: pharmacotherapy notes and only pointed to here.

16.1 The definition: a hypomania and a depression, but never a mania

Two episodes required, one episode forbidden. DSM-5-TR Criterion A for bipolar II disorder requires that criteria have been met for at least one hypomanic episode (Criteria A to F under Hypomanic Episode) *and* at least one major depressive episode (Criteria A to C under Major Depressive Episode); Criterion B states plainly that **there has never been a manic episode** (DSM-5-TR 2022). The presence of even one lifetime manic episode instantly re-diagnoses the

patient as bipolar I disorder and excludes bipolar II. ICD-11 mirrors this exactly: bipolar type II disorder (6A61) requires a history of at least one hypomanic episode and at least one depressive episode, with **no history of manic or mixed episodes** (ICD-11 CDDR). The disorder is therefore defined by a specific pair plus an absolute exclusion: a hypomania, a depression, and never a mania.

RULE **bipolar ii needs a hypomania and an MDE, never a mania.** At least one hypomanic episode plus at least one major depressive episode, with no lifetime manic episode, is the whole definition; one mania makes it bipolar I.

TRAP **Do not diagnose bipolar II without a documented hypomanic episode.** A recurrent, early, atypical depression *suggests* bipolarity, but the label requires a genuine hypomanic episode on the record, not a temperament, a family history or a hunch.

16.2 The hypomania threshold: the same symptoms as mania, for four days

Mania's symptom set at a lower altitude. DSM-5-TR Criterion A for a hypomanic episode requires a distinct period of abnormally and persistently elevated, expansive, or irritable mood *and* abnormally and persistently increased activity or energy, lasting at least **four consecutive days** and present most of the day, nearly every day (DSM-5-TR 2022). Within that window, Criterion B requires **three or more** of the seven-symptom set (the same DIGFAST set as mania), rising to **four or more if the mood is only irritable**: inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual, flight of ideas, distractibility, increase in goal-directed activity or psychomotor agitation, and excessive involvement in activities with a high potential for painful consequences (DSM-5-TR 2022). The single number that separates hypomania from mania is the duration floor: **four days** for hypomania against **at least one week** for mania. ICD-11 keeps the same symptom picture but does not fix a day-count, requiring only that the disturbance persist for **at least several days** (ICD-11 CDDR); when the exam wants a number, quote the DSM-5-TR four days.

RULE **Hypomania is at least four days and under the ceilings.** The DSM-5-TR duration floor is four consecutive days (ICD-11 says at least several days), and the episode must stay below marked impairment, psychosis and hospitalisation.

16.3 The three ceilings: observable change without marked impairment, psychosis or admission

What is present, and what must be absent. Two things must be positively present. DSM-5-TR Criterion C requires that the episode is associated with an **unequivocal change in functioning that is uncharacteristic** of the individual when not symptomatic, and Criterion D requires that the disturbance in mood and the change in functioning are **observable by others** (DSM-5-TR 2022). Three things must be absent, and they are the crux. DSM-5-TR Criterion E states the episode is **not severe enough to cause marked impairment** in social or occupational functioning or to necessitate hospitalisation, and that **if there are psychotic features, the episode is, by definition, manic** (DSM-5-TR 2022). So hypomania is defined **without marked impairment**, without psychotic features and without hospitalisation. Any one of impairment, psychosis or

hospitalisation, on its own, converts the episode from hypomania into mania, and therefore the patient from bipolar II into bipolar I. ICD-11 phrases the same ceilings: the mood disturbance is not sufficiently severe to result in marked impairment or to require intensive treatment such as hospitalisation, and is not accompanied by delusions or hallucinations (ICD-11 CDDR).

at least four days	**at least several days**	**3 (or 4)**	**at least 2 wk**
HYPOMANIC EPISODE (DSM-5-TR)	HYPOMANIC EPISODE (ICD-11)	DIGFAST SYMPTOMS, 4 IF IRRITABLE-ONLY	THE REQUIRED MAJOR DEPRESSIVE EPISODE

TRAP **Do not upgrade an impairing episode to "hypomania".** If the high caused marked impairment, needed admission, or carried any psychotic feature, it was a manic episode; calling it hypomania to fit a bipolar II label is the classic error.

WORKED EXAMPLE

A 27-year-old woman presents with her fourth episode of low mood since age 20: each time she sleeps eleven hours, feels leaden and craves carbohydrate. She denies ever being "manic". On careful behavioural-activation screening she recalls two distinct spells, each lasting five to six days, of needing only four hours of sleep, redecorating the flat overnight, talking so fast that friends teased her and feeling unusually confident, changes her sister clearly noticed. There was no marked impairment, no admission and no psychosis. Count it: elevated mood plus increased activity, over four days, with decreased need for sleep, pressured speech, grandiosity and goal-directed activity (four DIGFAST symptoms), observable by others and under all three ceilings. That is a hypomanic episode, and with recurrent major depression the diagnosis is bipolar II disorder. An antidepressant alone would have been the wrong first move.

16.4 The clinical reality: presents depressed, hypomania under-recognised, and a heavy burden

The illness you meet is depression; the diagnosis you make is bipolar. Individuals with bipolar II disorder **typically present to a clinician during a major depressive episode** and are unlikely to complain of hypomania, because they either do not recognise its symptoms or consider the state desirable (DSM-5-TR 2022). Hypomania by definition does not cause significant impairment, so the impairment, and hence the presentation, comes from the depressive episodes or from the persistent, unpredictable mood instability; collateral history from family is often what establishes the diagnosis (DSM-5-TR 2022). Critically, DSM-5-TR is explicit that bipolar II disorder **is not a "milder form" of bipolar I disorder**: compared with bipolar I, patients have greater chronicity of illness and spend, on average, **more time in the depressive phase**, which can be severe and disabling, and the overall bipolar suicide burden is high (DSM-5-TR 2022). The one-line management pointer: because the presenting state is bipolar depression, the treatment is guideline-anchored and phase-based, led by mood-stabilising and atypical-antipsychotic agents rather than an antidepressant alone, and the full plan is taught in the bipolar-management topic and the Mood disorders: pharmacotherapy notes (CANMAT 2018).

COMMON TRAP

Treating the depressive presentation of bipolar II as unipolar major depression and starting an antidepressant alone. The switch, cycling and mixed-state risks, and the guideline-preferred bipolar-depression agents, sit in the Mood disorders: pharmacotherapy notes and the bipolar-management topic; the reflex to hold here is to screen every depression for a past hypomanic episode before committing.

16.5 Nosology: ICD-11 gives bipolar II its own category, ICD-10 does not

A coding difference the exam can probe. DSM-5-TR and ICD-11 both recognise bipolar II as a discrete disorder: DSM-5-TR codes it F31.81, and ICD-11 gives it code 6A61 with the essential features stated above (DSM-5-TR 2022; ICD-11 CDDR). ICD-10, by contrast, has **no separate bipolar II category**: bipolar affective disorder is coded under F31 on a history of discrete episodes of mania, hypomania and depression, so a bipolar II picture maps onto F31 (for example F31.0 for a current hypomanic episode, or F31.3 to F31.5 for the depressive episodes) rather than to a dedicated code (ICD-11 CDDR mapping table). For the exam: name bipolar II as its own disorder in DSM-5-TR (F31.81) and ICD-11 (6A61), and flag that ICD-10 folds it under F31 without a standalone bipolar II label.

PEARL

Bipolar II is defined by the softest high and the heaviest lows: the hypomania is quiet and often welcomed, but the depressions are more chronic and occupy more of the lifetime clock than in bipolar I. That asymmetry, not "mild mania", is why bipolar II is a serious diagnosis and never a lesser one (DSM-5-TR 2022).

FEATURE	HYPOMANIC EPISODE	MANIC EPISODE
Minimum duration	At least four consecutive days (ICD-11: at least several days)	**At least one week (or any duration if hospitalised)**
Symptom set and count	Same DIGFAST set, three or more (four if irritable-only)	Same DIGFAST set, three or more (four if irritable-only)
Change in functioning	Unequivocal, uncharacteristic, observable by others	Present, but reaching marked impairment
Marked impairment	**Absent (without marked impairment)**	Present (marked social/occupational impairment)
Psychotic features	**Absent (any psychosis makes it manic)**	May be present; if present, the episode is manic
Hospitalisation	**Not required**	May be required; need for admission defines mania
Diagnosis it defines (with MDE)	Bipolar II disorder	Bipolar I disorder

The hypomania-versus-mania grid: identical symptom set and count, but hypomania is shorter and stays under the three ceilings (impairment, psychosis, admission); the highlighted cells are the features that keep the episode hypomanic rather than manic.

MNEMONIC

FOUR DAYS, NO CEILING BROKEN

Read it as the whole hypomania test: at least FOUR DAYS of the manic symptom set, with NO CEILING BROKEN, no marked impairment, no psychosis, no hospitalisation. Break any one ceiling and it is mania; pair the intact hypomania with a major depression and it is bipolar II.

HOLD THIS

Hypomania is the manic symptom set for at least four days (ICD-11: at least several days), observable, without marked impairment, without psychosis and without hospitalisation; bipolar II needs one such hypomanic episode plus one major depressive episode and never a manic episode, and it presents depressed with the hypomania missed.

GOOD TO REMEMBER

- **Hypomanic episode:** the manic symptom set (three or more DIGFAST, four if irritable-only) lasting at least four days, with an observable, uncharacteristic change in functioning but *without marked impairment*, without psychotic features and without hospitalisation; hold "at least four days (DSM-5-TR), at least several days (ICD-11), and no ceiling broken."
- **Bipolar II disorder:** at least one hypomanic episode and at least one major depressive episode, with no lifetime manic episode; the one discriminator is a documented genuine hypomanic episode plus an intact "never a mania"; hold the code F31.81 (DSM-5-TR) / 6A61 (ICD-11).
- **The three mania-makers (excluded in hypomania):** marked impairment, any psychotic feature, or the need for hospitalisation; the one discriminator is that any single one converts hypomania to mania and bipolar II to bipolar I; hold "any one makes it mania, not hypomania."
- **Clinical reality and burden:** presents in the depressive phase with the hypomania under-recognised, not a milder illness, with more lifetime time spent depressed than in bipolar I and a high suicide risk; the one discriminator is the depressive-predominant, quiet-high profile; hold "presents depressed, screen every depression for a past hypomanic episode."
- **Nosology:** a discrete disorder in DSM-5-TR (F31.81) and ICD-11 (6A61), but ICD-10 has no separate bipolar II and folds it under F31; hold "ICD-11 6A61 primary, ICD-10 F31 (no standalone bipolar II)."

17 · Cyclothymia

Why this matters. **Cyclothymia** is the chronic, sub-threshold floor of the bipolar spectrum: numerous ups and downs, neither of which is ever severe or long enough to become a full hypomanic or a full major depressive episode. The examiner tests it because it is doubly easy to get wrong, over-read as ordinary moodiness or a personality problem, or under-read and missed as a bipolar diathesis that will later declare itself. The single reflex to build is that **cyclothymic disorder** is **chronic sub-threshold bipolarity**, defined by duration and persistence rather than the depth of any one swing, and that it sits on a continuum with the **cyclothymic temperament** at one end and bipolar I or bipolar II at the other (Kaplan & Sadock 2024; Akiskal 2007).

Nosology is given ICD-11 primary (the ICD-11 CDDR term is cyclothymic disorder), with the DSM-5 (the DSM-5-TR) cross-mapped and ICD-10 flagged where Indian exams still cite it (ICD-10 uses the bare term cyclothymia, F34.0). The raw descriptive definitions of the individual hypomanic and depressive symptoms are owned by the Psychometry, Assessment and

Descriptive Psychopathology notes and cross-referenced here, not re-derived; the deep drug pharmacology, dosing and treatment-resistance algorithms belong to the Mood disorders: pharmacotherapy notes; and the full soft-bipolar spectrum is laid out in this chapter's unipolar-versus-bipolar-spectrum topic, of which cyclothymia is one rung.

17.1 The core criteria: two years of sub-threshold ups and downs

The defining criterion of cyclothymic disorder is **at least two years** (**at least 1 year in children and adolescents**) of numerous periods of hypomanic symptoms that do **not** meet the threshold for a hypomanic episode and numerous periods of depressive symptoms that do **not** meet the threshold for a major depressive episode (DSM-5-TR Criterion A; ICD-11 CDDR). Over that span the symptoms must be present for at least **half the time** (ICD-11 CDDR phrases this as "more days than not"), and the patient must never have been symptom-free for more than **two months** at a time (DSM-5-TR Criterion B). Crucially, criteria for a major depressive, manic, or hypomanic episode must **never** have been met (DSM-5-TR Criterion C), and the pattern must cause clinically significant distress or impairment (DSM-5-TR Criterion F). It is the "never symptom-free for more than two months" clause plus the "never a full episode" clause together that fix cyclothymia as chronic and sub-threshold rather than as an early bipolar disorder.

RULE **Cyclothymia is chronic sub-threshold bipolarity.** At least two years (one year in youth) of numerous hypomanic and depressive symptoms, present at least half the time, never symptom-free for more than two months, and never once reaching full episode threshold.

17.2 The exclusions and the conversion rule

The remaining criteria are exclusions and a conversion clause. The mood swings must not be better explained by a schizophrenia spectrum or other psychotic disorder (DSM-5-TR Criterion D), and must not be attributable to a substance or medication (especially stimulants, including withdrawal) or another medical condition such as hyperthyroidism (DSM-5-TR Criterion E; ICD-11 CDDR). The conversion rule is the high-yield twist: if, **after** the initial two years (one year in youth), the patient goes on to experience a full major depressive, manic, or hypomanic episode, the diagnosis **changes** to major depressive disorder, bipolar I disorder, or a bipolar II or other specified bipolar and related disorder respectively, and the cyclothymic disorder label is dropped (DSM-5-TR; ICD-11 CDDR). ICD-11 adds that during the first two years there must never have been a two-week period meeting depressive-episode requirements, and that individuals with cyclothymic disorder do not typically show psychotic symptoms (ICD-11 CDDR).

CRITERION	DSM-5-TR (CYCLOTHYMIC DISORDER)	ICD-11 CDDR (CYCLOTHYMIC DISORDER)
Duration	**At least 2 years; at least 1 year in children and adolescents**	**At least 2 years; a briefer initial period (about 1 year) may suffice in children**
Content	Numerous periods of hypomanic symptoms and of depressive symptoms, both sub-threshold	Numerous hypomanic and depressive periods; depressed mood may present as irritability in youth

CRITERION	DSM-5-TR (CYCLOTHYMIC DISORDER)	ICD-11 CDDR (CYCLOTHYMIC DISORDER)
Persistence	**Symptoms present at least half the time; never symptom-free for more than 2 months**	**Present more days than not; no prolonged (2 months or more) symptom-free period since onset**
Episode ceiling	Full major depressive, manic, or hypomanic episode never met	**No history of manic or mixed episodes; no depressive-episode-level 2-week period in the first 2 years**
Exclusions	Not a psychotic disorder; not a substance, medication, or medical condition (e.g. hyperthyroidism)	Not a substance, medication (e.g. stimulants), or medical condition; psychosis atypical
Impact	Clinically significant distress or impairment in functioning	Significant distress about the mood instability, or impairment sustained only through extra effort

DSM-5-TR and ICD-11 CDDR agree closely: the highlighted cells are the load-bearing discriminators, the two-year floor, the at-least-half-the-time persistence with no two-month gap, and the never-a-full-episode ceiling.

TRAP **Do not keep the cyclothymia label once a full episode appears.** A subsequent manic episode makes it bipolar I; a depressive episode with a past hypomanic episode makes it bipolar II; the cyclothymic disorder diagnosis is then dropped.

17.3 Position on the bipolar spectrum, temperament, and progression risk

Cyclothymia is one of the attenuated, temperamental variants at the mild end of the bipolar spectrum, the "soft bipolar" territory Kraepelin and Kretschmer described as predisposing substrates and Akiskal formalised (Kaplan & Sadock 2024; Akiskal 2007). Two related ideas sit here. First, the cyclothymic temperament is the trait-level, lifelong version, biphasic mood lability that is a habitual baseline rather than a disorder, and it shades into cyclothymic disorder when it produces distress or impairment; the disorder is often "considered to reflect a temperamental predisposition" to the other bipolar disorders (DSM-5-TR). Second, in Akiskal's numbered spectrum, cyclothymic depressions define **bipolar two-and-a-half**, depressive episodes arising on a cyclothymic base, positioned between bipolar II and the antidepressant-associated bipolar III (Akiskal 2007; see this chapter's unipolar-versus-bipolar-spectrum topic). On progression, DSM-5-TR gives a **15% to 50%** risk that a person with cyclothymic disorder will subsequently develop bipolar I or bipolar II disorder, with higher conversion rates in youth than in adults (DSM-5-TR); ICD-11 concurs that these individuals are at high risk of converting, while noting that in children the most common trajectory is actually remission (ICD-11 CDDR).

at least 2 years DURATION (1 YEAR IN YOUTH)	**at least half the time** SYMPTOMS PRESENT	**15% to 50%** PROGRESSION TO BIPOLAR I OR II	**0.4% to 2.5%** LIFETIME PREVALENCE

17.4 Epidemiology and onset

The lifetime prevalence of cyclothymic disorder in the United States and Europe is approximately **0.4% to 2.5%**, rising to around **3% to 5%** in mood-disorder clinic samples (DSM-5-TR). In the general population it is about equally common in males and females, although in clinical settings females may present for treatment more often (DSM-5-TR). Onset is typically insidious, in adolescence or early adult life, and the course is persistent; in children the onset of mood symptoms is usually **before age 10**, with irritability and sleep disturbance the prominent presenting features, and cyclothymic disorder is thought to be under-diagnosed in this age group despite being more common there than bipolar I or bipolar II (DSM-5-TR; ICD-11 CDDR). First-degree relatives show raised rates of major depressive disorder, bipolar I and bipolar II disorder, and of substance-related disorders, and cyclothymic disorder itself is more common among the relatives of people with bipolar I disorder (DSM-5-TR).

INDIA

Cyclothymic disorder is rarely a stand-alone presenting complaint in Indian practice: the sub-threshold swings are commonly brought to attention only when a full episode supervenes or when comorbid substance use surfaces, and the label is easily missed against a backdrop of "moody temperament". ICD-10 (F34.0, cyclothymia) remains in day-to-day coding use, so the resident should be able to map the ICD-11 cyclothymic disorder criteria onto the older category. No India-specific brand name is relevant here; drug brands belong to the Mood disorders: pharmacotherapy notes.

17.5 The differential: cyclothymia versus borderline personality disorder

The classic trap is mistaking cyclothymia for the emotional instability of a borderline personality disorder, and the two can genuinely co-occur, so the discrimination is on quality and content of the affective shifts rather than their mere presence (DSM-5-TR; Kaplan & Sadock 2024). In borderline personality disorder the mood instability sits in the domains of **anxiety, irritability, and sadness**, usually reactive to interpersonal triggers (rejection, abandonment), and **elation, euphoria, and increased energy are not characteristic**; there is enduring disturbance of self-image and unstable, idealising-then-devaluing relationships (DSM-5-TR). In cyclothymia the shifts are into genuine hypomanic territory, elevated mood, increased energy, decreased need for sleep, and they are episodic and often lack an adequate precipitant (endoreactive), without the fixed self-functioning and interpersonal pathology that define a personality disorder (Kaplan & Sadock 2024; ICD-11 CDDR). ICD-11 makes the operational point: assess personality outside a mood episode, and assign both diagnoses only if each set of requirements is independently met (ICD-11 CDDR).

FEATURE	CYCLOTHYMIC DISORDER	BORDERLINE PERSONALITY DISORDER
Poles of instability	**Hypomanic (elation, energy, reduced sleep) alternating with sub-threshold depression**	**Anxiety, irritability, sadness; elation and euphoria not characteristic**
Trigger	Often endoreactive, lacking an adequate precipitant; episodic	Typically reactive to interpersonal events (rejection, abandonment)
Core disturbance	An affective (mood) diathesis; self-image intact between swings	**Enduring identity disturbance and unstable idealise-devalue relationships**
Time frame	Sub-threshold mood periods over at least 2 years, no full episode	Pervasive trait pattern from adolescence, across contexts

The discriminator is the up-pole and the core disturbance: true hypomanic colour and an intact between-swing self point to cyclothymia; anxiety-irritability-sadness swings with identity disturbance point to borderline personality disorder.

17.6 Management pointer: mood stabiliser, and caution with antidepressants

Management is a one-line pointer here, with the detailed agents, dosing and algorithms owned by the Mood disorders: pharmacotherapy notes. There are no firm guideline recommendations specific to cyclothymic disorder, and no clear consensus on the most effective pharmacotherapy (Tasman). The pragmatic stance is to treat it as attenuated bipolarity: favour a **mood stabiliser** over an antidepressant, with some evidence that lamotrigine stabilises some of the symptoms of cyclothymia (Manning et al. 2005, cited in Tasman), and structured psychotherapy has support, a sequential CBT-plus-well-being-therapy programme outperformed routine care in a controlled trial with gains maintained at two years (Fava et al. 2011). The **caution with antidepressants** is the examinable point: antidepressants can mobilise hypomania and can aggravate a cycling course in a bipolar-spectrum patient, so an antidepressant used alone, without mood-stabiliser cover, risks switching or destabilisation (Kaplan & Sadock 2024).

TRAP **Do not start an antidepressant alone in cyclothymia.** It can mobilise hypomania and worsen cycling; the mood-stabiliser-first logic of the bipolar spectrum applies to its sub-threshold floor too.

MNEMONIC

TWO-TWO-NEVER

Two years of sub-threshold swings (one in youth), present at least half the time and never symptom-free for more than two months, and never once a full episode: the three numbers that lock cyclothymic disorder.

GOOD TO REMEMBER

- **Cyclothymia (cyclothymic disorder):** chronic sub-threshold bipolarity, **at least two years** (one year in youth) of numerous hypomanic and depressive symptoms that never meet full episode threshold, present at least half the time, never symptom-free for more than **two months**, causing distress or impairment; ICD-11 primary, DSM-5-TR cross-mapped, ICD-10 F34.0.
- **Progression:** a **15% to 50%** lifetime risk of converting to bipolar I or bipolar II disorder (higher in youth), the one number to hold; a full episode reclassifies and drops the diagnosis.
- **Cyclothymic temperament:** the lifelong trait-level version, the habitual biphasic-labile baseline that shades into the disorder when it causes distress; Akiskal's cyclothymic depressions define bipolar two-and-a-half.
- **Management:** mood stabiliser preferred (lamotrigine has some evidence; Manning et al. 2005) with structured psychotherapy (Fava et al. 2011); caution with antidepressants, which can mobilise hypomania.

PEARL

Screen every apparently "unipolar" chronic depression and every "moody personality" for the cyclothymic pattern: a history of numerous short, endoreactive highs with reduced sleep need and elevated energy, alongside sub-threshold lows over years, is chronic sub-threshold bipolarity, and it changes the treatment logic from antidepressant-first to mood-stabiliser-first.

HOLD THIS

Cyclothymia is chronic sub-threshold bipolarity: at least two years (one in youth) of numerous hypomanic and depressive symptoms, present at least half the time, never symptom-free for more than two months and never a full episode, carrying a 15% to 50% risk of progression to bipolar I or II; treat with a mood stabiliser, be cautious with antidepressants, and do not mistake it for the emotional instability of a personality disorder.

18 · Mixed features and mixed affective states

Why this matters. A **mixed affective** presentation is where opposite-pole symptoms co-occur inside one mood episode: depressive symptoms intruding on a manic or hypomanic picture, or manic symptoms intruding on a depressive one. The examiner rewards three moves here. First, the nosological shift from a self-standing **mixed episode** in ICD-10 to a **mixed-features qualifier** attached to an episode in DSM-5, with ICD-11 sitting between the two. Second, the two classic clinical pictures, **dysphoric mania** and agitated (mixed) depression, and their Kraepelinian ancestry. Third, and most testable, the clinical weight: mixed features flag underlying bipolarity, predict a worse course and a higher suicide risk, and blunt the antidepressant response, so they change what you prescribe.

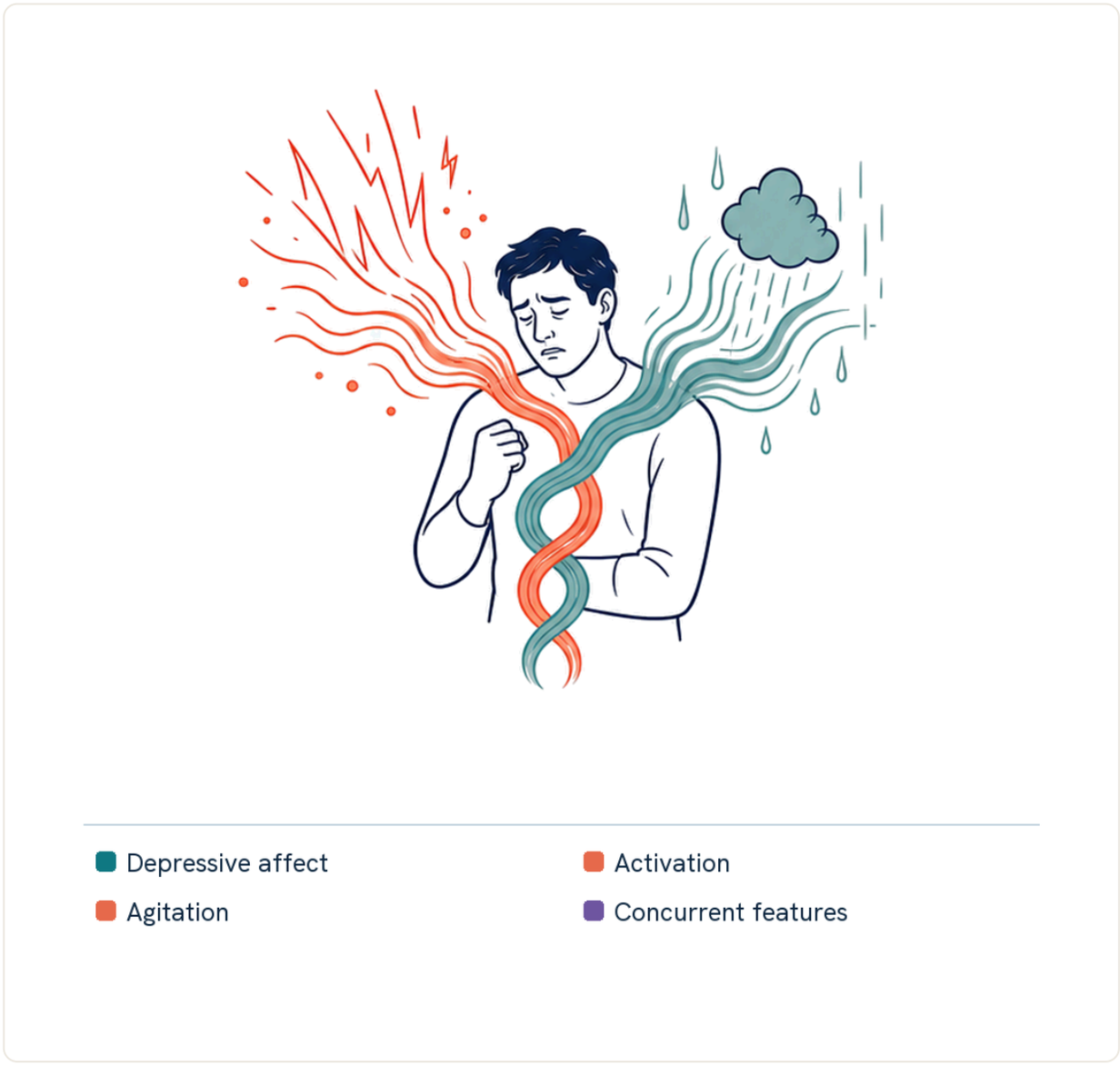

Fig 11.9 Mixed features combine elements from the opposite mood pole in the same episode, for example depressive affect with increased activation or agitation, rather than simple sequential switching.

Nosology is given ICD-11 primary, with the DSM-5 (the DSM-5-TR) rule cross-mapped and ICD-10 flagged because Indian exams still cite its mixed episode (F38.00 in the mood-disorders block, and F31.6 for bipolar affective disorder, current episode mixed). The full manic-episode and major-depressive-episode criteria on which this rests are the canonical property of the manic-episode and MDD topics; the raw descriptive definitions of the individual mood symptoms belong to the Psychometry, Assessment and Descriptive Psychopathology notes. The deep pharmacology of the antimanic and antidepressant agents is owned by the Mood disorders: pharmacotherapy notes, and the guideline-level management of a mixed presentation is owned by the bipolar-management topic; what is taught here is the concept, the criteria for the qualifier, and the discrimination.

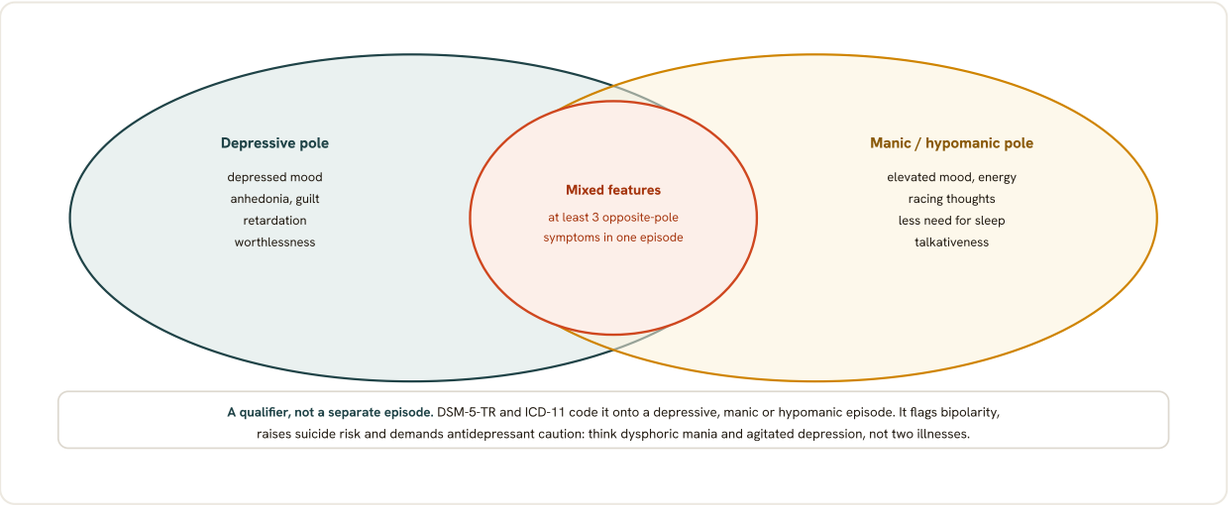

Fig 11.10 Mixed features: opposite-pole symptoms co-occurring within one episode. The DSM-5-TR "with mixed features" specifier needs at least three non-overlapping symptoms of the opposite pole and attaches to a depressive, manic or hypomanic episode rather than standing alone. The overlap is what separates true mixed features from a purely agitated depression or a straightforward dysphoric mania, and it flags bipolarity, a higher suicide risk and the need to avoid an antidepressant alone.

18.1 The core concept: opposite-pole symptoms inside one episode

A **mixed affective** state is defined by the simultaneous or rapidly alternating presence of symptoms of both mood poles within a single episode (Kaplan & Sadock 2024). The manic (or hypomanic) and the depressive symptoms are not sequenced across separate episodes but braided together in the same window: a patient may be flooded with racing thoughts, pressured speech and goal-directed overactivity while at the same time carrying dysphoric mood, hopelessness and active suicidal ideation. The clinical texture is one of internal contradiction, high energy driving a black mood, and it is this coupling of drive to despair that makes the state so dangerous. Transient tearfulness at the height of mania, or a few racing thoughts in a depression, is not a mixed state; the threshold is that *several* prominent contrapolar symptoms co-occur (ICD-11 CDDR).

RULE **Mixed means both poles, at once, in one episode.** Several prominent symptoms of the opposite pole must co-occur or alternate rapidly within a single episode; momentary lability at a pole-transition does not qualify.

18.2 From the ICD-10 mixed episode to the DSM-5 and ICD-11 qualifier

The nosology has moved from an episode to a specifier. ICD-10 classified a **mixed affective episode** as a distinct episode type: either a mixture, or a rapid alternation (within a few hours), of manic and depressive symptoms lasting at least two weeks. DSM-5 abolished the standalone DSM-IV "mixed episode" (which had required full criteria for both mania and depression nearly every day for a week) and replaced it with a **with mixed features qualifier** that is appended to a manic, hypomanic or major depressive episode (DSM-5-TR). ICD-11 takes an intermediate route: it keeps a named **mixed episode** as one of its mood-episode descriptions inside bipolar type I disorder (6A60), rather than reducing it to a pure specifier, defining it by several prominent manic symptoms occurring simultaneously or alternating rapidly with several prominent depressive symptoms across at least two weeks (ICD-11 CDDR). The single point to hold is the

direction of travel: the entity has migrated from a rare, all-or-none episode toward a dimensional feature that is far more commonly detected.

SYSTEM	HOW A MIXED PRESENTATION IS CODED	THRESHOLD
ICD-10	Mixed affective episode: a self-standing episode type (F38.00; bipolar current episode mixed F31.6)	**Mixture or rapid alternation of manic and depressive symptoms for at least 2 weeks**
DSM-IV	Mixed episode: a self-standing episode type	Full criteria for both mania and depression, nearly every day, for at least 1 week
DSM-5-TR	**"With mixed features" qualifier on a manic, hypomanic or depressive episode**	At least 3 non-overlapping opposite-pole symptoms on most days of the episode
ICD-11	Mixed episode retained as a mood-episode description within bipolar type I (6A60)	Several prominent manic and several prominent depressive symptoms, simultaneous or rapidly alternating, for at least 2 weeks

The migration of the mixed presentation across systems: from a standalone episode (ICD-10, DSM-IV) to a specifier (DSM-5-TR), with ICD-11 keeping a named mixed episode; the highlighted cells carry the modern thresholds.

TRAP **Do not expect DSM-5 to have a "mixed episode".** DSM-5-TR deleted the standalone mixed episode and replaced it with a "with mixed features" specifier; only ICD-10, DSM-IV and (as a retained description) ICD-11 name a mixed episode.

18.3 The DSM-5 rule: three non-overlapping opposite-pole symptoms

The DSM-5-TR **with mixed features** specifier applies when full criteria are met for one episode and **at least three** symptoms of the opposite pole are present on the majority of days of the episode (DSM-5-TR). The design is deliberately restrictive: the contrapolar symptom list is trimmed to the symptoms that are **non-overlapping** between the two poles. For a **depressive episode with mixed features**, the three-plus manic symptoms drawn on are elevated/expansive mood, grandiosity, talkativeness/pressured speech, flight of ideas or racing thoughts, increased energy or goal-directed activity, involvement in risky pleasurable activity, and decreased need for sleep. For a **manic or hypomanic episode with mixed features**, the three-plus depressive symptoms are dysphoria or depressed mood, anhedonia, psychomotor retardation, fatigue, worthlessness or guilt, and recurrent thoughts of death or suicidality. Critically, symptoms that are *shared* across both poles, namely irritability, distractibility, psychomotor agitation and insomnia, are excluded from the counting because they cannot discriminate the opposite pole (DSM-5-TR). If full criteria for both mania and depression are met simultaneously, the episode is coded as manic with mixed features, mania winning on severity (DSM-5-TR).

at least 3	most days	at least 2 wk	non-overlapping
OPPOSITE-POLE SYMPTOMS (DSM-5-TR)	OF THE EPISODE	ICD-11 MIXED EPISODE	IRRITABILITY/AGITATION EXCLUDED

COMMON TRAP

Counting irritability, distractibility, agitation or insomnia toward a DSM-5-TR mixed-features specifier. These four are common to both poles and are deliberately excluded; only the non-overlapping opposite-pole symptoms count. This is the single most tested detail of the specifier.

18.4 Dysphoric mania: the classic mixed manic picture

The prototype mixed manic state is dysphoric mania, also called mixed mania. It is a manic syndrome carrying a dysphorically excited mood, so the drive of mania is yoked to the misery of depression: irritability, anger, panic, pressured speech, agitation, severe insomnia, grandiosity, hypersexuality, and, ominously, suicidal ideation and persecutory ideas can all coexist (Kaplan & Sadock 2024). Two to four depressive symptoms (depressed mood, helplessness, hopelessness, fatigue, anhedonia, guilt, or suicidal ideation) arising in the setting of a manic syndrome are enough to define the mixed manic state, and such states occur in around **50%** of bipolar patients at some point in the illness, though full-blown co-occurrence of mania and complete depression (true "dysphoric mania" in the strict sense) is relatively uncommon (Kaplan & Sadock 2024). Mixed mania is over-represented in women, often arising as mania intruding on a depressive or dysthymic baseline; in men it more often arises through comorbid substance or alcohol use (Kaplan & Sadock 2024). A severely psychotic mixed state, with hallucinations and Schneiderian symptoms, can be genuinely hard to separate from schizoaffective disorder, which is cross-referenced to the Other psychotic disorders, delusional syndromes and catatonia notes.

GOOD TO REMEMBER

- **Dysphoric (mixed) mania:** a manic syndrome with a dysphoric, irritable, agitated mood and depressive admixtures; the one to hold is that suicidal ideation can co-occur with full manic drive. Roughly **50%** of bipolar patients have a mixed state at some point (Kaplan & Sadock 2024).

18.5 Agitated and mixed depression: the depressive-pole picture

The mirror picture is the depressive episode carrying manic admixtures: an **agitated, mixed depression**. Here the depressive syndrome runs with intrusions of the opposite pole, racing or crowded thoughts, inner tension and restlessness, psychomotor activation, pressured speech, and, at the severe end, sexual arousal and increased energy despite the depressed mood (Kaplan & Sadock 2024). This is the "depression with increased energy or irritability" that patients themselves may not label as anything but a bad depression (DSM-5-TR). Depressive mixed states are strikingly common on the bipolar side of the ledger: they occur in as much as **60%** of bipolar II depressions and in around **30%** of ostensibly "unipolar" major depressions, a finding that repositions a substantial slice of "unipolar" depression as latently bipolar (Kaplan & Sadock 2024). The agitated, mixed depression is the presentation most dangerous to mismanage, because the reflex to reach for an antidepressant is exactly wrong (see 18.7).

GOOD TO REMEMBER

- **Agitated/mixed depression:** a depressive episode with racing thoughts, inner tension, activation and pressured speech; the discriminating feature is manic admixture inside a depression. It appears in up to **60%** of bipolar II and about **30%** of "unipolar" depressions (Kaplan & Sadock 2024).

18.6 The Kraepelinian mixed states: the historical scaffold

The concept is Kraepelinian in origin. Emil Kraepelin held that manic-depressive illness was one disease whose surface state was set by three independent axes, mood, thought or ideation, and psychomotor activity, each of which could run high (manic) or low (depressive). When the three axes did not move together, so that, for instance, mood was depressed while thought and activity were accelerated, the result was a **mixed state** rather than a pure mania or depression (Kaplan & Sadock 2024). This cross-combination of the three axes is the historical scaffold behind the modern qualifier, and it explains why mixed states are best thought of dimensionally rather than as a single stereotyped picture; the pure "excited depression" and "depressive or anxious mania" of the classic descriptions are simply particular settings of the three dials. The examiner point is the framework, that Kraepelin generated the mixed states by dissociating mood, thought and psychomotor activity, not any single memorised list.

PEARL

Kraepelin's insight was that mania and depression are not opposite ends of one dial but the joint state of three separate dials (mood, thought, psychomotricity); a mixed state is simply any setting where those dials disagree. Modern "mixed features" is that idea made operational.

18.7 Why it matters: bipolarity, worse course, suicide, antidepressant caution

Mixed features are not a curiosity; they carry heavy prognostic and management freight. Four consequences are examinable. First, **they flag bipolarity**: mixed features in a major depressive episode are a recognised risk factor for the later emergence of bipolar I or bipolar II disorder, so their presence should shift the diagnostic bet toward the bipolar spectrum (DSM-5-TR). Second, **a worse course**: the presence of mixed features in an episode is associated with a poorer prognosis and a poorer lithium response (DSM-5-TR; Kaplan & Sadock 2024). Third, **a higher suicide risk**: mixed features are associated with increased suicide attempts, the coupling of depressive hopelessness to manic drive and impulsivity being the lethal combination (DSM-5-TR); the clinical assessment of that risk is owned by the Somatic-symptom, sexual, impulse-control disorders and suicide notes. Fourth, **a poorer antidepressant response and a real hazard**: an antidepressant given alone into a mixed depression can worsen the mixed and manic pole and destabilise the illness, so the management pivots away from antidepressant monotherapy toward mood stabilisers or atypical antipsychotics (Kaplan & Sadock 2024). The guideline-level detail of that management is the property of the bipolar-management topic and the Mood disorders: pharmacotherapy notes.

RULE **Mixed features flag bipolarity and raise suicide risk.** Contrapolar symptoms in a depression predict a bipolar course, a poorer lithium response and more suicide attempts, and they change management.

TRAP **Do not treat an agitated, mixed depression with an antidepressant alone.** Antidepressant monotherapy into a mixed depression can worsen the mixed/manic pole; screen every activated depression for mixed features and past hypomania first.

INDIA

In Indian practice, where many bipolar presentations first reach care during a depressive phase, an agitated, mixed depression is a frequent and easily missed presentation; the working caution is to screen every depression for a past hypomanic episode and for current contrapolar symptoms before committing to an antidepressant. Severe, psychotic or life-threatening mixed states are a recognised indication for ECT, which is widely available in Indian teaching hospitals; the technique itself is owned by the ECT and neurostimulation notes.

GOOD TO REMEMBER

- **Mixed features (the concept):** opposite-pole symptoms co-occurring within one episode; now a qualifier, not a separate episode (DSM-5-TR), with ICD-11 retaining a named mixed episode.
- **The DSM-5 rule:** at least three non-overlapping opposite-pole symptoms on most days; irritability, distractibility, agitation and insomnia are excluded from the count.
- **Clinical weight:** mixed features predict bipolarity, a worse course, a poorer lithium response, and a higher suicide risk, and mandate antidepressant caution.
- **Kraepelin:** mixed states arise when mood, thought and psychomotor activity dissociate; the historical origin of the modern specifier.

HOLD THIS

Mixed features = at least three non-overlapping opposite-pole symptoms inside one episode (a DSM-5-TR qualifier, an ICD-11 mixed episode); they flag bipolarity, worsen course, raise suicide risk, and forbid an antidepressant alone in a mixed depression.

19 · Rapid cycling bipolar disorder

Why this matters. **Rapid cycling** is not a separate diagnosis but a **course specifier** applied to bipolar I or bipolar II disorder, and it is examined because it changes both the prognosis and the treatment logic. The single reflex to build is that rapid cycling means **four or more episodes** of any polarity in a twelve-month window, that it is disproportionately driven by **antidepressant exposure** and by **hypothyroidism**, and that the correct response to a worsening cycle is usually to withdraw the antidepressant rather than to add another one (Maudsley 2021).

Nosology is given ICD-11 primary, where a rapid cycling qualifier can be added to bipolar type I and bipolar type II disorder, with the DSM-5 (the DSM-5-TR) "with rapid cycling" specifier cross-mapped and ICD-10 flagged where Indian exams still cite it. The raw descriptive definitions of the individual manic, hypomanic and depressive symptoms are owned by the Psychometry, Assessment and Descriptive Psychopathology notes and cross-referenced here; the full soft-

bipolar spectrum, the manic-episode criteria and the bipolar II hypomania threshold are laid out elsewhere in this chapter; and the deep drug pharmacology, dosing and treatment-resistance algorithms belong to the Mood disorders: pharmacotherapy notes.

19.1 The definition: four or more episodes in twelve months

Rapid cycling is defined as bipolar disorder in which **four or more episodes** of a mood disturbance occur within a twelve-month period (Maudsley 2021; Kaplan & Sadock 2024). Three points make the definition examinable. First, the episodes may be of **any polarity**, depressive, manic, hypomanic or mixed, counted in any combination, so four depressive episodes, or two manic plus two depressive, or four clear switches in polarity, all qualify (Maudsley 2021). Second, each counted episode must **meet the duration and symptom criteria for a full episode** of its type (a major depressive episode, a manic, a hypomanic or a mixed episode), so a merely labile mood does not count. Third, the episodes must be **demarcated** from one another, either by a period of partial or full remission of at least **two months**, or by a switch to an episode of the opposite polarity (DSM-5-TR). It is the counting of *episodes*, not the counting of mood swings, that residents most often get wrong.

RULE **Rapid cycling is four or more episodes in twelve months and is often antidepressant-driven.** Four or more full episodes of any polarity within twelve months, each demarcated by a two-month remission or a switch of polarity, applied as a specifier to bipolar I or bipolar II.

four or more episodes
IN TWELVE MONTHS

at least 2 months
REMISSION DEMARCATING EPISODES

commoner in women
RAPID-CYCLING SEX DISTRIBUTION (DSM-5-TR)

19.2 The ultra-rapid and ultradian variants

Beyond the twelve-month definition sit two faster, non-official descriptors used in the literature and worth naming (Kaplan & Sadock 2024). Ultra-rapid cycling denotes phases of mania and depression that alternate very rapidly, in the order of days to weeks (described as "in a matter of hours or days"). Ultra-ultra-rapid cycling, also called ultradian cycling, denotes distinct mood shifts occurring within a twenty-four-hour period, that is, within one day; it is described particularly in paediatric-onset bipolar disorder, where children characteristically exhibit ultradian cycling, irritability and explosive temper outbursts rather than the discrete episodes seen in adults (Kaplan & Sadock 2024). These variants are not separate diagnoses and lack formal operational criteria; treat them as descriptive intensifiers of the rapid cycling course.

TERM	FREQUENCY OF SWITCHING	STATUS
Rapid cycling	**Four or more full episodes in 12 months**	Formal specifier (DSM-5-TR; ICD-11 qualifier)
Ultra-rapid cycling	**Switches over days to weeks**	Descriptive, non-official
Ultra-ultra-rapid (ultradian) cycling	**Distinct shifts within a single 24-hour day**	Descriptive, non-official; typical of paediatric-onset

The formal boundary is the twelve-month, four-episode line; ultra-rapid and ultradian are progressively faster descriptive labels without their own criteria.

19.3 Associations and precipitants: women, bipolar II, thyroid, antidepressants

Rapid cycling clusters with a recognisable set of associations that the examiner expects listed (Maudsley 2021). It is **commoner in women**, although the guidelines give no precise sex ratio (DSM-5-TR), and it is **well recognised in bipolar II** as well as in bipolar I. It is associated with **hypothyroidism** and low thyroxine states, and rapid cycling has been linked to the presence of antithyroid antibodies even where overt thyroid dysfunction is absent (Gan et al. 2019, cited in Maudsley 2021). The most examinable precipitant is **antidepressant exposure**, especially the tricyclic antidepressants, which can accelerate the cycle (Maudsley 2021). Rapid cyclers also carry more depressive morbidity, higher rates of anxiety disorders, substance use and borderline personality disorder, and greater functional impairment than non-rapid cyclers (Maudsley 2021).

MNEMONIC

WATCH the cycle: Women, Antidepressants, Thyroid (low), bipolar-two, Chronic morbidity

The five things that drive or mark rapid cycling: female sex (a female preponderance, with no precise ratio given), antidepressant exposure (especially tricyclics), hypothyroidism or antithyroid antibodies, a bipolar II diathesis, and a heavier depressive and comorbid burden.

19.4 Prognosis: a poorer-outcome, harder-to-treat course

Rapid cycling carries a **poorer prognosis** than a non-rapid cycling course. It is generally held to be **less responsive to drug treatment**, entails considerable depressive morbidity and suicide risk, and is associated with poorer functioning, more obesity, and the need to be treated with more drugs and at somewhat higher doses (Maudsley 2021). Importantly, lithium is **less likely to be effective** in rapid cycling than in non-rapid cycling illness (Maudsley 2021), a point that shapes the management pointer below. Rapid cycling is not necessarily permanent: it may come and go, and spontaneous or treatment-related remission of the rapid cycling pattern occurs in around a third of rapid cyclers (Maudsley 2021).

19.5 Management principles: withdraw the antidepressant, treat the thyroid, combine stabilisers

Detailed agents, doses and algorithms are owned by the Mood disorders: pharmacotherapy notes; the principles here are a guideline-level pointer. There is **no formal first-choice agent or combination** for rapid cycling, and NICE concluded that there is no evidence to support managing a rapid cycling illness any differently from a more conventional bipolar course (NICE, cited in Maudsley 2021). The pragmatic staged strategy is: first, **review and often withdraw antidepressants** in all patients, since antidepressants are implicated in driving and sustaining the cycle; second, **evaluate and treat precipitants**, in particular thyroid dysfunction (including antithyroid antibodies), alcohol and external stressors; and third, **optimise and consider combining mood stabilisers**, using plasma levels, favouring combinations such as lithium plus valproate, lithium plus lamotrigine, or valproate plus carbamazepine, with adjunctive atypical antipsychotics (for example quetiapine, olanzapine or aripiprazole) where needed (Maudsley 2021). Because lithium is less effective here, valproate and lamotrigine-containing combinations

often carry the weight, and lamotrigine is favoured where the burden is predominantly depressive.

TRAP **Chasing each low with more antidepressant accelerates the cycling.** Adding an antidepressant to treat every depressive dip in a rapid cycler tends to speed the cycle rather than settle it; the corrective move is to withdraw the antidepressant and optimise mood-stabiliser cover.

WORKED EXAMPLE

A woman with bipolar II disorder, treated with an SSRI for recurrent depression, presents with five distinct mood episodes over the past year, brief hypomanias alternating with fuller depressions. She is now cycling faster on a recently increased antidepressant dose. The examinable move is not to add a second antidepressant but to recognise antidepressant-driven rapid cycling: check thyroid function, review and taper the antidepressant, and optimise or combine mood stabilisers (Maudsley 2021).

INDIA

In Indian practice the tricyclic antidepressants remain in wide use, so antidepressant-driven acceleration of cycling is a real and preventable scenario; screening thyroid function is inexpensive and worthwhile in any bipolar patient whose course speeds up. Coding still frequently uses ICD-10, where rapid cycling is not a discrete category, so the resident should be able to map the ICD-11 rapid cycling qualifier and the DSM-5-TR "with rapid cycling" specifier onto the older bipolar affective disorder codes. Drug brand names belong to the Mood disorders: pharmacotherapy notes.

19.6 Nosological mapping: ICD-11, DSM-5-TR and ICD-10

The three systems handle rapid cycling as a course modifier, not a stand-alone illness. ICD-11 allows a rapid cycling qualifier to be added to bipolar type I disorder and bipolar type II disorder. The DSM-5-TR carries an explicit **"with rapid cycling"** specifier defined by at least four mood episodes in the previous twelve months that meet criteria for a major depressive, manic, hypomanic or mixed-features episode and are demarcated by at least two months of partial or full remission or by a switch to the opposite polarity (DSM-5-TR). ICD-10 has no discrete rapid cycling category, so the pattern is captured descriptively under bipolar affective disorder. Whatever the system, the operational content is identical: four or more full episodes, any polarity, in twelve months.

PEARL

Rapid cycling is a red flag to re-audit the drug chart before escalating: an unrecognised antidepressant or an untreated hypothyroid state is frequently the engine of the cycle, and removing the driver often does more than adding a further agent (Maudsley 2021).

GOOD TO REMEMBER

- **Rapid cycling bipolar disorder:** a course specifier on bipolar I or bipolar II, defined by **four or more episodes** of any polarity (depressive, manic, hypomanic or mixed) within twelve months, each meeting full-episode criteria and demarcated by a **two-month** remission or a polarity switch; the one number to hold is four episodes in a year.
- **Ultra-rapid and ultradian variants:** ultra-rapid cycling switches over days to weeks; ultra-ultra-rapid (ultradian) cycling switches within a single 24-hour day and is typical of paediatric-onset bipolar disorder; both are descriptive, not formal diagnoses.
- **Associations and drivers:** commoner in women and well recognised in bipolar II; hypothyroidism and antithyroid antibodies, and antidepressant exposure (especially tricyclics), drive it; the course is poorer and lithium is less effective.
- **Management pointer:** withdraw antidepressants, treat the thyroid and other precipitants, and favour lithium, lamotrigine or valproate combinations; no formal first-choice agent exists (Maudsley 2021). Details in the Mood disorders: pharmacotherapy notes.

HOLD THIS

Rapid cycling is four or more full episodes of any polarity in twelve months, a specifier on bipolar I or II that is commoner in women and bipolar II and is often driven by antidepressants and by hypothyroidism; the corrective move is to withdraw the antidepressant, treat the thyroid, and combine mood stabilisers (lithium, lamotrigine, valproate) rather than to chase each low with more antidepressant.

20 · Course, prognosis and outcome of bipolar disorder

Why this matters. Bipolar disorder is the paradigm **recurrent, lifelong mood illness**. The single fact that reorganises everything downstream is that it is a disorder of **recurrence, not of one-off episodes**: most patients recover symptomatically from any given episode, yet the great majority relapse, carry **sub-syndromal symptoms** and cognitive and functional impairment between episodes, and lose years of life to suicide and to cardiovascular and metabolic disease (Kaplan & Sadock 2024; Shorter Oxford 2018). The examinable reflex is to read every bipolar presentation as a point on a long trajectory and to think maintenance from the outset.

Nosology is given ICD-11 primary, with the DSM-5-TR cross-mapped and ICD-10 flagged where Indian exams still cite it; the raw descriptive definitions of the individual mood symptoms and the rating scales are owned by the Psychometry, Assessment and Descriptive Psychopathology notes. The manic-episode and depressive-episode criteria, the soft-bipolar spectrum and the rapid cycling specifier are laid out elsewhere in this chapter. Guideline-level maintenance drug choices, dosing and treatment-resistance algorithms belong to the Mood disorders: pharmacotherapy notes and are only pointed to here; clinical suicide risk assessment and safety planning belong to the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

20.1 The natural history: recurrence with inter-episode recovery but residual impairment

The defining shape of the **course** is Kraepelinian: acute episodes end and a temporary recovery occurs, unlike schizophrenia where acute exacerbations merge into a chronic deficit state, so it is **recurrence, not permanent chronicity**, that is the essential feature (New Oxford 2020). **Nearly all patients recover from the acute episode**, yet **at least 90% experience further episodes** of

major mood disturbance over follow-up (Shorter Oxford 2018; Kaplan & Sadock 2024). The recovery is, however, incomplete: over long-term follow-up patients are symptomatic with mood disturbance of varying severity for about **one-third** of the time, and in bipolar I disorder syndromal or sub-syndromal symptoms are present an average of about **50%** of the time (Shorter Oxford 2018; Kaplan & Sadock 2024). In both bipolar I and bipolar II this residual burden is **predominantly depressive**: bipolar I patients spend depressive to manic symptom-time in a ratio of about **3:1**, and in bipolar II the average patient spends roughly **37 times** more days depressed than hypomanic (Kaplan & Sadock 2024, from the Judd cohorts). These inter-episode sub-syndromal symptoms are not benign: they themselves increase the risk of a full-blown mood episode, and multiple episodes track with cognitive impairment, structural brain change and functional decline (Kaplan & Sadock 2024).

RULE **Bipolar is a recurrent, lifelong illness even between episodes, so think maintenance early.** At least 90% relapse, the inter-episode state carries sub-syndromal (mostly depressive) symptoms and cognitive and functional impairment, so long-term prophylaxis is planned from the outset, not after the third admission.

TRAP **Treating bipolar as a series of unrelated one-off episodes.** Managing each mania or depression as a self-limiting event, stopping treatment on recovery, ignores that over 90% recur and that euthymia is rarely symptom-free; it is the commonest structural error in bipolar management.

20.2 Episode frequency over the lifetime and the tendency to shortening cycles

The **episode frequency** accumulates across the lifespan. Bipolar disorder usually begins as depression, with the first manic episode manifesting on average about **5 years** later, and the average length of a manic episode, treated or untreated, is about **6 months** (Shorter Oxford 2018). Over a 25-year follow-up bipolar patients experience, on average, about **10 further episodes** of major mood disturbance (Shorter Oxford 2018). Crucially, in some patients the illness is not stationary: the **interval between episodes becomes progressively shorter with both age and the number of episodes**, a pattern captured by the kindling or neuroprogressive (staging) model, in which repeated episodes lower the threshold for the next, reduce the likelihood of remission and worsen cognitive and neurologic function (Shorter Oxford 2018; Kaplan & Sadock 2024). Frequent episodes also alter the response to treatment: patients with many prior episodes are less likely to respond to acute treatment and to prophylaxis (Kaplan & Sadock 2024). Kindling is a heuristic model, not an established mechanism, and the shortening-cycle pattern is seen in only a subset rather than universally; it is best held as a rationale for early, sustained prophylaxis rather than as a proven law of the illness.

at least 90%	about 10	about one-third
RECUR (FURTHER MOOD EPISODE)	FURTHER EPISODES OVER 25 YEARS	OF TIME SYMPTOMATIC LONG-TERM

20.3 Predictors of poorer outcome and of better outcome

The **prognosis** is stratified by a recognisable set of predictors that the examiner expects listed against each other (Kaplan & Sadock 2024; Shorter Oxford 2018). Markers of a **poorer outcome** include **early age of onset**, a **mixed** and **rapid-cycling** course, the presence of **psychotic**

features, comorbid **substance use**, and **poor adherence** to treatment, together with a greater number and severity of prior episodes, comorbid anxiety, and persistent cognitive deficits and mood instability. A **better outcome** is associated with the mirror image: later and clearly episodic onset, a classical euphoric-mania course with full inter-episode euthymia, absence of psychosis and of substance comorbidity, good treatment adherence, and preserved cognition; bipolar II disorder as a whole carries a somewhat better functional outcome than bipolar I (Shorter Oxford 2018). Even so, the long-term prognosis is sobering: fewer than **20%** of bipolar patients achieve a 5-year period of clinical stability with good social and occupational performance (Shorter Oxford 2018).

DOMAIN	PREDICTS POORER OUTCOME	PREDICTS BETTER OUTCOME
Age of onset	**Early onset**	Later, clearly episodic onset
Episode type/course	**Mixed features; rapid-cycling course**	Classical euphoric mania; full inter-episode euthymia
Psychosis	**Psychotic features present**	No psychosis
Comorbidity	**Substance use; anxiety comorbidity**	No substance or anxiety comorbidity
Adherence	**Poor adherence**	Good treatment adherence
Episode burden	**Many/severe prior episodes; persistent cognitive deficits**	Few episodes; preserved cognition
Subtype	Bipolar I (greater manic morbidity)	Bipolar II somewhat better functional outcome

Predictors of outcome in bipolar disorder; the discriminating markers of a worse course are early onset, a mixed or rapid-cycling pattern, psychosis, substance use and poor adherence.

MNEMONIC

The worse course is EMPS-A: Early onset, Mixed/rapid-cycling, Psychosis, Substance use, poor Adherence

The five high-yield predictors of a poorer bipolar outcome: Early onset, a Mixed and rapid-cycling course, Psychotic features, Substance use, and poor Adherence. Their mirror image predicts a better outcome.

20.4 Mortality: the elevated suicide risk

Bipolar disorder carries one of the highest suicide risks in psychiatry. The standardized mortality ratios for suicide in bipolar disorder range from about **10 to 30**, meaning bipolar patients are roughly 10 to 30 times more likely to die by suicide than the general population (Kaplan & Sadock 2024). Over a 40-year follow-up of hospitalised patients, about **8% of men and 5% of women** died by suicide (Nordentoft et al. 2011, in Shorter Oxford 2018). The risk is **front-loaded and state-dependent**: it is higher **early in the course** of the illness, during acute mood episodes (especially with mixed features), during and around hospitalisation, and within **4 to 12 weeks** of discharge (Kaplan & Sadock 2024). Established risk markers, from the ISBD Task Force,

include a depressive or mixed first and current episode, greater number and severity of episodes, rapid cycling, anxiety, atypical features, hopelessness, a first-degree family history of mood disorder or suicide, and prior suicide attempts (Schaffer et al. 2015, in Kaplan & Sadock 2024). The detailed clinical risk assessment and safety planning belong to the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

TRAP **Assuming the danger is only during depression, and only in established illness.** Suicide risk is highest early in the course, in mixed states, and in the weeks around discharge, so vigilance cannot be relaxed once the acute low lifts.

20.5 Mortality: excess cardiovascular and metabolic death and the life-years lost

The excess mortality of bipolar disorder is **not accounted for by suicide alone.** The high mortality is driven also by general medical conditions, above all **cardiovascular disease**, and by the secondary consequences of comorbid substance misuse and smoking, compounded by the metabolic effects of long-term psychotropic, particularly antipsychotic, treatment (Shorter Oxford 2018; Goodwin et al. 2016). In a large Danish cohort, bipolar disorder was associated with a reduction in life expectancy of about **13 years in men and 9 years in women**, and about **two-thirds of this reduction was accounted for by natural causes** (chiefly cardiovascular disease), with the remainder due to suicide and accidents (Kessing et al. 2015, in Shorter Oxford 2018). The clinical corollary is that maintenance of a bipolar patient is not only mood-episode prophylaxis but active attention to cardiometabolic risk: weight, glucose, lipids, smoking and blood pressure. The specific monitoring schedules for individual mood stabilisers and antipsychotics belong to the Mood disorders: pharmacotherapy notes.

10 to 30	about 13 y / 9 y	about two-thirds
SMR FOR SUICIDE	LIFE-YEARS LOST, MEN / WOMEN	OF LIFE-YEARS LOST FROM NATURAL CAUSES

INDIA

In Indian practice the same recurrent, lifelong logic holds, and the cardiometabolic burden is amplified by the high background prevalence of diabetes and cardiovascular disease and by the widespread use of tricyclic antidepressants, which can destabilise the course. The National Mental Health Survey of India (2015 to 2016) established mood disorders as a substantial and largely untreated burden with a wide treatment gap, which makes early recognition and sustained maintenance, rather than episode-by-episode crisis care, the practical priority. Coding still frequently uses ICD-10, where bipolar affective disorder is a single category without the ICD-11 bipolar type I and type II split; the resident should be able to map between them. Drug brand names belong to the Mood disorders: pharmacotherapy notes.

20.6 Putting the outcome together: what "outcome of bipolar" means for management

The **outcome of bipolar** disorder is best summarised as a favourable *episode* outcome sitting on top of an unfavourable *illness* outcome. Acute episodes almost always remit, but across the lifespan the illness recurs in more than 90%, leaves residual mostly depressive symptomatology for about a third of the time, erodes cognition and function, and shortens life. This is why the

guideline consensus, led by the CANMAT/ISBD framework and echoed by NICE, is that long-term prophylaxis should be planned early, in bipolar I typically after the first manic episode, and why psychosocial adjuncts (psychoeducation, IPSRT, family-focused therapy and CBT) are added to reduce relapse and improve adherence (Kaplan & Sadock 2024). The specific first-line and next-line maintenance agents, the phase-by-phase drug logic and the treatment-resistance pathways are owned by the Mood disorders: pharmacotherapy notes; the point to carry from the course and prognosis is the indication for that maintenance, not the drug list itself.

PEARL

The prognostic asymmetry is the teaching point: nearly everyone recovers from the acute episode (good episode outcome) yet fewer than one in five achieves 5 years of stable good functioning (poor illness outcome). It is that gap, filled by sub-syndromal symptoms, cognitive drift and cardiometabolic risk, that maintenance treatment exists to close (Shorter Oxford 2018).

GOOD TO REMEMBER

- **Natural history:** a **recurrent** illness with inter-episode recovery in most, but residual (mostly depressive) sub-syndromal symptoms and cognitive and functional impairment persist between episodes; at least **90%** recur and patients are symptomatic about **one-third** of the time.
- **Episode frequency and kindling:** about **10** further episodes over 25 years, first mania roughly **5 years** after depression onset; in some the cycle shortens with age and episode number (kindling, a model not a proven law).
- **Predictors of worse outcome:** early onset, a mixed and rapid-cycling course, psychosis, substance use and poor adherence; the mirror predicts better outcome, and fewer than **20%** reach 5 years of stable good functioning.
- **Suicide mortality:** standardized mortality ratio for suicide about **10 to 30**; risk highest early, in mixed states and within **4 to 12 weeks** of discharge.
- **Cardiometabolic mortality and life-years:** excess death from cardiovascular and metabolic disease as well as suicide, with life expectancy reduced about **13 years (men) and 9 years (women)**, two-thirds from natural causes (Kessing et al. 2015).

HOLD THIS

Bipolar disorder is a recurrent, lifelong illness in which acute episodes remit but over 90% relapse, the inter-episode state carries residual mostly depressive symptoms and cognitive and functional impairment, mixed and rapid-cycling courses (with early onset, psychosis, substance use and poor adherence) predict a worse outcome, and mortality is high from both suicide (SMR about 10 to 30) and cardiovascular and metabolic disease (about 13 years of life lost in men, 9 in women): so plan maintenance from the outset rather than treating episodes as unrelated one-offs.

21 · Bipolar disorder in special populations

Bipolar disorder does not read the textbook the same way at every age or in every physiological state. Three **special populations** bend the diagnosis and the safe management enough to earn their own topic: the child, the older adult, and the woman in the peripartum. Each carries a signature examiner-favourite error, and each error is a mirror image of the same underlying principle, that bipolar disorder is defined by discrete **episodes** and that a "manic" presentation must always be interrogated for a non-affective cause before it is owned as primary bipolarity.

This topic teaches the discrimination in each population, not the deep drug pharmacology: the full agent-level detail, dosing and treatment-resistant algorithms belong to the Mood disorders: pharmacotherapy notes, and the wider perinatal frame is developed in the Perinatal/women's mental health and emergency psychiatry notes. The full manic-episode and depressive-episode criteria live in this chapter's own episode topics; here we apply them at the extremes of the lifespan. Nosology is given ICD-11-primary, DSM-5-TR cross-mapped.

21.1 Paediatric bipolar disorder: the diagnostic controversy

An overdiagnosis debate, resolved by insisting on episodicity. **Paediatric bipolar** disorder became one of the most contested diagnoses in child psychiatry after a sharp late-twentieth-century rise in the rate at which clinicians, mostly in the United States, applied the bipolar label to children. DSM-5-TR is explicit that this increase "appears to be attributable to clinicians combining at least two clinical presentations into a single category," namely classic episodic mania and non-episodic severe irritability, both of which were being called bipolar disorder in children (DSM-5-TR 2022). The correction was twofold: DSM-5 reserved the term bipolar disorder for episodic presentations, and it created a new home for the chronically irritable child. Both DSM-IV and DSM-5-TR require that children, exactly as adults, show distinct episodes of mania or hypomania to qualify for bipolar I or bipolar II (DSM-5-TR 2022; Kaplan & Sadock 2024).

RULE **Require clear episodicity before diagnosing paediatric bipolar.** There must be a distinct time period, of the required duration, in which mood and behaviour were markedly and unmistakably different from the child's own baseline.

21.2 The distinction from disruptive mood dysregulation disorder

Episodic mania versus chronic, non-episodic irritability. Disruptive mood dysregulation disorder was added to DSM-5 precisely to capture the chronically irritable child who is not bipolar. Its core is chronic, severe, persistent irritability with two manifestations: frequent temper outbursts, on average **three or more times per week**, grossly out of proportion to provocation, and a persistently irritable or angry mood present between outbursts, most of the day nearly every day, noticeable to others (DSM-5-TR 2022). The outbursts must run for **at least 1 year** in **at least two settings**; onset is before **age 10** years; the diagnosis is not applied below a developmental age of 6 and is validated for the **6 to 18** year range (DSM-5-TR 2022). The single discriminating feature is longitudinal course: bipolar disorders are episodic, disruptive mood dysregulation disorder is not.

WORKED EXAMPLE

A 9-year-old boy has raged three to four times a week for eighteen months, at home and at school, and is sullen and touchy in between. He has never shown a distinct several-day stretch of elated or expansive mood, decreased need for sleep or grandiosity that stood out from his usual self. This is chronic irritability, and the correct diagnosis is disruptive mood dysregulation disorder, not paediatric bipolar disorder. Elevated or expansive mood and grandiosity, common in mania, are not characteristic of disruptive mood dysregulation disorder, and their absence here is diagnostic (DSM-5-TR 2022).

FEATURE	PAEDIATRIC BIPOLAR DISORDER	DISRUPTIVE MOOD DYSREGULATION DISORDER
Course	**Episodic: discrete episodes distinct from baseline**	**Chronic, non-episodic, persistent irritability**
Hallmark mood	Elevated / expansive mood, grandiosity present	Irritable / angry mood; elation and grandiosity absent
Temper outbursts	Within an episode	3 or more per week, over 1 year, in 2 or more settings
Onset criterion	Any age, but rare pre-adolescence	Before age 10; validated for 6 to 18 years
Longitudinal outcome	Recurrent bipolar illness	**Unipolar depressive / anxiety disorders, not bipolar**
Exclusion	Excludes if criteria for another cause met	Cannot coexist with, or follow, any manic/hypomanic episode

The one discriminator is episodicity: a manic or hypomanic episode ever, even one lasting more than one day, forbids disruptive mood dysregulation disorder (DSM-5-TR 2022).

TRAP **Do not diagnose bipolar from chronic irritability alone in a child.** Non-episodic severe irritability is disruptive mood dysregulation disorder and predicts unipolar depression and anxiety, not bipolar disorder; conversion to bipolar disorder is very low.

GOOD TO REMEMBER

- **Paediatric bipolar disorder:** bipolar disorder in a child, requiring the same episodic mania/hypomania as adults; the one discriminator is a distinct episode markedly different from the child's baseline; hold "episodicity is mandatory; rare pre-adolescence."
- **Disruptive mood dysregulation disorder:** chronic non-episodic severe irritability with frequent outbursts; the one discriminator is that it is never episodic and elation/grandiosity are absent; hold "3+ outbursts/week, over 1 year, onset before age 10, validated 6 to 18 years."

21.3 Elderly bipolar disorder: later-onset ("secondary" or vascular) mania

New mania in later life is organic until proven otherwise. **Elderly bipolar** disorder splits into two populations: those with typical younger onset who have aged, and those with a genuinely later age of onset, usually at **40 or 50 years or older** (Tasman 2015). The later-onset group is enriched with identifiable medical, particularly neurological, factors that may be causing the mania: such factors are found in **12 to 38%** of later-onset cases (Tasman 2015). This is the

domain of secondary mania, conceptualised by Krauthammer and Klerman (1978) as mania occurring close on the heels of a specific physiological insult: stroke, head trauma, dementia, brain tumours and metastases, and endocrine or drug-induced states (Tasman 2015). Where cerebrovascular disease drives it, the term **vascular mania** is used, the manic analogue of vascular depression.

RULE **Exclude an organic cause in new late-life mania.** First-onset mania in an older adult mandates neurological and medical workup for a secondary cause before it is called primary bipolar disorder.

21.4 Elderly bipolar disorder: the organic differential and drug sensitivity

A wider differential and a narrower therapeutic window. Because the organic yield is high, the older adult with new mania carries a heavier burden of causes to exclude than the young adult: stroke and other cerebrovascular disease, space-occupying lesions, dementia, delirium, hyperthyroidism, and drug or steroid effects all sit in the differential (Tasman 2015; Kaplan & Sadock 2024). Management is then constrained by age-related pharmacokinetics: reduced renal clearance, greater sensitivity to central nervous system effects, and more interacting comorbid medication all narrow the safe dosing range, lithium especially. Guideline-anchored practice reflects this: CANMAT advises that in older adults lithium be started at a low dose, for example **150 mg** nightly, targeting a lower serum level of **0.4 to 0.8 mEq/L**, with lithium level and renal function monitored every **3 to 6 months** and 5 to 7 days after any dose or interacting-drug change (CANMAT 2018). The agent-level detail sits in the Mood disorders: pharmacotherapy notes; the catatonia and organic-psychosis boundaries are developed in the Other psychotic disorders, delusional syndromes and catatonia notes.

TRAP **Do not miss a vascular or organic mania in an older adult.** Anchoring on primary bipolar disorder and skipping the neurological and metabolic workup misses stroke, tumour, dementia and endocrine causes, and risks lithium toxicity from age-reduced clearance.

40 to 50+ yr	12 to 38%	0.4 to 0.8 mEq/L
TYPICAL LATER-ONSET AGE	LATER-ONSET CASES WITH NEUROLOGICAL FACTORS	LITHIUM TARGET IN OLDER ADULTS (CANMAT)

INDIA

In Indian geriatric practice the high organic yield of late-life mania is a live concern: cerebrovascular disease and untreated endocrine disorder are common, and a first manic presentation after 50 routinely prompts neuroimaging and thyroid and metabolic screening before a primary bipolar label is accepted. Lithium remains affordable and widely available, but the same age-reduced renal clearance applies, so lower starting doses, lower target levels and closer renal monitoring are standard.

GOOD TO REMEMBER

- **Elderly bipolar disorder (later-onset):** new bipolar disorder arising at 40 to 50 years or older; the one discriminator is the high load of identifiable organic cause; hold "neurological factors in 12 to 38%; workup before diagnosis."
- **Secondary / vascular mania:** mania on the heels of a physiological insult (Krauthammer and Klerman) or driven by cerebrovascular disease; the one discriminator is a demonstrable medical cause; hold "stroke, tumour, dementia, endocrine; exclude before calling it primary."
- **Drug sensitivity in the elderly:** age-reduced renal clearance and CNS sensitivity narrow the window; the one discriminator is lower dosing and lower targets; hold "lithium start 150 mg nightly, target 0.4 to 0.8 mEq/L (CANMAT)."

21.5 Bipolar in pregnancy: the peripartum relapse risk

The postpartum is the single highest-risk window in the illness. Bipolar in pregnancy and the peripartum is defined less by pregnancy itself than by the puerperium: the BAP guidance states plainly that the postpartum period "carries very high relapse risk for bipolar disorder" and that focus of care planning should be increased in women of childbearing potential for this reason (BAP, in _MGMT-GUIDELINES). Postnatal bipolar recurrences, and new-onset bipolar and other affective postpartum psychoses, are to be treated as psychiatric emergencies: they tend to commence suddenly in the first few days after delivery, progress rapidly, and be severe (BAP, in _MGMT-GUIDELINES). Pregnancy does not protect against recurrence, and discontinuing prophylactic mood stabilisers near conception roughly **doubles** the recurrence risk, shortens the time to recurrence and increases time spent ill during pregnancy (BAP, in _MGMT-GUIDELINES). The wider perinatal frame, including puerperal psychosis and maternity blues, is developed in the Perinatal/women's mental health and emergency psychiatry notes.

RULE **Treat postpartum bipolar recurrence as an emergency.** New-onset or recurrent bipolar and affective postpartum psychosis begins abruptly in the first days after delivery, escalates fast, and warrants urgent assessment and admission.

21.6 Bipolar in pregnancy: the teratogenicity trade-offs

Avoid valproate in women of childbearing potential. The dominant teratogenicity rule is that valproate is avoided in women of childbearing potential: CANMAT advises avoiding divalproex in pregnancy due to teratogenicity, using monotherapy at the minimum effective dose, supplementing high-dose folic acid at **5 mg/day**, and monitoring with foetal ultrasound where lithium is used in the first trimester (CANMAT 2018). BAP goes further on the practical mechanics: if a woman planning pregnancy is already on valproate, withdraw it gradually over at least 4 weeks while she uses effective contraception (BAP, in _MGMT-GUIDELINES). Antipsychotics generally form the mainstay of perinatal bipolar treatment because they have a better risk-benefit ratio than valproate and carbamazepine and a larger reproductive evidence base; if lithium is used, plasma levels are measured monthly until 36 weeks then weekly until delivery, with the dose suspended around delivery to avoid toxicity (BAP, in _MGMT-GUIDELINES). This topic gives the direction of travel only; the agent-by-agent teratogenic detail is a pointer to the Mood disorders: pharmacotherapy notes and to the perinatal notes.

TRAP **Do not start or continue valproate in a woman of childbearing potential.** Valproate is the highest-teratogenicity mood stabiliser; the guideline default in this group is to avoid it and to prefer an antipsychotic, with folic acid supplementation where an anticonvulsant is unavoidable.

PEARL

The peripartum management problem is a scheduling problem as much as a drug problem: relapse risk peaks in the first postpartum days, so a plan made in pregnancy that specifies what to restart, and when, on the first day after childbirth (for example restarting a previously effective antipsychotic such as quetiapine or olanzapine) can pre-empt an early relapse (BAP, in _MGMT-GUIDELINES). Sleep protection and mood self-monitoring are part of the same relapse-prevention scaffold.

GOOD TO REMEMBER

- **Bipolar in pregnancy / peripartum:** a high-relapse state dominated by the postpartum window; the one discriminator is that the puerperium, not pregnancy, is the danger zone; hold "postpartum recurrence is an emergency; discontinuing prophylaxis near conception roughly doubles recurrence risk."
- **Valproate in women of childbearing potential:** the highest-teratogenicity mood stabiliser, to be avoided; the one discriminator is the teratogenic default to avoid; hold "avoid valproate; prefer antipsychotic; folic acid 5 mg/day if an anticonvulsant is unavoidable (CANMAT)."

21.7 The unifying principle across all three populations

Episodicity and exclusion, applied at both ends of the lifespan. The three special populations rehearse the same two disciplines. In the child, insist on a discrete episode before diagnosing bipolar disorder, and route chronic irritability to disruptive mood dysregulation disorder. In the older adult, insist on excluding an organic or vascular cause before owning a new mania as primary. In the peripartum woman, insist on relapse-prevention planning and on avoiding the teratogenic agent. Each is a specific instance of the general rule that bipolar disorder is an episodic illness whose "manic" presentations must always be tested for a non-affective explanation, and whose treatment must be tuned to the physiology of the person in front of you.

MNEMONIC

CHILD, ELDER, MOTHER

CHILD: demand episodicity (else it is disruptive mood dysregulation disorder). ELDER: exclude organic/vascular cause. MOTHER: postpartum emergency, avoid valproate. Three populations, three signature errors, one principle: episodes and exclusion.

HOLD THIS

Require clear episodicity before diagnosing paediatric bipolar disorder (else it is disruptive mood dysregulation disorder), exclude an organic or vascular cause in new late-life mania, and in the peripartum treat postpartum recurrence as an emergency while avoiding valproate in women of childbearing potential.

22 . Management of bipolar disorder: guidelines-first

Bipolar disorder is a lifelong, phasic illness, and its management is organised not by a single drug list but by **phase**: the drug that quiets an acute mania is not the drug that lifts a bipolar depression, and neither is automatically the drug you keep for maintenance. The board answer is a guideline answer. This note builds the plan on a **LOCUS to FOCUS to MODUS** spine: **LOCUS** (where you treat and how you keep the patient safe), **FOCUS** (the phase you are treating), and **MODUS** (the first-line and next modalities each guideline recommends). We LEAD with CANMAT (the CANMAT and ISBD 2018 bipolar guidelines, Yatham et al.), then state where the Indian Psychiatric Society and NICE sit.

The deep drug pharmacology, the full dosing tables, the adverse-effect profiles and the treatment-resistant-mania algorithm are not taught here: they are owned by, and cross-referred to, the Mood disorders: pharmacotherapy notes. This note stays at guideline level: which agent is first-line, in which phase, and the single monitoring headline. The manic-episode and depressive-episode criteria themselves are taught in full elsewhere in this chapter; the restraint and de-escalation technique is cross-referred to the Perinatal/women's mental health and emergency psychiatry notes.

22.1 LOCUS: where to treat, and the safety base

Admit for acute mania with risk. The default LOCUS for a florid **acute mania** is inpatient when there is risk to self or others, psychotic features, severe functional collapse, exhaustion or dehydration, or when the patient is non-adherent and cannot be safely held at home (CANMAT 2018, Kaplan & Sadock 2024). Maintenance, by contrast, is an outpatient enterprise: stable, adherent euthymic patients are followed in the clinic. The universal base under every phase is the same: a written safety and risk plan, a **mood diary** for early-warning-sign monitoring, sleep and routine stabilisation, and structured psychoeducation for the patient and, wherever possible, the family.

Suicide risk is elevated across the illness and formal risk assessment is cross-referred to the Somatic-symptom, sexual, impulse-control disorders and suicide notes; the clinical suicide-risk detail lives there.

RULE **Admit the risky mania.** Acute mania with risk, psychosis or non-adherence is an inpatient problem; maintenance is an outpatient one.

22.2 LOCUS: the crisis, severe agitation and the first-line intramuscular options

When an acutely manic patient is severely agitated and oral therapy is refused or unsafe, verbal de-escalation comes first, but if pharmacological control is needed CANMAT names a first-line parenteral set: intramuscular aripiprazole, intramuscular lorazepam, inhaled loxapine, or intramuscular olanzapine (CANMAT 2018). A practical caution repeated across guidelines: do not give intramuscular olanzapine and parenteral benzodiazepine together closely because of the risk of excessive sedation and cardiorespiratory depression. This is behavioural control of the crisis, not the definitive mood treatment, which is chosen in 22.3.

WORKED EXAMPLE

A man is brought in floridly manic, has not slept for four nights, is threatening staff and spits out oral medication. LOCUS: admit. Crisis MODUS: de-escalate, then offer a first-line intramuscular option (IM aripiprazole, IM lorazepam, inhaled loxapine or IM olanzapine). FOCUS once settled: an acute-mania first-line agent per 22.3, and stop any antidepressant he arrived on.

22.3 FOCUS: acute mania, the CANMAT first-line plan

For **acute mania**, CANMAT (CANMAT 2018) sets a clear first-line tier. First-line **monotherapy** is lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone or cariprazine. First-line **combination**, favoured in severe mania, is an atypical antipsychotic (quetiapine, aripiprazole, risperidone or asenapine) plus lithium or divalproex. The single most important co-prescribing move: **discontinue any antidepressant** the patient is on when they present with mania (CANMAT 2018). Second-line options (olanzapine, carbamazepine, ziprasidone or haloperidol) belong to the pharmacotherapy notes.

The minimal serum-level pointer. When lithium is used for the acute phase, the target is a serum level of **0.8 to 1.2 mEq/L** (CANMAT 2018); divalproex targets roughly **350 to 700 micromol/L**. Full titration, loading and monitoring detail is cross-referred to the Mood disorders: pharmacotherapy notes. Antipsychotics act faster than a mood stabiliser started alone, but lithium retains a distinct anti-suicidal and mood-stabilising signature (the Lithium Handbook 2023), which is why the severe presentation gets both.

RULE **Stop the antidepressant, start lithium, valproate or an atypical.** Acute mania: monotherapy with a first-line agent, or an atypical plus lithium/divalproex if severe.

TRAP **Continuing the antidepressant.** Leaving an antidepressant running in a manic patient fuels the episode; discontinue it and reassess the diagnosis in a first presentation.

22.4 FOCUS: bipolar depression, the CANMAT first-line plan

For **bipolar depression** (acute bipolar I depression), CANMAT first-line is quetiapine monotherapy (target about 300 mg/day), lurasidone (as monotherapy or adjunctive to lithium or divalproex), lithium monotherapy, and lamotrigine (monotherapy or adjunctive, target at least 200 mg/day with slow titration) (CANMAT 2018). The governing principle is that **antidepressant monotherapy is avoided**: if any antidepressant is used at all it is only adjunctive to a mood stabiliser or antipsychotic, and only in pure, non-mixed depression.

The two cautions. In **mixed features** and in **rapid cycling**, antidepressants are best avoided altogether because they can worsen the mixed state or accelerate the cycling; CANMAT reserves any antidepressant use for pure non-mixed bipolar II depression as a second-line option (CANMAT 2018). This is the highest-yield discrimination in the whole note.

RULE **Reach for quetiapine, lurasidone or lamotrigine and a mood stabiliser, not an antidepressant alone.** That is the first-line bipolar depression answer.

TRAP **Antidepressant monotherapy in bipolar depression.** It risks a switch into mania or hypomania and can precipitate rapid cycling; never give an antidepressant alone in a bipolar depression.

22.5 FOCUS: maintenance, the CANMAT first-line plan and the monitoring headline

For **maintenance**, CANMAT first-line monotherapy is lithium, quetiapine, divalproex, lamotrigine, asenapine or aripiprazole (CANMAT 2018). Adjunctive structured psychoeducation (for example the Barcelona or Life Goals programmes, at least five sessions) is itself a first-line relapse-prevention intervention in euthymic patients. For the non-adherent patient, offer a long-acting injectable antipsychotic (risperidone LAI two-weekly or aripiprazole once-monthly) to prevent relapse. A memory hook: lamotrigine is the depression-pole protector, aripiprazole prevents manic but not depressive episodes, and lithium leads because it covers both poles and lowers suicide risk.

The monitoring headline. Maintenance lithium is run to a serum level of **0.6 to 1.0 mEq/L**, with baseline and periodic **renal and thyroid function** (thyroid, renal function and plasma calcium at six months then at least annually) (CANMAT 2018). Full monitoring schedules for every agent are in the Mood disorders: pharmacotherapy notes.

0.8 to 1.2 mEq/L	0.6 to 1.0 mEq/L	at least 200 mg/day
LITHIUM, ACUTE PHASE	LITHIUM, MAINTENANCE	LAMOTRIGINE TARGET, BIPOLAR DEPRESSION

22.6 The first-line map by phase

The whole plan collapses into one grid. This is the table to hold.

PHASE (FOCUS)	FIRST-LINE MONOTHERAPY (CANMAT)	THE ONE MOVE
Acute mania	Lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone or cariprazine	**Discontinue any antidepressant; add atypical + lithium/divalproex if severe**
Acute mania, severe agitation (crisis)	IM aripiprazole, IM lorazepam, inhaled loxapine or IM olanzapine	**Behavioural control first, then a mood agent**
Bipolar depression	Quetiapine, lurasidone (mono or adjunctive to lithium/divalproex), lithium, lamotrigine (adjunctive)	**No antidepressant monotherapy; caution in mixed features and rapid cycling**
Maintenance	Lithium, quetiapine, divalproex, lamotrigine, asenapine or aripiprazole	**Add psychoeducation; LAI if non-adherent; lithium leads**

CANMAT/ISBD 2018 first-line options by bipolar phase; deeper dosing and second-line agents are in the Mood disorders: pharmacotherapy notes.

22.7 MODUS across guidelines: IPS and NICE alongside CANMAT

The Indian Psychiatric Society. The **indian psychiatric society** guideline for bipolar disorder has been updated: the 2025 IPS bipolar update (IPS 2025, Menon et al., Indian J Psychiatry

2026;68:8-43) supersedes the 2017 Shah guideline. For acute mania the 2025 update names lithium, divalproex, risperidone, quetiapine, aripiprazole, asenapine and cariprazine as first-line monotherapy (with the indigenous protein-kinase-C inhibitor endoxifen, 8 mg/day, as an additional Indian option), adds an antipsychotic to lithium or divalproex for severe or psychotic mania, and discontinues any antidepressant; for acute bipolar depression it names the olanzapine-fluoxetine combination, quetiapine, lurasidone and cariprazine as first-line and does not recommend unopposed antidepressant monotherapy; for maintenance it is lithium-led, with lamotrigine for the depression-pole prophylaxis; and it adds a separate section for bipolar II disorder, given its high Indian prevalence. It notes that sublingual dexmedetomidine, approved abroad for bipolar agitation, is not yet available in India. The IPS therefore agrees with CANMAT on the phase-based spine and differs mainly in emphasising lithium and valproate as the practical Indian first-line (IPS 2025, Menon et al.).

NICE. NICE (CG185) recommends an antipsychotic (for example haloperidol, olanzapine, quetiapine or risperidone) first-line for acute mania, switching to an alternative antipsychotic and then adding lithium, or valproate if lithium is unsuitable, if response is inadequate; for bipolar depression NICE favours a psychological intervention plus quetiapine, or olanzapine (with or without fluoxetine) or lamotrigine, and it positions lithium first-line for long-term maintenance with valproate or olanzapine as alternatives. Valproate is not to be offered to women of childbearing potential.

HOLD THIS

Phase decides the drug: acute mania stop the antidepressant and give lithium, valproate or an atypical; bipolar depression give quetiapine, lurasidone or lamotrigine (never an antidepressant alone); maintenance lithium leads.

22.8 India: lithium, ECT and the acute behavioural disturbance

INDIA

Lithium remains a workhorse first-line and maintenance mood stabiliser in Indian practice: it is inexpensive, widely available and well suited to a resource-limited, high-treatment-gap setting (the treatment gap for mental disorders in India runs about 70% to 92%) (Kaplan & Sadock 2024). Newer agents such as lurasidone, vortioxetine and cariprazine see minimal Indian use, mainly on cost grounds, so the practical first-line set skews to lithium, valproate and the older atypicals. ECT is widely used in India and is a genuine option for severe, psychotic, catatonic or treatment-resistant mania and for life-threatening presentations where a rapid response is needed; the ECT technique itself is cross-referred to the ECT and neurostimulation notes.

For acute behavioural disturbance in Indian inpatient settings, de-escalation and the least-restrictive approach come first, with parenteral options (an intramuscular antipsychotic or lorazepam) if needed; physical restraint is a last resort governed by the Mental Healthcare Act 2017 and must be time-limited and documented. The restraint and de-escalation detail is cross-referred to the Perinatal/women's mental health and emergency psychiatry notes.

GOOD TO REMEMBER

- **Acute mania (CANMAT first-line):** lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone or cariprazine; the one move is stop the antidepressant, and add an atypical plus lithium/divalproex if severe. Lithium acute level 0.8 to 1.2 mEq/L.
- **Severe agitation, crisis (CANMAT first-line IM):** intramuscular aripiprazole, intramuscular lorazepam, inhaled loxapine or intramuscular olanzapine; this is behavioural control, not the mood treatment.
- **Bipolar depression (CANMAT first-line):** quetiapine, lurasidone, lithium or adjunctive lamotrigine; the discriminator is never an antidepressant alone, and caution in mixed features and rapid cycling. Lamotrigine target at least 200 mg/day.
- **Maintenance (CANMAT first-line):** lithium, quetiapine, divalproex, lamotrigine, asenapine or aripiprazole, plus psychoeducation, plus an LAI if non-adherent; lithium leads. Maintenance level 0.6 to 1.0 mEq/L with renal and thyroid monitoring.
- **Indian Psychiatric Society:** the 2025 IPS bipolar update (Menon et al., superseding Shah 2017); first-line mania is lithium, divalproex, risperidone, quetiapine, aripiprazole, asenapine or cariprazine (add an antipsychotic if severe, stop the antidepressant; endoxifen an Indian option), bipolar depression is the olanzapine-fluoxetine combination, quetiapine, lurasidone or cariprazine (no unopposed antidepressant), maintenance is lithium-led with lamotrigine for the depressive pole, and a separate bipolar II section is added.
- **NICE (CG185):** antipsychotic first-line for acute mania, quetiapine/olanzapine-fluoxetine/lamotrigine for bipolar depression, lithium first-line for maintenance; no valproate in women of childbearing potential.

PEARL

The board question almost always turns on the phase and the antidepressant. Name the phase, and the first-line list follows; in mania you stop the antidepressant, and in bipolar depression you never start one alone.

23 · Differentiate: the mood-disorder interleaved differential

Why this matters. The mood disorders share a small pool of cross-sectional symptoms, so the examiner rarely tests whether a patient is depressed; the marks are in telling apart two entities that look identical on the day of assessment. This is the discrimination step: one interleaved **differential** that lays the mood syndromes side by side and, for each pairing, names the single feature that separates them. Hold the whole grid as a set of one-line discriminators rather than a mass of overlapping criteria, and the viva becomes a lookup.

The organising principle across the entire family is **polarity**. Almost every mood pairing collapses to one question: has there ever been a hypomanic or manic episode. Get that reflex right and the unipolar-versus-bipolar split, the bipolar-subtype split and the mixed-state count all fall into place; the depressive criteria and the manic-episode criteria themselves are taught in full elsewhere in these mood notes and are only invoked here as the yardsticks the differential measures against. The raw descriptive definitions of the individual mood symptoms and the rating scales are owned by the Psychometry, Assessment and Descriptive Psychopathology notes.

23.1 Unipolar versus bipolar depression: the same cross-section, told apart by history

The hardest and highest-yield pairing is **unipolar versus bipolar** depression, because the depressive episode in front of you can be phenomenologically identical in the two illnesses. A bipolar patient in the depressed phase meets exactly the same depressive-episode criteria as a unipolar patient; the two cannot be reliably separated on current symptomatology alone (Stahl 2021). What **distinguishes** them is not the cross-section but the longitudinal history: bipolar disorder requires at least one past hypomanic or manic episode, and unipolar major depressive disorder requires that no such episode has ever occurred. This is why the single most important move in every depression is to **screen for a past hypomanic** episode before the label is written. The failure is common and costly: over a third of patients diagnosed unipolar are eventually re-diagnosed bipolar, and as many as 60% of bipolar II patients are first labelled unipolar, because past hypomania is often pleasant and unreported and because bipolar patients usually present in the depressed phase (Stahl 2021).

Because the current picture will not settle it, the clinician leans on soft **pointers to bipolarity** that raise suspicion without being diagnostic (Stahl 2021; Akiskal 2007): an **early age of onset** (classically before 25 years); **atypical features** (hypersomnia, hyperphagia, leaden paralysis) or **psychotic features** in the depression; a **postpartum onset**, which carries a strong bipolar association; a **family history** of bipolar disorder; an **antidepressant-induced switch** into hypomania or mania on treatment; and a course of shorter but more frequent depressive episodes. None of these confirms bipolarity, but each should trigger a deeper hypomania screen. The definitive item, however, is always the same: a documented past hypomanic or manic episode.

RULE **Polarity is the master discriminator across the mood disorders.** A single past hypomanic or manic episode converts a unipolar depression into a bipolar one and changes first-line treatment; so screen every depression for a past hypomanic episode before the diagnosis is written.

TRAP **Letting a cross-sectional depression hide an underlying bipolarity.** The depressive episode looks the same in both illnesses; skip the lifetime hypomania screen and a bipolar depression is mislabelled unipolar and mistreated with an antidepressant alone.

23.2 MDD versus persistent depressive disorder versus adjustment disorder: duration, threshold and the stressor

Three depressive-spectrum diagnoses are separated on the axes of **duration**, **symptom threshold** and the **relationship to a stressor**, and they are constantly confused. Major depressive disorder is a full-threshold episode of **at least two weeks**: the whole five-of-nine cluster, most of the day nearly every day. Persistent depressive disorder (DSM-5-TR; the ICD-11 relative is dysthymic disorder) is a low-grade but chronic depression lasting **at least two years** (at least one year in children and adolescents), sub-threshold or threshold in intensity, with symptom-free intervals never exceeding two months. Adjustment disorder with depressed mood is the odd one out: it is defined by its tie to an identifiable psychosocial **stressor**, with symptoms arising within three months of the stressor and, once the stressor and its consequences resolve, remitting within six months (DSM-5-TR), and crucially it does **not** meet the full criteria for a major depressive

episode. So the discrimination is threefold: MDD on the two-week full-threshold episode, persistent depressive disorder on the two-year chronic floor, and adjustment disorder on the proportionate, stressor-locked, sub-threshold reaction. The pivotal test between adjustment disorder and MDD is whether the full episode threshold is met: if it is, a stressor does not downgrade the diagnosis to adjustment disorder.

at least 2 wk	at least 2 yr	within 3 mo	within 6 mo
MDD EPISODE FLOOR	PERSISTENT DEPRESSIVE DISORDER	ADJUSTMENT-DISORDER ONSET AFTER STRESSOR	ADJUSTMENT RESOLVES AFTER STRESSOR ENDS

23.3 The depressive subtypes against each other: melancholic versus atypical on mood reactivity

Within a confirmed depressive episode, the two classic subtypes are told apart by a single axis, **mood reactivity**, and the examiner rewards that one word. Melancholic depression is anchored on the **loss** of reactivity: the mood does not lift even transiently in response to normally pleasurable events, and it carries the reverse of the atypical vegetative pattern, namely early-morning awakening, a diurnal variation with mood worst in the morning, marked psychomotor change, anorexia and weight loss, and profound non-reactive despair (DSM-5-TR; Kaplan & Sadock 2024). Atypical depression is defined by **preserved mood reactivity** (the mood brightens in response to positive events) plus reverse-vegetative signs, at least two of hyperphagia or weight gain, hypersomnia, leaden paralysis, and long-standing interpersonal rejection sensitivity (DSM-5-TR). The single discriminator to hold is therefore mood reactivity: absent in melancholia, present in atypical depression; and because the atypical, reverse-vegetative pattern carries an affinity with the bipolar spectrum, atypicality should itself prompt a bipolar screen (Akiskal 2007).

23.4 Bipolar I versus II versus cyclothymia: mania versus hypomania versus sub-threshold

The bipolar subtypes are stratified purely on the **height of the highest pole ever reached**. Bipolar I disorder requires at least one full manic episode, defined by elevated or irritable mood and increased activity or energy lasting **at least one week** (or any duration if hospitalisation is needed), with marked functional impairment, and psychosis is permitted (its presence forces the manic rather than hypomanic label); a depressive episode is not even required for the diagnosis (DSM-5-TR). Bipolar II disorder requires at least one hypomanic episode, the same symptom picture lasting **at least four days**, but by definition **without** marked impairment, without hospitalisation and **without psychosis** (any psychotic feature makes the episode manic, not hypomanic), plus at least one major depressive episode (DSM-5-TR). Cyclothymic disorder is the sub-threshold floor: numerous periods of hypomanic and depressive symptoms over **at least two years** (one year in youth) that never at any point meet full criteria for a hypomanic, manic or major depressive episode (DSM-5-TR). The ladder is clean: full mania to bipolar I, hypomania plus depression to bipolar II, sub-threshold oscillation to cyclothymia. The distinction that decides bipolar I versus II is the mania-versus-hypomania boundary (the one-week, impairment, hospitalisation and psychosis markers), and diagnosing bipolar II without a documented hypomanic episode is the classic error.

COMMON TRAP

Calling a hypomania a mania (or the reverse). The hypomanic and manic pictures share their symptom list; the split is on duration (four days versus one week), severity (no marked impairment versus marked impairment), setting (no hospitalisation versus hospitalisation) and psychosis (absent in hypomania, since any psychotic feature upgrades the episode to manic). Get the boundary wrong and bipolar II is mislabelled bipolar I, or a genuine mania is under-treated as a hypomania.

23.5 Mixed features versus agitated depression versus dysphoric mania: the count of opposite-pole symptoms

The mixed-state pairings are separated by **how many opposite-pole symptoms are counted, and against which base episode**. A DSM-5-TR mixed features specifier attaches to a full episode of one pole carrying **at least three** non-overlapping symptoms of the opposite pole on most days; the shared symptoms, irritability, distractibility, psychomotor agitation and insomnia, are deliberately excluded from the count because they cannot discriminate the opposite pole (DSM-5-TR). This is exactly what **distinguishes** mixed features from a merely **agitated depression**: an agitated depression is a depressive episode whose restlessness and agitation are non-specific arousal, not counted manic symptoms, so with fewer than three genuine opposite-pole (manic) items it stays a plain unipolar-type depression with no mixed specifier. Dysphoric mania is the converse base episode: a full manic syndrome carrying three or more depressive symptoms, so the depression is intruding on a mania rather than the reverse. The single discriminator across all three is therefore the count and provenance of the opposite-pole symptoms: three or more true contrapolar symptoms earn the mixed specifier, and the base pole (depressive versus manic) decides whether the mixed picture is a depression with mixed features or a dysphoric mania. The deeper mixed-state phenomenology and its Kraepelinian roots are developed in the mixed-features topic of these notes.

PAIRING	WHAT LOOKS THE SAME	THE ONE DISCRIMINATOR
Unipolar versus bipolar depression	The cross-sectional depressive episode is identical in both	**A past hypomanic or manic episode (present = bipolar); pointers = early onset, atypical/psychotic features, postpartum onset, family history, antidepressant-induced switch**
MDD versus persistent depressive disorder	Both are depressive, low-mood states	**Duration and threshold: MDD = full episode at least 2 weeks; persistent depressive disorder = chronic sub/threshold at least 2 years**

PAIRING	WHAT LOOKS THE SAME	THE ONE DISCRIMINATOR
MDD versus adjustment disorder	Low mood after life events in both	**Adjustment disorder is stressor-locked and does NOT meet the full episode threshold; onset within 3 months, resolves within 6 months of the stressor ending**
Melancholic versus atypical depression	Both are subtypes of a depressive episode	**Mood reactivity: absent (non-reactive) in melancholic, preserved (reactive) in atypical**
Bipolar I versus bipolar II	Both have depressive and elevated-mood episodes	**Mania versus hypomania: at least 1 week with impairment/hospitalisation/psychosis-permitted (I) versus at least 4 days, no marked impairment, no psychosis (II)**
Bipolar II versus cyclothymia	Both are non-manic bipolar-spectrum states	**A full hypomanic AND a full major depressive episode (II) versus numerous sub-threshold periods over at least 2 years never meeting an episode (cyclothymia)**
Mixed features versus agitated depression	A restless, distressed depressive picture in both	**At least 3 non-overlapping manic symptoms counted (mixed) versus non-specific agitation with too few true manic items (plain depression)**
Mixed features versus dysphoric mania	Opposite-pole symptoms co-occur in both	**The base episode: depression carrying 3 or more manic symptoms (depression with mixed features) versus mania carrying 3 or more depressive symptoms (dysphoric mania)**

The interleaved mood differential: each pairing shares a cross-section but splits on one discriminator (the highlighted cell). Polarity, a past hypomania or mania, is the discriminator that recurs across the whole grid.

GOOD TO REMEMBER

- **Unipolar versus bipolar depression:** identical cross-section; the discriminator is a past hypomanic or manic episode, so screen every depression for a past hypomania; the number to hold is onset before **25 years** as a bipolar pointer.
- **MDD versus persistent depressive disorder:** full episode **at least two weeks** versus chronic sub/threshold depression **at least two years** (one year in youth).
- **MDD versus adjustment disorder:** the stressor-locked reaction that does not meet the full episode threshold; onset **within three months**, resolves **within six months** of the stressor ending (DSM-5-TR).
- **Melancholic versus atypical:** the one discriminator is **mood reactivity**, absent in melancholic, preserved in atypical.
- **Bipolar I versus II:** mania (**at least one week**, impairment, hospitalisation, psychosis permitted) versus hypomania (**at least four days**, no marked impairment, no psychosis).
- **Bipolar II versus cyclothymia:** a full hypomanic plus a full depressive episode versus numerous sub-threshold periods over **at least two years** never meeting an episode.
- **Mixed features versus agitated depression versus dysphoric mania:** the count and base pole, **at least three** non-overlapping opposite-pole symptoms earn the specifier; base depression = depression with mixed features, base mania = dysphoric mania.

MNEMONIC

FAST FAP

The pointers to bipolarity in a depression: **F**amily history of bipolar disorder, **A**typical (or psychotic) features, **S**witch on antidepressant, **T**iming of onset early (before 25 years), **F**requent but shorter episodes, **A**fter delivery (postpartum onset). Any of these should trigger a deeper past-hypomania screen; none of them replaces finding the episode itself.

HOLD THIS

Every mood-disorder differential resolves to one question first, has there ever been a hypomanic or manic episode; screen it in every depression, because a past hypomania is the single feature that separates unipolar from bipolar and reorders the whole grid.

Mood disorders: neurobiology and aetiology

24 · The monoamine hypothesis and its limitations

Why this matters. The **monoamine hypothesis** is the historical spine of biological psychiatry and the one neurochemical model every examiner expects a resident to state, defend and then puncture. It is taught here in the mood-neurobiology band under a strict rule: never as a settled cause, always as a mechanism handed straight to its own limitation. The high-yield move is to give the hypothesis, cite the two classes of evidence that built it (the pharmacological and the depletion evidence), and then produce the therapeutic-lag problem and the failure of acute depletion in healthy controls as the two facts that break it. The synaptic mechanics and the pathway anatomy of the monoamines are owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the mood application is taught here.

The frame to carry: this is the oldest of the mood-neurobiology hypotheses and, in its original strong form, now regarded as obsolete (Kaplan & Sadock 2024). What survives is a refined version in which the monoamine change is a trigger for slower adaptive changes downstream (receptor sensitivity, second-messenger and neurotrophic signalling, neuroplasticity), not the primary lesion. Teaching it well means teaching the arc from a chemistry story to a plasticity story.

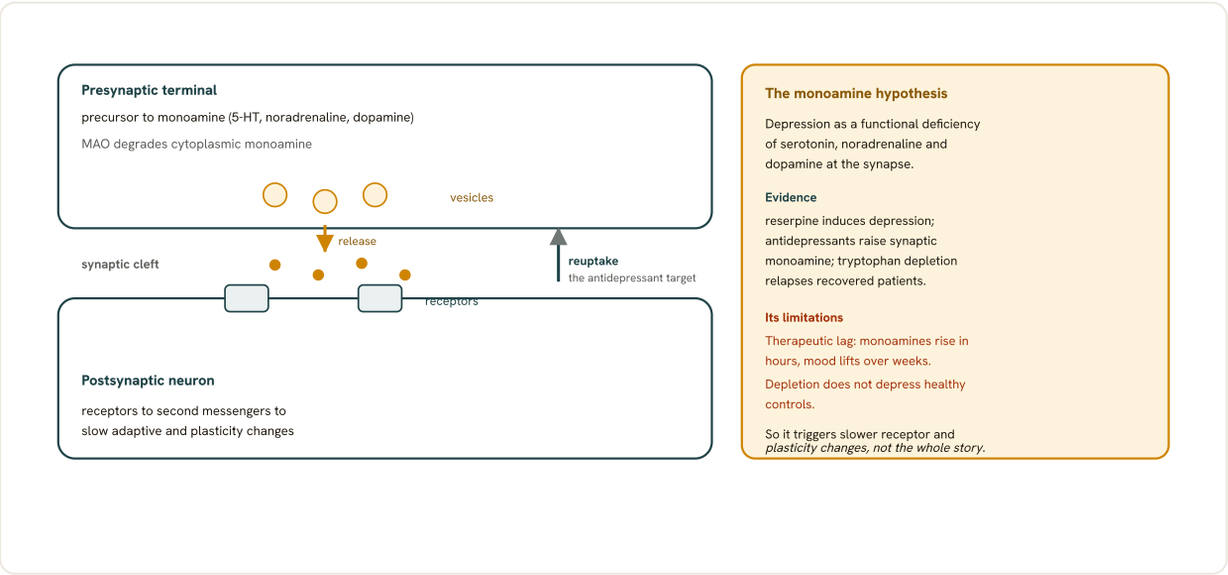

Fig 11.11 The monoamine hypothesis at the synapse, taught with its limits. A monoamine is synthesised, packaged, released into the cleft, and cleared by the reuptake transporter (the target of most antidepressants) and by MAO; the hypothesis holds that depression is a functional deficiency of serotonin, noradrenaline and dopamine. Its own evidence and its limitations sit side by side: the therapeutic lag and the failure of depletion to depress healthy controls are why the monoamine change is now read as the trigger for slower receptor and plasticity adaptations rather than the whole cause.

24.1 The hypothesis: a functional deficiency of synaptic monoamines

The **monoamine hypothesis** proposes that depressive disorder arises from a functional deficiency of one or more **monoamine** neurotransmitters at synapses in the brain (Shorter Oxford 2018; Kaplan & Sadock 2024). Three transmitters are implicated: serotonin (5-HT), noradrenaline (NA), and dopamine (DA), the latter two being catecholamines. In its early form the hypothesis pointed to a simple reduced provision of the amine at the synapse; more recent elaborations restate it as altered provision, turnover or receptor function rather than a bare fall in concentration (Shorter Oxford 2018). Schildkraut's original catecholamine hypothesis of 1965 framed depression as a deficiency, and mania as an excess, of catecholamines (chiefly noradrenaline) at functionally important adrenergic receptor sites, with a parallel serotonin ("indoleamine") hypothesis following (Kaplan & Sadock 2024). The examinable core is one line: depression as a functional deficiency of serotonin, noradrenaline and dopamine at the synapse.

RULE **Teach the monoamine hypothesis with the therapeutic-lag limitation attached.** The hypothesis is depression as a synaptic deficiency of 5-HT, NA and DA; the same breath must state that monoamines rise in hours while mood recovers over weeks.

24.2 The pharmacological evidence: reserpine and the antidepressants

The first pillar is pharmacological, and it runs in two directions that neatly bracket the hypothesis (Kaplan & Sadock 2024). Downwards: reserpine, an antihypertensive alkaloid of *Rauwolfia serpentina* that depletes monoamines by blocking their vesicular storage (VMAT2), was observed to precipitate depression as a side effect during the treatment of hypertension. Upwards: the antidepressants of the era, the tricyclic antidepressants and the monoamine oxidase inhibitors, were known to increase the amount of neurotransmitter available at monoamine synapses, the tricyclics by blocking reuptake and the MAOIs by blocking enzymatic breakdown. A supporting observation completed the picture: potent noradrenergic and dopaminergic agonists such as amphetamine and cocaine induce euphoria and activation, followed by a depression-like withdrawal crash (Kaplan & Sadock 2024). The logic is a bidirectional inference: drugs that lower synaptic monoamines depress, drugs that raise them treat depression, so a monoamine deficiency must underlie the illness.

PEARL

Reserpine is the reference toxin of the whole model: an antihypertensive that empties monoamine vesicles and, in a minority of exposed patients, precipitates a depressive syndrome. It is the single drug the examiner links to the monoamine hypothesis, and its Indian pedigree is genuine, the Rauwolfia snakeroot of Ayurvedic tradition.

24.3 The depletion evidence: tryptophan depletion relapses recovered patients

The second pillar is the tryptophan depletion paradigm, the most direct experimental test of the serotonin limb (Companion 2010; Shorter Oxford 2018). Serotonin synthesis depends on its dietary precursor amino acid, L-tryptophan; loading a subject with a mixture of large neutral amino acids that both competes with tryptophan for the brain transporter and accelerates peripheral tryptophan metabolism drives brain tryptophan, and therefore 5-HT synthesis and release, to very low levels. The striking finding is not in the well but in the recovered: in patients who have recovered from a depressive episode on a serotonin-selective reuptake inhibitor, acute tryptophan depletion produces a transient but clear-cut return of severe depressive symptoms (Delgado 1999; Companion 2010). The specificity is instructive, patients maintained on a noradrenaline-reuptake inhibitor such as desipramine do not relapse to tryptophan depletion, and the mirror manoeuvre for catecholamines, catecholamine depletion with alpha-methyl-para-tyrosine (AMPT), preferentially relapses noradrenergically-treated patients (Companion 2010; Shorter Oxford 2018). This double dissociation directly implicates the monoamines in the maintenance of recovery.

WORKED EXAMPLE

A euthymic patient, well for a year on an SSRI, is enrolled in a challenge study and given a tryptophan-free amino-acid drink. Within hours their plasma tryptophan falls and, over the same day, low mood, retardation and cognitive gloom return in a stereotyped replay of their prior episode; the state resolves as tryptophan is restored. The same patient had they been maintained on desipramine would very likely not have relapsed to tryptophan depletion. The lesson the examiner wants: depletion relapses the recovered along the transmitter axis of their treatment, which supports a monoamine role in relapse but, crucially, does not show that a deficiency caused the first episode.

24.4 The first limitation: the therapeutic-lag problem

The most powerful objection is a timing mismatch, the therapeutic-lag problem, and it is the single limitation to hold (Kaplan & Sadock 2024). Monoamine-enhancing antidepressants raise synaptic monoamine availability essentially at once: reuptake blockade elevates brain monoamines within **hours**, directly registered by in vivo microdialysis in animal models. Yet the clinical antidepressant response is delayed and measured in **weeks**, classically two to four weeks or longer before mood lifts. If a bare synaptic deficiency were the lesion, correcting it in hours should relieve the illness in hours. It does not. The therapeutic lag is therefore the fact that forces the model to change: the acute rise in monoamines cannot itself be the therapeutic event, and something slower, adaptive and downstream of the transporter must be doing the work. This is the **limitations of the monoamine** hypothesis in one clean argument.

hours	weeks	3
SYNAPTIC MONOAMINE RISE	CLINICAL ANTIDEPRESSANT RESPONSE	MONOAMINES: 5-HT, NA, DA

HOLD THIS

Antidepressants raise synaptic monoamines within hours, but mood recovers only over weeks: this therapeutic lag is the key limitation and the reason the monoamine change is read as a trigger for slower plasticity, not the lesion itself.

24.5 The second limitation: acute depletion does not depress healthy controls

The second decisive limitation belongs to the depletion experiments themselves (Companion 2010; Shorter Oxford 2018). Acute monoamine depletion, whether of serotonin by tryptophan depletion or of catecholamines by AMPT, does not reliably produce a depressive episode in healthy controls with no personal or family history of mood disorder. Where any effect is seen in the unaffected it is mild, transient and partial, and it clusters in vulnerable subgroups: a mood-lowering effect in women and in men with a family history of affective disorder, rather than a full syndrome in the general population (Companion 2010). The interpretation is exactly the one that undoes the strong hypothesis: lowering brain monoamines is not sufficient to cause depression. Depletion unmasks a latent vulnerability in those already predisposed or in remission from illness; it does not manufacture the disorder de novo. A deficiency that cannot induce the illness in a healthy brain cannot be its simple cause.

TRAP **Do not present "a chemical imbalance" as the settled cause of depression.** Acute monoamine depletion does not depress healthy controls and CSF and GWAS studies find no consistent monoamine deficit; the imbalance line is a patient-facing oversimplification, not the pathophysiology.

24.6 The wider limitations: the biochemical evidence never converged

Beyond timing and depletion, the direct biochemical search for a monoamine deficit largely failed, and these are the **limitations** that the examiner rewards a candidate for naming (Kaplan & Sadock 2024; Shorter Oxford 2018). Meta-analyses comparing CSF levels of the noradrenaline metabolite MHPG and the serotonin metabolite 5-HIAA found no consistent difference between depressed patients and controls; pharmacological "probe" studies found roughly 40% of patients with no measurable aberration of NA or 5-HT signalling; and genome-wide association studies found no evidence implicating monoamine-related genes in the aetiology of major depressive disorder (Kaplan & Sadock 2024). Low CSF 5-HIAA, where found, tracks impulsive and aggressive behaviour across diagnoses rather than depression specifically (Shorter Oxford 2018). Several studies in fact report elevated, not reduced, monoamine metabolites in untreated patients that normalise on recovery, consistent with altered monoamine signalling being a compensatory or secondary phenomenon rather than the primary lesion (Kaplan & Sadock 2024). The original monoamine hypotheses are therefore now viewed as obsolete in their strong form, with monoamine systems reconceived as broad neuromodulatory systems whose disturbance may be secondary or epiphenomenal.

24.7 The refinement: monoamines as the trigger for downstream plasticity

The resolution is not to discard the monoamines but to demote them from lesion to trigger (Kaplan & Sadock 2024; Shorter Oxford 2018). The refined account reads the acute rise in synaptic monoamines as the first step in a slower cascade: sustained transporter blockade drives adaptive receptor changes (down-regulation and desensitisation of, for example, post-synaptic and autoreceptor targets), engages second-messenger and gene-transcription signalling, and over weeks recruits neurotrophic and neuroplastic mechanisms, notably up-regulation of BDNF, increased synaptogenesis and hippocampal neurogenesis (Kaplan & Sadock 2024; Shorter Oxford 2018). This timescale of adaptation, measured in weeks, matches the therapeutic lag that the bare deficiency model could not explain. On this view the monoamine changes are the starting point, not the whole story: they set in motion the receptor-sensitivity, downstream-signalling and neuroplasticity changes that constitute the actual antidepressant mechanism. The synaptic mechanics and the pathway anatomy underlying this cascade are cross-referenced to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the neurotrophic and HPA hypotheses that extend it are taught in the neighbouring mood-neurobiology topics; and the deep pharmacology of the individual agents is owned by the Mood disorders: pharmacotherapy notes.

STRAND	THE CLAIM	THE LIMITATION TO ATTACH
Pharmacological evidence	Reserpine depletes monoamines and depresses; TCAs and MAOIs raise synaptic monoamines and treat	**Reserpine depression is a minority effect; correlation of drug action with mood does not prove a deficiency lesion**
Depletion evidence	Tryptophan depletion relapses recovered SSRI-treated patients; AMPT relapses noradrenergically-treated patients	**Does not depress healthy controls with no vulnerability; unmasks latent risk rather than causing illness**
The therapeutic lag	Monoamines predict the transmitter target of antidepressants	**Monoamines rise in hours, mood improves over weeks: the acute rise is not the therapeutic event**
Direct biochemistry	A measurable monoamine deficit should mark the depressed brain	**CSF metabolites, probe studies and GWAS show no consistent monoamine deficit**
The refinement	Monoamine change is the trigger for slower adaptive changes	Receptor down-regulation, second-messenger and neurotrophic (BDNF) signalling and neuroplasticity, on the weeks timescale, do the therapeutic work

The monoamine hypothesis taught mechanism-with-limitation: each evidential strand paired with the fact that breaks the strong form and drives the shift to a downstream-plasticity account; highlighted cells are the limitations the examiner tests.

MNEMONIC

SNAP: Synapse deficiency, No lag fit, Amine depletion spares the healthy, Plasticity downstream

Synapse: the claim is a functional deficiency of 5-HT, NA and DA at the synapse. **N**o lag fit: monoamines rise in hours, mood in weeks. **A**mine depletion spares the healthy: acute depletion does not depress controls, only relapses the vulnerable. **P**lasticity downstream: the refinement, monoamine change triggers receptor and neurotrophic adaptation.

INDIA

Reserpine, the cornerstone of the pharmacological evidence, is an alkaloid of *Rauwolfia serpentina*, the Indian snakeroot used in Ayurvedic and traditional practice long before its twentieth-century use as an antihypertensive and early antipsychotic; its depressogenic reputation is the origin of the whole monoamine story (Kaplan & Sadock 2024; Maudsley). This chapter is otherwise generic on drug detail, which belongs to the Mood disorders: pharmacotherapy notes.

GOOD TO REMEMBER

- **Monoamine hypothesis:** depression as a functional deficiency of serotonin (5-HT), noradrenaline (NA) and dopamine at the synapse; three amines, catecholamines being NA and DA (Schildkraut 1965).
- **Pharmacological evidence:** reserpine depletes monoamines and depresses; TCAs and MAOIs raise synaptic monoamines and treat depression.
- **Depletion evidence:** tryptophan depletion transiently relapses recovered SSRI-treated patients (not desipramine-treated); the one eponym is Delgado.
- **The key limitation (therapeutic lag):** monoamines rise within **hours** but mood improves over **weeks**, so the acute rise cannot be the therapeutic event.
- **Second limitation:** acute monoamine depletion does not depress healthy controls, it only unmasks latent vulnerability.
- **The refinement:** the monoamine change is a trigger for slower adaptive changes (receptor down-regulation, second-messenger and neurotrophic BDNF signalling, neuroplasticity); a starting point, not the whole story.

25 · The HPA axis, cortisol, the DST and stress models

Why this matters. After the monoamine story, the **hpa axis** is the second pillar of mood neurobiology, and it carries the single most durable biological finding in the field: hyperactivity of the hypothalamic-pituitary-adrenal axis in major depression is, in the words of the standard text, one of the most consistent findings in biological psychiatry (Kaplan & Sadock 2024). This topic is taught the same way as its neighbour, mechanism handed straight to its limitation. The examinable arc is three-part: raised **cortisol** with blunted feedback in depression; the **dexamethasone suppression** test as the classic putative biological marker that failed to become a clinical test because of poor specificity; and the **stress**-diathesis and glucocorticoid-cascade models that link early adversity, chronic cortisol and hippocampal damage.

The frame to carry: the HPA changes are a robust *state* abnormality (they largely normalise on recovery), the DST is a real neuroendocrine window but never a diagnostic test, and chronic cortisol is neurotoxic to the hippocampus, which ties this topic to the neurotrophic and neuroimaging accounts. The axis mechanics themselves, the anatomy of the CRH-ACTH-cortisol loop and the receptor biology, are owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the mood application is taught here.

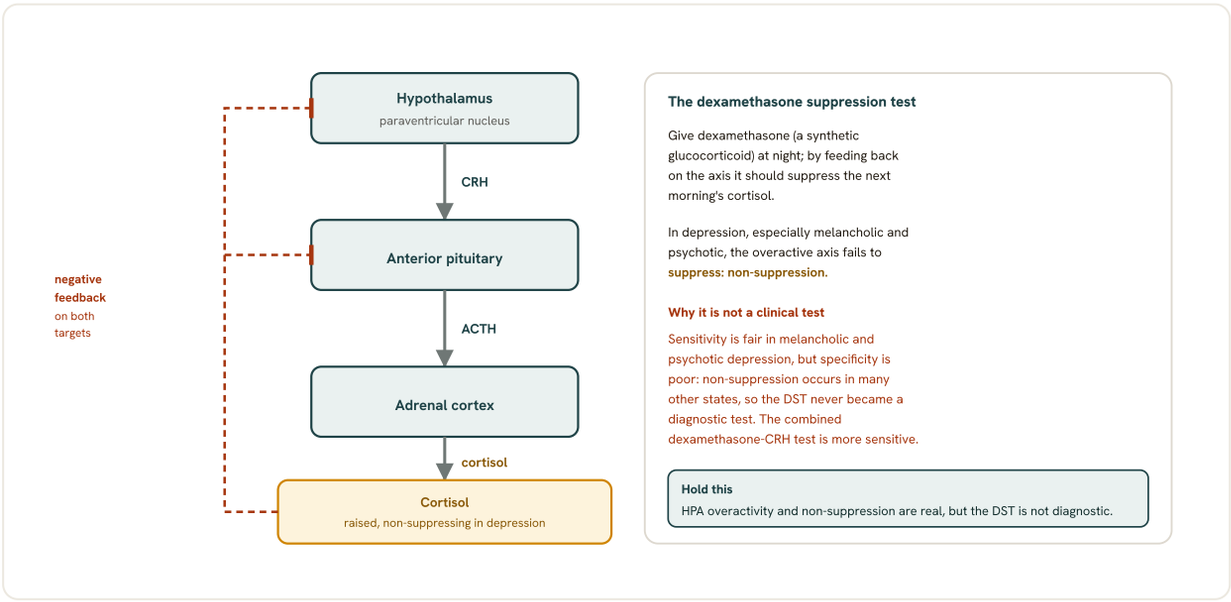

Fig 11.12 The HPA axis and the dexamethasone suppression test. CRH drives ACTH drives cortisol down the spine, and cortisol feeds back negatively on both the pituitary and the hypothalamus to switch the axis off. In depression the axis is overactive and the feedback is blunted, so dexamethasone fails to suppress the morning cortisol. The DST shows real HPA dysregulation but its poor specificity is why it never became a clinical diagnostic test.

25.1 HPA-axis overactivity in depression: the robust finding

The core. Hyperactivity of the HPA axis in major depression is one of the most consistent findings in biological psychiatry, recognised for over fifty years (Kaplan & Sadock 2024). The reported abnormalities cluster into five: **hypercortisolaemia** (raised plasma, urinary-free and CSF cortisol), resistance to dexamethasone suppression of cortisol (a measure of impaired negative feedback), a blunted ACTH response to intravenous CRH challenge, an increased cortisol response in the combined dexamethasone/CRH test, and elevated CSF CRH concentrations (Kaplan & Sadock 2024). A significant proportion of depressed patients hypersecrete cortisol, and this tends to normalise on recovery (Companion 2010). The most characteristic pattern is loss of the normal evening nadir, so cortisol is elevated near sleep onset and on first awakening; raised cortisol at these times has been shown to predict increased risk of future depression (Kaplan & Sadock 2024; Companion 2010).

RULE **HPA overactivity in depression is a state marker, not a trait or a cause.** Hypercortisolaemia, dexamethasone non-suppression and raised CSF CRH are the robust findings, and they largely remit when the patient recovers.

25.2 Blunted feedback and the glucocorticoid-receptor account

Impaired negative feedback. Cortisol release is held in check by a negative-feedback loop acting through low-affinity glucocorticoid receptors (GRs) and high-affinity mineralocorticoid receptors (MRs), with the hippocampus, rich in both, an important feedback site (Kaplan & Sadock 2024). In depression this brake is weakened: there is decreased sensitivity to glucocorticoid fast feedback as well as altered slow feedback, so a normally suppressive signal fails to shut the axis down (Kaplan & Sadock 2024). The diminished responsivity to dexamethasone seen in depressed patients gave rise to the glucocorticoid-receptor hypothesis of depression, in which HPA

dysfunction and the depressive syndrome are linked to genetic or acquired defects of glucocorticoid receptors (Shorter Oxford 2018). This account has a therapeutic hook: different classes of antidepressant increase glucocorticoid-receptor expression in animal studies, so one mechanism of antidepressant action may be to normalise excessive HPA activity by restoring feedback (Shorter Oxford 2018).

25.3 Adrenal and pituitary changes

End-organ correlates. Sustained central drive leaves structural and functional traces on the gland. Alterations in HPA function in depression include increased adrenal size and increased adrenal sensitivity to ACTH, alongside the blunted ACTH response to CRH (Kaplan & Sadock 2024). The picture fits a driven axis: hypothalamic CRH hypersecretion downregulates pituitary CRH receptors (the leading explanation for the blunted ACTH response), while the adrenal, chronically stimulated, enlarges and becomes hyper-responsive to ACTH so that cortisol output is high even when the pituitary signal is blunted (Kaplan & Sadock 2024). These are the end-organ counterparts of the central overactivity, and like the hormonal findings they behave as state markers that track the episode.

25.4 The link to melancholic and psychotic depression

Where the signal is strongest. HPA overactivity is not evenly distributed across depression: it concentrates in the more biological subtypes. Dexamethasone non-suppression is more common in depressed patients with melancholia, though it has not been reliably tied to any single symptom (Shorter Oxford 2018). The association is strongest of all in psychotic depression: some features of psychotic depression in particular appear to be mediated by hypercortisolaemia (Kaplan & Sadock 2024). Mechanistic support comes from treatment: mifepristone (RU-486), a glucocorticoid-receptor antagonist, has been reported to alleviate psychosis and depression in psychotic depression not associated with Cushing syndrome, and psychotic depression is explicitly described as a condition associated with HPA-axis dysregulation and glucocorticoid-receptor abnormalities (Kaplan & Sadock 2024). The clinical read is that the deeper the melancholic or psychotic colouring, the more likely the HPA axis is dysregulated. Mood-with-psychotic-features as a diagnostic entity is developed in the Other psychotic disorders, delusional syndromes and catatonia notes.

WORKED EXAMPLE

A severely retarded, guilt-ridden inpatient with nihilistic delusions has a morning cortisol at the upper limit and fails to suppress on an overnight 1 mg dexamethasone test. The temptation is to read the non-suppression as confirming the depression. It does not: non-suppression marks HPA dysregulation, which is genuinely more likely in this melancholic, psychotic presentation, but it is neither necessary nor sufficient for the diagnosis, which remains clinical. The finding is a correlate of severity and subtype, not a diagnostic ticket.

25.5 The dexamethasone suppression test: the principle

How the test works. The dexamethasone suppression test (DST) probes the integrity of glucocorticoid negative feedback (Companion 2010; Shorter Oxford 2018). A dose of the

synthetic corticosteroid dexamethasone, classically **1 mg** given overnight, acts at pituitary glucocorticoid receptors to suppress ACTH release and therefore endogenous cortisol; plasma cortisol is measured the next day. In a normally sensitive axis cortisol is suppressed. *Non-suppression*, a failure of cortisol to fall (or an early escape from suppression), indicates that feedback is impaired, implying either reduced sensitivity of the receptor-mediated brake and/or enhanced central drive to release cortisol (Companion 2010). About **50%** of depressed inpatients fail to show the normal suppression, and non-suppression reflects the underlying hypercortisolaemia (Shorter Oxford 2018; Companion 2010). This is the one-line principle: dexamethasone normally suppresses cortisol, and non-suppression indicates impaired feedback.

25.6 The DST as a putative biological marker, and why it failed

The historical hope. In the early 1980s the DST was proposed as a diagnostic biological marker for melancholic (endogenous) depression. The founding study reported that the 1 mg DST had high specificity, about **96%**, and sensitivity around **67%** for melancholia (Carroll et al 1981; Companion 2010). The problem, and the examinable core of this topic, is that the high specificity held only against normal controls and collapsed once other patient groups were included, and the result proved difficult to replicate (Companion 2010). Non-suppression is not confined to mood disorders: it also occurs in mania, chronic schizophrenia and dementia, and can be produced by weight loss or altered dexamethasone metabolism (Shorter Oxford 2018; Companion 2010). This lack of diagnostic specificity is exactly what killed the early hope that dexamethasone non-suppression could serve as a diagnostic marker of melancholic depression (Shorter Oxford 2018). The DST therefore never became a clinical diagnostic test: sensitivity is reasonable in melancholic and psychotic depression, but specificity is poor.

TRAP **Do not quote the DST as a clinical test to diagnose depression.** Non-suppression also occurs in mania, chronic schizophrenia and dementia; its poor specificity is precisely why it never entered clinical diagnostic use.

1 mg	~50%	~96% / ~67%
OVERNIGHT DEXAMETHASONE DOSE	DEPRESSED INPATIENTS NON-SUPPRESS	SPECIFICITY / SENSITIVITY, MELANCHOLIA (CARROLL 1981, POORLY REPLICATED)

25.7 The combined dexamethasone-CRH test: a more sensitive refinement

The refinement. The limits of the bare DST prompted a more sensitive probe, the combined dexamethasone/CRH test (Kaplan & Sadock 2024). It uses two opposing stimuli: dexamethasone to inhibit and CRH to stimulate. Typically 1.5 mg of dexamethasone is given in the evening, plasma cortisol is measured about 16 hours later the next day, and an infusion of 100 micrograms of CRH is then given with cortisol and ACTH measured repeatedly over the following 75 minutes (Kaplan & Sadock 2024). Depressed patients show an exaggerated cortisol (and ACTH) response to the CRH challenge despite dexamethasone pre-treatment, and this test detects HPA dysregulation more sensitively than the DST alone (Kaplan & Sadock 2024). Critically, the refinement does not rescue the diagnostic idea: abnormalities in the combined test appear across bipolar disorder, major depression, schizophrenia and PTSD, so its sensitivity and specificity still

do not make it a reliable diagnostic tool (Kaplan & Sadock 2024). Its main value has been as a state-dependent research marker of HPA-axis abnormality, normalising with clinical recovery.

PEARL

The DST and the dexamethasone/CRH test are *state* markers, not *trait* markers: the abnormalities remit when the patient recovers, and normalisation of the dexamethasone/CRH response (like the fall of elevated CSF CRH after ECT or fluoxetine) tracks treatment response. Persistent non-normalisation during treatment can be a harbinger of relapse (Kaplan & Sadock 2024).

25.8 The stress and stress-diathesis models: early-life adversity

Stress into biology. The stress-diathesis model holds that a depressive episode emerges from the interaction of a predisposing vulnerability (diathesis) with precipitating stress, and the HPA axis is the mechanism that translates one into the other. Depressed patients experience more negative life events than non-depressed patients, particularly chronic stress (Kaplan & Sadock 2024). The crucial developmental claim is that early-life stress sensitises the HPA axis and raises the risk of later depression (Kaplan & Sadock 2024). Adults abused as children show altered HPA responses to stress; depressed women who were victims of childhood abuse show an exaggerated ACTH and cortisol response to a psychosocial stressor, presumably from CRH hypersecretion, and depressed men with a history of childhood abuse show marked HPA hyperactivity on the combined dexamethasone/CRH test (Kaplan & Sadock 2024). Childhood maltreatment is described as leaving a neurohormonal "scar" of CRH hypersecretion that becomes a vulnerability factor for mood and anxiety disorders (Kaplan & Sadock 2024). This is the mechanistic bridge by which early adversity is written into adult risk, and it interlocks with the gene-environment findings taught in the neighbouring mood-neurobiology topic.

RULE **Early-life adversity sensitises the HPA axis.** Childhood maltreatment leaves a CRH-hypersecretion "scar" that exaggerates the later cortisol response to stress and raises the vulnerability to depression.

25.9 The glucocorticoid cascade and hippocampal neurotoxicity

When cortisol turns on the brain. If stress-induced cortisol secretion is not contained, persistently elevated levels become harmful, and the hippocampus is particularly vulnerable (Kaplan & Sadock 2024). High glucocorticoid levels impair cell survival, alter cell metabolism and change cell morphology; genomic and non-genomic actions of cortisol in hippocampal cells promote enzymatic processes that can lead to cell death (Kaplan & Sadock 2024). This is the glucocorticoid-cascade hypothesis: the hippocampus normally mediates negative feedback of cortisol release, so cortisol-induced hippocampal damage impairs that feedback, which permits still higher cortisol, which does further damage, a self-amplifying loop (Kaplan & Sadock 2024). It offers a mechanism for the reduced hippocampal volume repeatedly reported in chronic depression, likely related to cortisol excess (Companion 2010). The loop is not one-way and not purely destructive: reducing cortisol can reverse it, decreasing cortisol after treatment of Cushing disease reverses hippocampal atrophy (Kaplan & Sadock 2024). This links directly to the neurotrophic account, where chronic stress and cortisol suppress BDNF and neurogenesis,

developed in the neighbouring topic; the imaging principles behind the volumetric findings are cross-referenced to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

TRAP **Do not read hippocampal volume loss as a fixed structural scar of depression.** The glucocorticoid-cascade damage is at least partly reversible: lowering cortisol (e.g. after treating Cushing disease, or with successful antidepressant treatment) can reverse hippocampal atrophy.

STRAND	THE MECHANISM / CLAIM	THE LIMITATION TO ATTACH
HPA overactivity	Hypercortisolaemia, blunted feedback, raised CSF CRH: the most consistent finding in biological psychiatry	**A state marker that normalises on recovery, not a trait or a proven cause**
Adrenal / pituitary change	Increased adrenal size and ACTH sensitivity; blunted ACTH to CRH from pituitary receptor downregulation	**End-organ correlates of central drive, not diagnostic and not specific to depression**
Subtype link	Non-suppression commoner in melancholia; hypercortisolaemia mediates features of psychotic depression	**A correlate of severity and subtype; the diagnosis stays clinical**
The 1 mg DST	Dexamethasone suppresses cortisol; non-suppression indicates impaired feedback; ~50% of depressed inpatients non-suppress	**Poor specificity (also mania, schizophrenia, dementia, weight loss); never became a clinical diagnostic test**
Combined dexamethasone/CRH test	More sensitive probe: exaggerated cortisol response despite dexamethasone	**Abnormal across bipolar, MDD, schizophrenia and PTSD, so still not a reliable diagnostic test**
Stress-diathesis / glucocorticoid cascade	Early-life adversity sensitises the HPA axis; chronic cortisol is neurotoxic to the hippocampus, a self-amplifying loop	Hippocampal damage is at least partly reversible when cortisol falls

The HPA-axis story taught mechanism-with-limitation: each strand paired with the fact that keeps it out of the clinic; the highlighted cells are the limitations the examiner tests, above all the DST's poor specificity.

MNEMONIC

HYPER: Hypercortisolaemia, feedback, Endless (state marker), Poor specificity, Early stress, Reversible hippocampus

Hypercortisolaemia with blunted feedback is the robust HPA finding in depression. **Y**ields the DST: dexamethasone normally suppresses cortisol; non-suppression means impaired feedback. **P**oor specificity: non-suppression also in mania, chronic schizophrenia and dementia, so the DST is not a diagnostic test. **E**arly-life stress sensitises the axis. **R**eversible: chronic cortisol harms the hippocampus, but lowering cortisol can reverse the atrophy.

INDIA

In Indian practice the DST is not used as a diagnostic test, consistent with the global position: it demonstrates HPA dysregulation but its poor specificity keeps it out of routine clinical diagnosis. The strong HPA signal in psychotic and melancholic depression is clinically relevant here because these are precisely the severe presentations for which ECT remains widely available and used in Indian psychiatric practice; the ECT technique itself is cross-referenced to the ECT and neurostimulation notes.

GOOD TO REMEMBER

- **HPA axis in depression:** hyperactivity is the most consistent finding in biological psychiatry: raised cortisol, blunted feedback, blunted ACTH to CRH, raised CSF CRH; a state marker that normalises on recovery (Kaplan & Sadock 2024).
- **Cortisol pattern:** loss of the evening nadir, cortisol high near sleep onset and on waking; raised cortisol predicts future depression risk.
- **Adrenal / pituitary:** increased adrenal size and ACTH sensitivity; pituitary CRH-receptor downregulation gives the blunted ACTH response.
- **Subtype link:** non-suppression commoner in melancholia; hypercortisolaemia mediates features of psychotic depression (mifepristone can help).
- **Dexamethasone suppression test:** 1 mg overnight; dexamethasone normally suppresses cortisol, non-suppression indicates impaired feedback; ~50% of depressed inpatients non-suppress; the one eponym is Carroll (1981).
- **The key limitation:** good sensitivity in melancholic/psychotic depression but poor specificity (also mania, chronic schizophrenia, dementia), so the DST never became a clinical diagnostic test.
- **Combined dexamethasone/CRH test:** more sensitive refinement (1.5 mg dexamethasone, then 100 microgram CRH infusion), but abnormal across many disorders, so still not diagnostic.
- **Stress / glucocorticoid cascade:** early-life adversity sensitises the HPA axis (CRH-hypersecretion "scar"); chronic cortisol is neurotoxic to the hippocampus in a self-amplifying loop, at least partly reversible when cortisol falls.

HOLD THIS

The DST shows HPA dysregulation (dexamethasone normally suppresses cortisol; ~50% of depressed inpatients fail to suppress) but is not a diagnostic test for depression: sensitivity is decent in melancholic and psychotic depression yet specificity is poor, because mania, chronic schizophrenia and dementia also non-suppress.

26 · Neuroplasticity, BDNF and the neurotrophic hypothesis

Why this matters. The **neurotrophic hypothesis** is the integrative model that examiners now expect after the monoamine story is punctured: it reframes depression not as a chemical deficit but as a state of impaired **neuroplasticity**, and it is the one account that offers a clean explanation for the therapeutic lag. The high-yield structure is the same discipline used across this mood-neurobiology band: state the mechanism, cite the two classes of supporting evidence (the structural imaging findings and the serum **bdnf** changes), then attach the limitations that keep it a leading but unproven account. It is also the bridge to the rapid-acting agents, because the glutamatergic/ketamine mechanism is best understood as a fast route into the very plasticity pathway this hypothesis describes.

The frame to carry: stress and glucocorticoids lower brain-derived neurotrophic factor and suppress hippocampal neurogenesis, while antidepressants, electroconvulsive therapy and exercise act downstream to raise BDNF and CREB signalling and restore plasticity, over a timescale that matches clinical recovery (Kaplan & Sadock 2024; Stahl 2021). The intracellular signalling mechanics (the Trk/CREB/mTORC cascades) and the neuroimaging principles are owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the mood application is taught here.

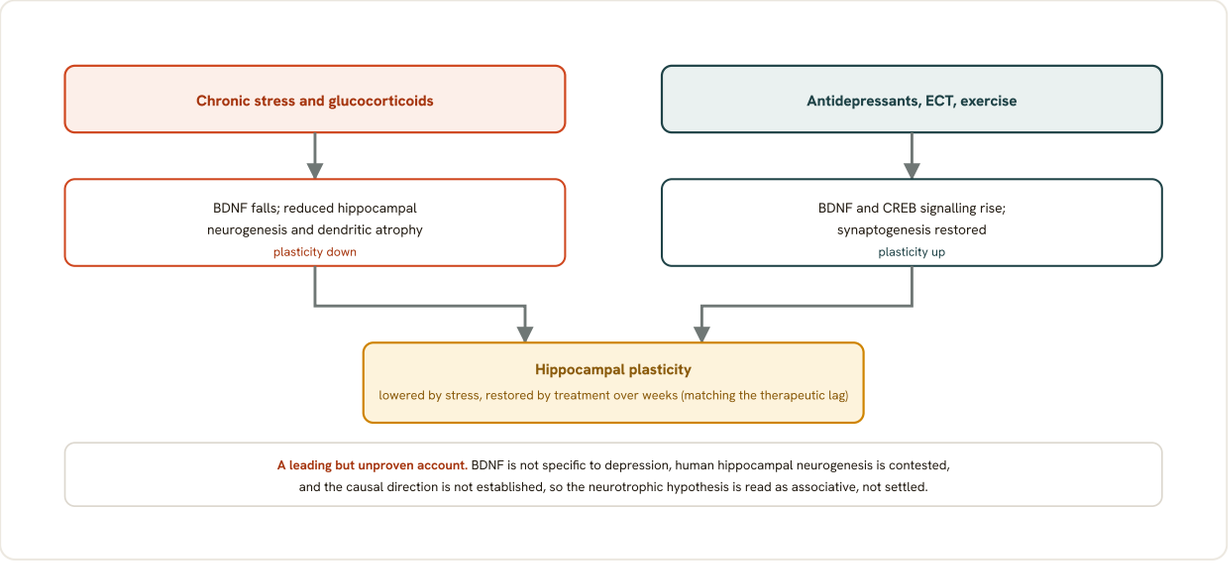

Fig 11.13 The neurotrophic hypothesis. Chronic stress and glucocorticoids lower BDNF and hippocampal neurogenesis, while antidepressants, ECT and exercise raise BDNF and CREB signalling and restore synaptogenesis; the two routes converge on hippocampal plasticity, which is reduced in depression and restored by treatment over the same weeks-long timescale as clinical improvement, which is what links it to the therapeutic lag. It is taught as a leading but associative account, not a proven cause.

26.1 The hypothesis: depression as impaired neuroplasticity

The neurotrophic hypothesis of depression proposes that stress, perhaps aided by cortisol hypersecretion, leads to atrophy and death of neurons and to downregulation of adult neurogenesis, particularly in the hippocampus (Shorter Oxford 2018, after Duman 2009). Reframed for the examiner, depression is read as a state of impaired neuroplasticity: not a bare shortage of a transmitter, but a failure to build and maintain the synaptic and cellular architecture that healthy mood regulation requires. The central molecule is BDNF (brain-derived neurotrophic factor), the best-studied neurotrophin in mood disorders, which supports neuronal maturation, survival, synaptic plasticity and the regulation of monoamine, glutamate and GABA release (Kaplan & Sadock 2024). Under chronic stress, corticotropin-releasing hormone and glucocorticoids suppress **bdnf** synthesis, and the loss of this trophic support is proposed to drive the loss of synaptic maintenance, dendritic arborisation and, in the model's strong form, neurons themselves (Kaplan & Sadock 2024; Stahl 2021). This is the plasticity story that the refined monoamine account hands over to: the monoamine change is the trigger, the neurotrophic and neuroplastic change is the proposed substrate.

RULE **The neurotrophic account links the therapeutic lag to slow plasticity change.** Stress lowers BDNF and neurogenesis; antidepressants raise them downstream over weeks, which is why mood recovers on the plasticity timescale, not the transmitter timescale.

26.2 Stress and glucocorticoids lower BDNF and suppress neurogenesis

The upstream limb is the stress-neurotrophin link. Acute and chronic stress trigger corticotropin-releasing hormone and the release of cortisol and other glucocorticoids, which, directly or indirectly, decrease the synthesis of key neurotrophic factors including BDNF (Kaplan & Sadock 2024). Prolonged glucocorticoid exposure and chronic stress suppress hippocampal neurogenesis, the generation of new neurons in the dentate gyrus, and are associated with structural change in the hippocampus in depressed humans, especially those with a history of early trauma (Kaplan & Sadock 2024). The hippocampus is the pivotal region because it is dense in glucocorticoid receptors and normally provides feedback inhibition of the HPA axis, so its trophic injury both reflects and perpetuates the stress response. The HPA-axis mechanics themselves are cross-referenced to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the point to hold here is directional: stress and cortisol drive BDNF and neurogenesis down.

26.3 Antidepressants, ECT and exercise raise BDNF and CREB signalling

The downstream limb is the treatment-neurotrophin link, and it is where the model earns its keep. A wide range of antidepressant interventions, the tricyclics, MAOIs, SSRIs, SNRIs, noradrenaline-reuptake inhibitors and ketamine, together with non-pharmacological treatments including electroconvulsive therapy, repetitive transcranial magnetic stimulation, exercise and psychotherapy, increase BDNF (Kaplan & Sadock 2024). Mechanistically, sustained monoamine signalling initiates second-messenger cascades that phosphorylate the transcription factor CREB (cyclic-AMP response element-binding protein), which drives expression of trophic genes, raising BDNF and promoting synaptogenesis, cell survival and neurogenesis (Stahl 2021; Kaplan & Sadock 2024). Crucially these adaptive changes unfold over **weeks**, the same timescale as clinical improvement, so the neurotrophic account supplies exactly what the bare monoamine model could not: a molecular event that correlates in time with recovery. That temporal match is the whole reason the hypothesis is taught, and it is what accounts for the therapeutic lag. The deep pharmacology of the individual agents belongs to the Mood disorders: pharmacotherapy notes; the ECT technique is owned by the ECT and neurostimulation notes.

HOLD THIS

Stress and glucocorticoids lower BDNF and hippocampal neurogenesis; antidepressants, ECT and exercise raise BDNF and CREB signalling downstream over weeks, and that plasticity timescale, not the hours-fast transmitter rise, is what matches clinical recovery and explains the therapeutic lag.

26.4 The supporting evidence: imaging and serum BDNF

Two lines of human evidence built the hypothesis (Kaplan & Sadock 2024; Shorter Oxford 2018). First, structural neuroimaging: depressed patients, particularly with recurrent or chronic

illness and early trauma, show reductions consistent with the model, including hippocampal structural change and reduced pyramidal-cell and glial density on postmortem study. Second, the serum BDNF signal: peripheral BDNF levels are reduced in depressed and manic bipolar patients relative to controls, low levels track clinical severity, and successful antidepressant treatment is associated with a rise in BDNF; one study reported that an increase in serum BDNF to **126% of baseline** after a week of treatment, alongside a 50% fall in HAM-D, predicted eventual response with high specificity (Kaplan & Sadock 2024). Serum BDNF thus behaves as a state marker that moves with illness and with treatment. Read carefully, this is associative evidence: BDNF changes travel with the depressive state and its resolution, which is consistent with the hypothesis but does not by itself establish that the BDNF change causes or resolves the illness.

weeks	**126%**	**hippocampus**
PLASTICITY CHANGE, MATCHES RECOVERY	SERUM BDNF AT 1 WK PREDICTING RESPONSE	KEY REGION FOR NEUROGENESIS SUPPRESSION

26.5 The limitations: a leading but unproven account

The hypothesis is powerful but must be stated with cautious causal language, because three limitations keep it unproven (Kaplan & Sadock 2024; Shorter Oxford 2018). First, **BDNF is not specific to depression.** Low BDNF is reported across many psychiatric and neurological conditions, the correlation with depression severity and recurrence has been inconsistent, and peripheral BDNF and proBDNF have proved too mixed and inconclusive to serve as reliable diagnostic biomarkers (Kaplan & Sadock 2024). Second, **human hippocampal neurogenesis is contested.** The extent, and even the existence, of ongoing neurogenesis in the adult human hippocampus remains disputed, so a mechanism resting on suppressed and restored human neurogenesis rests on uncertain ground. Third, **the causal direction is unproven.** Reduced BDNF, smaller hippocampal volume and impaired neurogenesis are associations; whether they cause depression, result from it, or are epiphenomena of the stress state that accompanies it has not been established. The honest examination line is therefore that the neurotrophic hypothesis is a leading integrative account that unifies stress, plasticity and treatment response, but it is not a proven pathophysiology.

TRAP **Do not state reduced neurogenesis as the proven cause of depression.** BDNF is not disorder-specific, human hippocampal neurogenesis is contested, and the causal direction is unproven; the findings are associative, so keep the language of a leading but unsettled model.

26.6 The bridge to rapid-acting agents: glutamate, ketamine and synaptogenesis

The neurotrophic frame directly previews the next topic. If restoring plasticity is the therapeutic event, an agent that produces a rapid burst of synaptogenesis should act fast, and that is exactly the proposed mechanism of the rapid-acting glutamatergic antidepressants (Tasman 2015; Kaplan & Sadock 2024). The NMDA-receptor antagonist ketamine increases glutamate transmission in the prefrontal cortex, thought to occur through blockade of NMDA receptors on tonic-firing GABAergic interneurons, disinhibiting glutamate release; the glutamate burst triggers BDNF release, which activates mTORC1 signalling and drives synthesis of the proteins needed for synaptogenesis, reinstating synaptic connections within hours rather than weeks

(Tasman 2015). The same account explains selectivity at the receptor level: synaptic NMDA activation promotes BDNF synthesis and is neuroprotective, whereas extrasynaptic NMDA activation suppresses BDNF, so extrasynaptic-preferring blockers such as esketamine and ketamine support BDNF while sparing normal transmission (Kaplan & Sadock 2024). This is the plasticity hypothesis running in fast-forward, and it is where the next topic on the rapid-acting agents begins.

ELEMENT OF THE HYPOTHESIS	THE CLAIM (EVIDENCE)	THE LIMITATION TO ATTACH
Upstream (stress)	Stress and glucocorticoids lower BDNF and suppress hippocampal neurogenesis (Kaplan & Sadock 2024)	**Human hippocampal neurogenesis is contested; the structural changes are associations, not established cause**
Downstream (treatment)	Antidepressants, ECT and exercise raise BDNF and CREB signalling over weeks, matching recovery (Kaplan & Sadock 2024; Stahl 2021)	**Correlation of the BDNF rise with recovery does not prove the BDNF change is the therapeutic mechanism**
Serum BDNF marker	Peripheral BDNF falls with the depressive state and rises with successful treatment	**Not specific to depression; correlation with severity and recurrence inconsistent, unreliable as a biomarker**
Rapid-acting bridge	Ketamine drives a glutamate burst, BDNF release and mTORC1-dependent synaptogenesis within hours (Tasman 2015)	The synaptic gains destabilise with stress and relapse, so restored plasticity is necessary but not sufficient for durable recovery

The neurotrophic hypothesis taught mechanism-with-limitation: each limb paired with the fact that keeps it a leading but unproven account; highlighted cells are the limitations the examiner tests.

PEARL

The single strongest argument for the neurotrophic hypothesis is timing: BDNF and CREB-driven plasticity changes accrue over **weeks**, in lockstep with clinical improvement, which is the therapeutic lag the monoamine model could never explain. Timing is the evidence that promotes plasticity from footnote to leading account.

INDIA

Electroconvulsive therapy is one of the interventions shown to raise BDNF, and it remains widely available and heavily used in Indian practice for severe, psychotic and treatment-resistant depression, where it is often the neurostimulation option most accessible to patients (Kaplan & Sadock 2024). The technique and its indications are owned by the ECT and neurostimulation notes; the point here is only that a genuinely plasticity-enhancing treatment is in routine Indian use.

GOOD TO REMEMBER

- **Neurotrophic hypothesis:** depression as impaired neuroplasticity; stress and cortisol lower BDNF and downregulate adult hippocampal neurogenesis (Duman 2009; Shorter Oxford 2018).
- **BDNF:** the best-studied neurotrophin in mood disorders; suppressed by glucocorticoids under chronic stress; the core molecule of the whole model (Kaplan & Sadock 2024).
- **Downstream restoration:** antidepressants, ECT, rTMS and exercise raise BDNF and CREB signalling and restore plasticity over **weeks**, matching clinical recovery and accounting for the therapeutic lag.
- **Supporting evidence:** hippocampal structural reductions on imaging and serum BDNF that falls with the depressive state and rises with treatment (a rise to **126% of baseline** at 1 week predicting response).
- **The limitations:** BDNF is not specific to depression, human hippocampal neurogenesis is contested, and the causal direction is unproven; the evidence is associative, so a leading but unsettled account.
- **Rapid-acting bridge:** ketamine raises glutamate and BDNF and drives mTORC1-dependent synaptogenesis within hours, the plasticity hypothesis in fast-forward.

27 · Glutamatergic and inflammatory hypotheses

Why this matters. After the monoamine and the neurotrophic accounts, two newer mood-neurobiology models earn examiner attention because each reframes depression around a mechanism the monoamine story could not reach. The **glutamatergic hypothesis** reads depression, in part, as a disorder of glutamatergic plasticity, and it is carried by the most dramatic pharmacological fact in modern affective neuroscience: the rapid antidepressant effect of ketamine, an NMDA-receptor antagonist. The **inflammatory hypothesis** reads a subgroup of depression as immune-driven, with raised pro-inflammatory cytokines, a sickness-behaviour phenotype and a kynurenine-pathway link that ties immunity back to glutamate. The high-yield move on both is identical to the rest of this band: state the mechanism with its supporting evidence, then attach the limitation, and never generalise either model to every depressed patient.

The frame to carry: both hypotheses are convergent and partial, not settled aetiologies. Each is best supported in a subgroup, the causal direction is unproven, and the field now treats them as complementary windows on a heterogeneous illness rather than a single lesion (Kaplan & Sadock 2024; New Oxford 2020). The synaptic mechanics of the glutamate and NMDA system and the anatomy of the immune-to-brain routes are owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the mood application is taught here, and the deep drug pharmacology of ketamine and esketamine is owned by the Mood disorders: pharmacotherapy notes.

27.1 The glutamatergic hypothesis: NMDA and glutamate dysregulation in depression

The **glutamatergic hypothesis** proposes that dysregulated **glutamate** signalling, and in particular altered function of the NMDA receptor, contributes to depressive pathophysiology (Kaplan & Sadock 2024). Glutamate is the principal excitatory transmitter, and excess glutamatergic stimulation is neurotoxic; glutamate binding to extrasynaptic NMDA receptors

(with the GluN2B subunit) produces excitotoxicity and suppresses BDNF synthesis, whereas activation of synaptic NMDA receptors (GluN2A subunit) promotes BDNF and is neuroprotective (Kaplan & Sadock 2024). The supporting evidence is the neuroimaging signal: magnetic resonance spectroscopy studies find altered glutamate markers in the hippocampi of chronically depressed patients versus controls, reduced glutamate in the ventromedial prefrontal cortex that correlates with illness duration, and lower anterior cingulate glutamate in both unipolar and bipolar depression, changes evident even at a first lifetime episode (Kaplan & Sadock 2024). This reframes depression, in part, as a disorder of **glutamatergic** plasticity rather than of monoamine tone alone.

PEARL

The synaptic-versus-extrasynaptic split is the mechanistic hinge: synaptic NMDA activity (GluN2A, d-serine coagonist) is neuroprotective and pro-BDNF, while extrasynaptic NMDA activity (GluN2B, glycine coagonist) is excitotoxic and suppresses BDNF (Kaplan & Sadock 2024). Chronic stress and hypercortisolaemia push glutamate transmission toward the harmful, atrophy-producing pole, tying the glutamate story to the hippocampal-volume and neurotrophic findings of the neighbouring topics.

27.2 The ketamine evidence: a rapid antidepressant via AMPA throughput and synaptogenesis

The clinical driver of the hypothesis is the striking rapid antidepressant effect of ketamine, a noncompetitive NMDA-receptor antagonist (Kaplan & Sadock 2024). Trullas and Skolnick first postulated in 1990 that reducing NMDA neurotransmission might be antidepressant; Berman and colleagues showed an antidepressant effect within 72 hours of a single subanaesthetic intravenous infusion in 2000; and Zarate and colleagues confirmed in 2006 a rapid response, with onset within **24 hours** and peak effect within **1 day**, in treatment-resistant unipolar and bipolar depression (Kaplan & Sadock 2024). The proposed mechanism is not simple receptor blockade but a downstream plasticity burst: NMDA antagonism at GABAergic inhibitory interneurons disinhibits presynaptic pyramidal neurons, producing a transient **glutamate** surge; the released glutamate drives an AMPA-receptor throughput that, via BDNF release, mTOR signalling and rapid protein synthesis, triggers **synaptogenesis** and synaptic potentiation (Kaplan & Sadock 2024). The examinable line: ketamine works through an AMPA-throughput and synaptogenesis burst, so its speed points to glutamatergic plasticity, not monoamine correction. Its intranasal S-enantiomer esketamine (Spravato) is FDA-approved for treatment-resistant depression; the dosing, adverse-effect and REMS detail is owned by the Mood disorders: pharmacotherapy notes.

RULE **Ketamine's rapid effect points to a glutamatergic mechanism beyond the monoamines.** An NMDA antagonist relieves depression within 24 hours by an AMPA-throughput and synaptogenesis burst, a timescale and mechanism the monoamine hypothesis cannot explain.

WORKED EXAMPLE

A patient with treatment-resistant depression, unimproved through serial monoamine antidepressants over months, receives a single subanaesthetic ketamine infusion and reports a clear lift in mood and a fall in suicidal ideation within a day, an effect that peaks at one day and wanes over several days without repeat dosing. The lesson the examiner wants: the response is far too fast for a monoamine mechanism and is read as evidence that acute glutamatergic plasticity (AMPA throughput, BDNF, synaptogenesis) can produce antidepressant effects, reframing depression as, in part, a disorder of glutamatergic plasticity. The pharmacology of repeat dosing and maintenance belongs to the Mood disorders: pharmacotherapy notes.

27.3 The inflammatory hypothesis: raised pro-inflammatory cytokines in a subgroup

The **inflammatory hypothesis** proposes that, in a subgroup of patients, depression is associated with a low-grade pro-inflammatory state (New Oxford 2020; Kaplan & Sadock 2024). The core finding is raised peripheral **cytokine** levels: elevated interleukin-6 (IL-6) has been reported repeatedly, alongside raised tumour necrosis factor alpha (TNF-alpha) and the downstream acute-phase marker C-reactive protein (CRP), with IL-6 rises linked to increased CRP (New Oxford 2020). Mechanistically, pro-inflammatory cytokines induce glucocorticoid resistance and promote HPA-axis hyperactivity, activate microglia to a pro-inflammatory phenotype, and amplify neuroinflammation through reactive oxygen and nitrogen species, producing sustained brain inflammation that may drive depressive-like states (New Oxford 2020). Crucially, the association holds in a subset: not all depressed patients show cytokine changes, and the elevation clusters in an inflamed subgroup rather than characterising the disorder as a whole (New Oxford 2020). This is the immune complement to the monoamine and glutamate stories, not a replacement for them.

IL-6	TNF-alpha	CRP
RAISED MOST CONSISTENTLY	RAISED PRO-INFLAMMATORY CYTOKINE	ACUTE-PHASE MARKER, SUBGROUP

27.4 Sickness behaviour and cytokine-induced depression: the interferon model

The strongest causal-direction evidence is cytokine-induced sickness behaviour and cytokine-induced depression (Kaplan & Sadock 2024; New Oxford 2020). Systemic immune activation produces **sickness behaviour**, a stereotyped state of low mood, anergia, anhedonia, anorexia, hypersomnia and social withdrawal that overlaps closely with the depressive syndrome; in humans, a low dose of endotoxin raises plasma IL-6 and TNF-alpha and lowers mood in healthy volunteers (New Oxford 2020). The clinical proof-of-principle is interferon therapy: interferon-alpha, given for hepatitis C or malignant melanoma, precipitates a depressive syndrome in a substantial proportion of treated patients, the clearest demonstration that raising a cytokine can produce depression rather than merely accompany it (Kaplan & Sadock 2024). Interferon-alpha administration also increases MRS glutamate signals and reduces presynaptic dopamine function, and its behavioural effects are attenuated by the serotonin-reuptake inhibitor paroxetine, linking the inflammatory model directly to the monoamine and glutamate systems (Kaplan & Sadock 2024).

PEARL

The interferon-alpha model is the examinable exemplar of cytokine-induced depression: a cytokine given as a licensed treatment reliably induces a depressive syndrome in a proportion of patients, which is why it is cited as the closest thing to an experimental proof that inflammation can cause, and not merely mark, depression (Kaplan & Sadock 2024).

27.5 The kynurenine pathway: the link from inflammation back to glutamate

The kynurenine pathway is the mechanistic bridge that joins the two hypotheses (New Oxford 2020; Kaplan & Sadock 2024). Pro-inflammatory cytokines, chiefly interferon-gamma and TNF-alpha, induce the enzyme indoleamine 2,3-dioxygenase (IDO), which shunts tryptophan away from serotonin synthesis and down the kynurenine pathway (New Oxford 2020). This has two consequences the examiner rewards. First, it depletes tryptophan and so limits serotonin synthesis, tying inflammation to the monoamine limb. Second, it shifts the balance of kynurenine metabolites toward the neurotoxic arm: the pro-inflammatory drive reduces the neuroprotective NMDA-antagonist metabolite kynurenic acid relative to the putatively neurotoxic metabolites 3-hydroxykynurenine and quinolinic acid, an NMDA-receptor agonist (New Oxford 2020). Because quinolinic acid is a glutamatergic NMDA agonist, inflammation feeds directly into the glutamate excitotoxicity story, and the kynurenic-acid-to-quinolinic-acid ratio correlates with hippocampal volume in mood disorders (New Oxford 2020). The kynurenine link is thus why the inflammatory and glutamatergic hypotheses are taught as one connected system.

27.6 The anti-inflammatory augmentation signal in inflamed subgroups

The therapeutic corollary is the anti-inflammatory augmentation signal, and it is instructive precisely because it is subgroup-restricted (New Oxford 2020). A proof-of-concept randomised controlled trial of infliximab, a TNF-alpha monoclonal antibody, improved symptoms specifically in treatment-resistant depression with high baseline inflammation, and the IL-6-receptor antagonist tocilizumab has been proposed on the same logic (New Oxford 2020). In bipolar depression, a meta-analysis found that anti-inflammatory drugs exert antidepressant effects and can potentiate monoaminergic antidepressants, with N-acetylcysteine showing an antidepressant and antioxidant effect (New Oxford 2020). The decisive qualifier is that positive results with anti-inflammatory agents appear restricted to the subset of patients with raised inflammatory biomarkers at baseline; they do not benefit unselected depressed patients (New Oxford 2020). The augmentation signal therefore supports the inflammatory hypothesis and simultaneously defines its boundary. The treatment-level detail of these augmentation strategies is owned by the Mood disorders: pharmacotherapy notes.

TRAP **Do not generalise the inflammatory model to every depressed patient.** Raised cytokines and anti-inflammatory response are found only in an inflamed subgroup; not all depressed patients show cytokine changes, and unselected patients do not benefit from anti-inflammatory drugs.

27.7 The limitations of both hypotheses: heterogeneity, subgroup and unproven causation

Both models share the same three limitations, and naming them is the mark of a candidate who understands the band (New Oxford 2020; Kaplan & Sadock 2024). First, heterogeneity:

depression is not a single disease, and neither glutamatergic nor immune abnormalities are uniform across patients. Second, subgroup restriction: the cytokine elevation and the anti-inflammatory response are confined to an inflamed minority, and the glutamate abnormalities are most marked in chronic and recurrent illness rather than universal. Third, causation is unproven: even the strongest evidence, the interferon model and the biomarker-stratified trials, establishes an association and a plausible mechanism, but for most patients it remains unclear whether the glutamate change or the inflammation is cause, consequence or epiphenomenon of the depressed state (New Oxford 2020; Kaplan & Sadock 2024). As with the monoamine hypothesis, each mechanism is best held as a partial window on a heterogeneous illness, taught with its limitation attached and never stated as the settled lesion.

HYPOTHESIS	THE CLAIM AND EVIDENCE	THE LIMITATION TO ATTACH
Glutamatergic	NMDA and glutamate dysregulation; MRS glutamate changes in depression; ketamine, an NMDA antagonist, gives a rapid antidepressant effect via AMPA throughput and synaptogenesis	**Glutamate changes cluster in chronic and recurrent illness; ketamine response is not universal; causation unproven**
Inflammatory	Raised IL-6, TNF-alpha and CRP in a subgroup; cytokine-induced sickness behaviour and interferon-induced depression; anti-inflammatory augmentation in inflamed patients	**Only a subgroup shows cytokine changes; unselected patients do not benefit from anti-inflammatory drugs; association not proven causal**
The shared link	Cytokines induce IDO, shunting tryptophan down the kynurenine pathway to the NMDA-agonist quinolinic acid, feeding inflammation into glutamate excitotoxicity	Connects the two models mechanistically but does not resolve whether either drives the primary illness

The two newer mood-neurobiology hypotheses taught mechanism-with-limitation, joined by the kynurenine pathway; highlighted cells are the subgroup-and-causation limitations the examiner tests.

MNEMONIC

GLUE: Glutamate plasticity, Ketamine rapid, Cytokines in a subgroup, Kynurenine link

GLutamate: depression as, in part, a disorder of glutamatergic plasticity. **K**etamine (in GlUE, the rapid arm): NMDA antagonist, rapid antidepressant via AMPA throughput and synaptogenesis. **U**nit of inflammation: raised IL-6, TNF-alpha and CRP in a subgroup only, with cytokine-induced sickness behaviour and interferon-induced depression. **E**nzyme link: cytokines induce IDO, driving the kynurenine pathway to the NMDA-agonist quinolinic acid, joining inflammation to glutamate.

INDIA

Ketamine is on the World Health Organization list of essential medicines and is widely available in Indian anaesthetic practice, which makes intravenous ketamine an accessible, low-cost option for treatment-resistant and acutely suicidal depression in Indian settings where intranasal esketamine is not routinely available; its use as an antidepressant remains off-label and specialist-supervised (Kaplan & Sadock 2024). This chapter is otherwise generic on drug detail, which belongs to the Mood disorders: pharmacotherapy notes.

HOLD THIS

Ketamine, an NMDA antagonist, produces a rapid antidepressant effect within 24 hours via an AMPA-throughput and synaptogenesis burst, reframing depression as, in part, a disorder of glutamatergic plasticity; the inflammatory hypothesis raises IL-6, TNF-alpha and CRP but only in a subgroup, and both models explain a subgroup, not all depression.

GOOD TO REMEMBER

- **Glutamatergic hypothesis:** NMDA and glutamate dysregulation in depression; supported by MRS glutamate changes; the one fact to hold is ketamine's rapid response.
- **Ketamine and esketamine:** an NMDA-receptor antagonist giving a rapid antidepressant effect (onset within **24 hours**) via an AMPA-throughput and synaptogenesis burst (BDNF, mTOR); drug detail owned by the Mood disorders: pharmacotherapy notes.
- **Inflammatory hypothesis:** raised pro-inflammatory cytokines (IL-6 most consistent, TNF-alpha, CRP) in a subgroup; the discriminating point is that it is subgroup-restricted, not universal.
- **Cytokine-induced depression:** sickness behaviour overlaps the depressive syndrome, and interferon-alpha therapy (hepatitis C, melanoma) induces depression, the clearest causal signal.
- **Kynurenine link:** cytokines induce IDO, shunting tryptophan to quinolinic acid, an NMDA agonist, joining inflammation to glutamate excitotoxicity.
- **Anti-inflammatory augmentation:** infliximab (anti-TNF) helps treatment-resistant depression with high baseline inflammation only; the signal defines its own subgroup boundary.
- **Shared limitations:** heterogeneity, only a subgroup, causation unproven; both explain a subgroup, not all depression.

28 · Genetics and gene-environment interaction in mood

Why this matters. Mood disorders are the family in which the **genetics of mood** is most examinable, because the two headline disorders sit at opposite ends of the heritability scale: bipolar disorder is one of the most heritable conditions in all of psychiatry, while major depression is only moderately heritable. The board move is to hold the two figures, to know that both are polygenic (many common variants of tiny effect, no single major gene), and to know that the strongest genetic signal for bipolar disorder is shared not with unipolar depression but with schizophrenia. On top of this genetic architecture the examiner wants one worked example of **gene-environment** interaction, the serotonin-transporter-by-stress story, taught with its controversy attached rather than as settled fact.

The frame to carry: mood disorders are complex, non-Mendelian, polygenic traits arising from the joint action of many small-effect genes in a context of environmental exposure, with the whole picture best read through a diathesis-stress lens (Shorter Oxford 2018; Kaplan & Sadock

2024). The raw descriptive definitions of the mood symptoms and the rating scales are cross-referenced to the Psychometry, Assessment and Descriptive Psychopathology notes; the HPA-axis mechanics that mediate the stress limb of gene-environment interaction are owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes and applied to mood in the neighbouring HPA topic.

28.1 Heritability: the concept and how it is measured

Heritability is the proportion of the variation of a trait in a population that can be attributed to variation in genetic factors (Kaplan & Sadock 2024). It is a population statistic, not an individual one: it cannot be applied to a single patient, and it varies with the population and the environmental conditions under which it is estimated (Shorter Oxford 2018). The classic tool is the twin study, which compares the concordance rate (the proportion of co-twins also affected) in monozygotic (MZ) versus dizygotic (DZ) pairs: because MZ twins share essentially all their genes and DZ twins about half, a higher MZ than DZ concordance implies a genetic contribution, and it is the *difference* in concordance, not the absolute MZ rate, that indexes heritability (Shorter Oxford 2018). Family studies (raised risk in first-degree relatives, expressed as morbid risk or expectancy rate) establish familial aggregation as a first step, and adoption studies separate the genetic from the shared-environmental component. A modest MZ concordance can still denote high heritability provided the DZ rate is much lower.

RULE **Heritability is the difference in concordance, not the MZ rate alone.** A bipolar MZ concordance near 60% with a DZ rate near 20% yields a heritability around 85%, because it is the MZ-minus-DZ gap that measures the genetic contribution.

28.2 The strong heritability of bipolar disorder

Bipolar disorder is among the most heritable of all psychiatric disorders, on a par with schizophrenia and autism (Shorter Oxford 2018; Kaplan & Sadock 2024). The concordance rate for mood disorder in the MZ co-twin of a bipolar proband is around **60%**, against only about **20%** in DZ co-twins, giving a heritability estimated at around **85%** (Bienvenu et al. 2011; Shorter Oxford 2018). The brief you must carry states the twin range for bipolar disorder as **60 to 85 percent**, reflecting the span of twin-derived estimates across studies; the widely quoted single figure is around 85% (Bienvenu et al. 2011). The same 60% MZ concordance also proves that genetics is not destiny: roughly 40% of MZ co-twins of a bipolar proband are unaffected, which means environmental (and stochastic) factors are also required (Craddock & Sklar 2013). First-degree relatives of bipolar probands carry a raised risk of both bipolar and unipolar mood disorder, and of schizoaffective disorder.

TRAP **Do not read the 60% MZ concordance as "60% genetic".** The 60% is the MZ concordance; the heritability is around 85%, and the 40% of discordant MZ pairs is precisely the evidence that environment matters.

GOOD TO REMEMBER

- **Bipolar heritability:** among the highest in psychiatry; twin estimates around **60 to 85 percent**, the headline figure around 85% (Bienvenu et al. 2011); MZ concordance ~60%, DZ ~20%.
- **The one discriminator:** bipolar disorder is far more heritable than major depression, and its molecular signal overlaps more with schizophrenia than with unipolar depression.
- **The number to hold:** ~85% (bipolar) versus 37% (major depression), both from the same twin synthesis (Bienvenu et al. 2011).

28.3 The moderate heritability of major depression

Major depression is only moderately heritable, and this contrast with bipolar disorder is a favourite examination point (Shorter Oxford 2018). Depression aggregates in families, with the risk in a first-degree relative of a proband raised about **threefold** (Sullivan et al. 2000; Shorter Oxford 2018). Twin studies confirm a genetic component, with MZ concordance around **45%** and DZ around **20%**, and the heritability of major depression has been estimated at **37%**, considerably less than that of bipolar disorder or schizophrenia (Bienvenu et al. 2011; Shorter Oxford 2018). The brief figure to carry is a moderate heritability of major depression of around **35 to 40 percent**, consistent with this 37% estimate. Two further points sharpen the picture. First, the environmental effect in depression is mediated mainly by influences specific to the individual (non-shared environment) rather than by shared family experience (Sullivan et al. 2000). Second, relatives of unipolar depressed probands do *not* show increased rates of bipolar disorder or schizoaffective disorder, which is a clean nosological asymmetry: bipolar loads for unipolar, but unipolar does not load for bipolar (Shorter Oxford 2018).

~85%	37%	threefold
BIPOLAR HERITABILITY	MAJOR DEPRESSION HERITABILITY	MDD RISK IN FIRST-DEGREE RELATIVES

GOOD TO REMEMBER

- **Major depression heritability:** moderate, around **35 to 40 percent** (estimate 37%, Bienvenu et al. 2011); MZ concordance ~45%, DZ ~20%; first-degree relative risk raised ~threefold.
- **The discriminating asymmetry:** bipolar probands raise relatives' risk of unipolar depression, but unipolar probands do not raise relatives' risk of bipolar disorder or schizoaffective disorder.
- **Environment in MDD:** acts mainly through non-shared (individual-specific) rather than shared family environment (Sullivan et al. 2000).

28.4 Familial aggregation and shared genetic loading across mood and psychotic disorders

The old Kraepelinian wall between the affective and the psychotic diatheses is genetically porous. First-degree relatives of bipolar probands carry raised risks not only of bipolar and unipolar disorder but of schizoaffective disorder, and molecular data now show that many of the risk alleles identified for bipolar disorder are also risk alleles for schizophrenia (Harrison 2016; Shorter Oxford 2018). It is striking that the molecular-genetic overlap in risk alleles is *greater* between bipolar disorder and schizophrenia than between bipolar disorder and unipolar depression (Harrison 2016). This shared loading is the genetic counterpart of the clinical spectrum and of schizoaffective disorder as an intermediate category; the mood-with-psychotic-

features and schizoaffective boundary is developed in the Other psychotic disorders, delusional syndromes and catatonia notes. The formal concept behind this cross-disorder sharing is **pleiotropy**: genes that affect multiple traits or increase risk for multiple disorders, so that many of the same genes raise the risk for schizophrenia, bipolar disorder and autism (Kaplan & Sadock 2024).

PEARL

The single most counter-intuitive genetic fact in mood disorders: bipolar disorder shares more genetic risk with schizophrenia than with unipolar depression (Harrison 2016). This is why cross-disorder GWAS repeatedly find loci that straddle the schizophrenia-bipolar border, and why the affective-psychotic dichotomy is better read as a genetic continuum than a boundary.

28.5 The molecular picture: polygenicity, GWAS loci of small effect, and polygenic risk scores

At the molecular level, mood disorders are **polygenic**: the inherited risk is conferred by hundreds, or even thousands, of genes each of small individual effect, rather than by a single major gene (Kaplan & Sadock 2024; Shorter Oxford 2018). Formally, polygenicity is a trait influenced by many genes of small individual effect (Kaplan & Sadock 2024). Early molecular strategies failed to deliver: linkage studies and candidate-gene association studies of mood disorders were largely unrevealing, positive findings proving difficult to replicate, consistent with small effect sizes and genetic heterogeneity (Shorter Oxford 2018). The breakthrough came from the genome-wide association study (GWAS), which tests SNP markers across the whole genome for association with disease in very large samples; adequately powered GWAS in tens of thousands of bipolar patients have found replicable risk loci, most famously CACNA1C, which encodes a subunit of the L-type voltage-gated calcium channel, with around ten replicated loci identified and calcium-channel signalling emerging as a candidate pathway (Harrison 2016; Shorter Oxford 2018). To aggregate this diffuse signal, the polygenic risk score (PRS) sums an individual's burden of risk alleles weighted by GWAS effect sizes, and can be used to estimate genetic liability and to test for shared risk between disorders (Kaplan & Sadock 2024). Two caveats are examinable: PRS still explains only a modest fraction of the twin heritability (the "missing heritability" gap), and current PRS suffer from a Eurocentric ancestry bias in the GWAS samples that limits their equity across populations (Kaplan & Sadock 2024).

RULE **Mood disorders are polygenic, not Mendelian.** Risk is spread across many common variants of small effect captured en masse by a polygenic risk score; there is no single "bipolar gene" or "depression gene".

TERM	DEFINITION	MOOD-DISORDER EXAMPLE
Heritability	Proportion of population trait variance attributable to genetic variation	**~85% bipolar, 37% major depression (Bienvenu et al. 2011)**
Polygenicity	A trait influenced by many genes of small individual effect	Hundreds to thousands of small-effect variants (Kaplan & Sadock 2024)
Pleiotropy	Genes that affect multiple traits or raise risk for multiple disorders	**Shared risk alleles across schizophrenia and bipolar disorder**
GWAS	Genome-wide test of SNP-marker association with disease	CACNA1C (L-type calcium channel) in bipolar disorder (Harrison 2016)
Polygenic risk score (PRS)	Weighted sum of an individual's risk alleles across the genome	Modest variance explained; Eurocentric-ancestry bias (Kaplan & Sadock 2024)

The molecular vocabulary of mood-disorder genetics, each term paired with its mood example; highlighted cells are the discriminators the examiner tests, the heritability contrast and the schizophrenia-bipolar pleiotropy.

28.6 Gene-environment interaction: the 5-HTTLPR-by-stress paradigm and its controversy

Gene-environment interaction (a genotype altering an individual's sensitivity to an environmental exposure) is examined through one paradigm case, and it must be taught with its controversy attached (Companion 2010; Kaplan & Sadock 2024). The 5-HTTLPR (the serotonin-transporter-linked polymorphic region, written 5-httlpr in some sources), a length polymorphism in the promoter (regulatory) region of the serotonin-transporter gene (SLC6A4) with a short (S) and a long (L) allele, alters transporter expression, the S allele being associated with lower expression and, it was proposed, greater environmental reactivity (Companion 2010). The landmark finding, the Caspi hypothesis, was that carriers of the short allele who were exposed to **stressful life events** or to childhood maltreatment showed a higher rate of depression than long-allele homozygotes with the same exposure, whereas in the absence of stress the genotypes did not differ (Caspi et al. 2003). This became the textbook illustration of a diathesis: the gene did not cause depression directly but moderated the depressogenic impact of adversity. The essential caveat is that later large meta-analyses questioned this specific 5-HTTLPR-by-stress interaction, several failing to replicate it (Risch et al. 2009; Munafo), so the finding is now presented as the classic but contested example rather than settled science. It is best held as the paradigm of gene-environment interaction whose specific effect remains disputed, not as an established mechanism (Companion 2010).

TRAP **Do not cite the 5-HTTLPR-by-stress interaction as settled.** Caspi et al. (2003) is the paradigm example, but later meta-analyses (Risch et al. 2009; Munafo) failed to replicate the specific interaction; state it always with its replication caveat.

WORKED EXAMPLE

Two adults suffer comparable severe life stressors in a year. On the Caspi model, the short-allele (S) carrier is at higher risk of developing a depressive episode than the long-allele (L/L) homozygote, because the S allele is proposed to raise stress-reactivity, while under low adversity the two genotypes look alike (Caspi et al. 2003). The examinable second half: when this was tested across many cohorts in meta-analysis, the specific genotype-by-stress interaction did not consistently replicate (Risch et al. 2009), so the example teaches the *principle* of gene-environment interaction and diathesis-stress, not a validated clinical predictor. No genotype should be used to counsel an individual patient about their depression risk.

28.7 Diathesis-stress and epigenetic framing

The integrating model is **diathesis-stress**: an inherited (or early-acquired) vulnerability, the diathesis, that is expressed as illness only when environmental stress exceeds the individual's capacity to cope (Companion 2010; New Oxford 2020). Individuals differ in the size of their diathesis, so a small stressor precipitates illness in the highly vulnerable while the resilient withstand large stressors; gene-environment interaction is simply the molecular instance of this model, the genotype setting the height of the vulnerability (Companion 2010). A complementary mechanism is **epigenetic**: environmental exposures, particularly early-life stress, can alter gene *expression* without changing the DNA sequence, through mechanisms such as DNA methylation and histone modification, and these changes can be stable and in some models transmitted across generations (Stahl 2021; Tasman 2015). Epigenetics thus supplies a molecular bridge between environment and the genome that helps explain how adversity leaves a durable biological trace on mood-disorder risk. Both frames answer the same examination cue: mood disorders are neither purely genetic nor purely environmental but emerge from the interplay, and the candidate who names diathesis-stress and epigenetic mediation while flagging the 5-HTTLPR replication caveat has the complete answer.

HOLD THIS

Bipolar disorder is highly heritable (twin estimates ~60 to 85%, headline ~85%) and major depression only moderately so (~35 to 40%, estimate 37%); both are polygenic, bipolar overlaps more with schizophrenia than with unipolar depression, and the 5-HTTLPR-by-stress interaction is the classic but contested example of gene-environment interaction.

INDIA

The genetic architecture of mood disorders is not population-specific in its broad form, but PRS derived from Eurocentric GWAS samples transfer poorly to South Asian and other non-European ancestries, so genetic risk prediction cannot yet be applied equitably to Indian patients (Kaplan & Sadock 2024). In routine Indian practice the practical message is unchanged: a detailed family history remains the single most useful genetic tool, and a bipolar family history in a patient presenting with depression is a red flag that should prompt screening for a past hypomanic episode before any antidepressant is started.

MNEMONIC

BIG-P: Bipolar Is Greatly heritable, Polygenic; Depression Moderate

Bipolar **I**s **G**reatly heritable (~85%), and **P**olygenic (many small-effect variants, overlapping schizophrenia); depression is only **M**oderate (~37%). The tail to append: 5-HTTLPR-by-stress is the classic gene-environment example, contested on replication.

GOOD TO REMEMBER

- **Genetics of mood, headline:** bipolar highly heritable (~60 to 85%, ~85%), major depression moderately heritable (~35 to 40%, 37%); both polygenic (Bienvenu et al. 2011; Kaplan & Sadock 2024).
- **Molecular signal:** GWAS loci of small effect, PRS aggregating them, CACNA1C the flagship bipolar locus; bipolar risk overlaps schizophrenia more than unipolar depression (Harrison 2016).
- **Gene-environment:** 5-HTTLPR short allele by stressful life events raising depression risk (Caspi et al. 2003) is the classic but contested example, later meta-analyses failing to replicate the specific interaction (Risch et al. 2009).
- **Framing:** diathesis-stress plus epigenetic mediation (methylation and histone change altering expression without changing sequence); polygenicity with gene-environment interplay is the rule.

29 · Neuroimaging and the limbic-cortical circuit model

Why this matters. The neurochemical hypotheses tell you which molecules are disturbed; **neuroimaging** tells you where in the brain the disturbance lives, and it is the bridge from a scattered list of findings to a single organising picture, the **limbic-cortical circuit model** of depression. The examinable arc is three-part and taught the same way as its neurobiology neighbours, each finding handed straight to its limitation: the structural changes (shrunken hippocampus and prefrontal cortex, white-matter hyperintensities in late-life and bipolar depression) and the functional changes (a hypoactive cognitive cortex over a hyperactive limbic core); the circuit model that ties these into a reciprocal dorsal-ventral imbalance hinged on the subgenual cingulate (the Mayberg model), which doubles as a treatment target; and the hard limitation that all of this is group-level and overlapping, never diagnostic in the single patient.

The frame to carry: imaging in mood disorder is a research and mechanistic tool, not a diagnostic test. Every finding here is a mean difference between a patient group and controls, with heavily overlapping distributions, so a scan cannot diagnose depression in the person in front of you. The imaging physics and the general anatomy of these regions are owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the mood application is taught here.

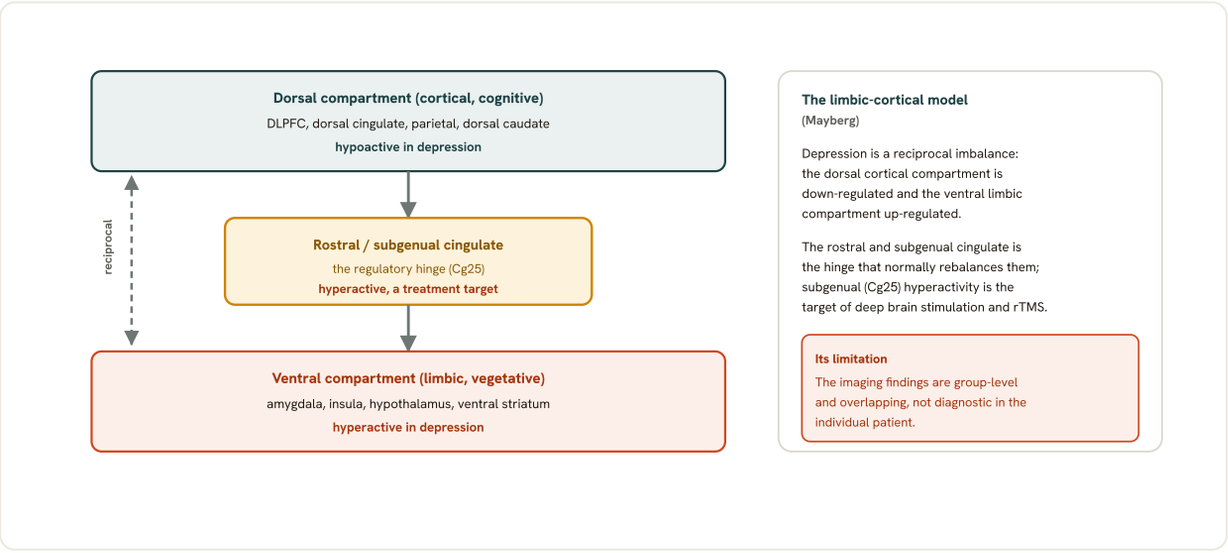

Fig 11.14 A schematic of the limbic-cortical circuit model of depression. The dorsal cortical compartment (cognitive) is down-regulated and the ventral limbic compartment (vegetative) up-regulated, and the two are reciprocally related. The rostral and subgenual cingulate is the hinge that normally rebalances them, and subgenual cingulate hyperactivity is a treatment target. The imaging findings are group-level and overlapping, not diagnostic in the individual.

29.1 Structural findings: hippocampal and prefrontal volume loss

The shrinking cortico-limbic core. Higher-resolution structural MRI documents reduced volume in a consistent set of mood-relevant regions: the hippocampus, the medial orbital cortex and the anterior cingulate (Kaplan & Sadock 2024). Morphological changes appear in both neurons and glia across the hippocampus, amygdala and prefrontal cortex (New Oxford 2020). The hippocampal signal is the most robust and carries a dose relationship: the volume reduction is directly proportional to the number and duration of depressive episodes, especially in early-onset MDD, and in several studies tracks illness chronicity such as lifetime days of untreated depression (Kaplan & Sadock 2024; New Oxford 2020). Mechanistically the loss is attributed partly to reduced glial support, to cortisol excess acting on the glucocorticoid-receptor-rich hippocampus, and to suppression of BDNF-mediated connectivity and neurogenesis, which is why this topic interlocks with the HPA and neurotrophic accounts (Kaplan & Sadock 2024; New Oxford 2020). Crucially the volume reduction is not purely a scar of chronic illness: it has been documented in younger patients in a first depressive episode and is partly heritable in primates (Kaplan & Sadock 2024).

RULE **Hippocampal volume loss in depression scales with illness burden.** The reduction is proportional to the number and duration of episodes, especially in early-onset MDD, and is linked to cortisol excess and suppressed BDNF and neurogenesis.

29.2 White-matter hyperintensities in late-life and bipolar depression

The vascular signature. A commonly observed abnormality in depressive disorders is an increased frequency of white-matter hyperintensities in subcortical regions, the periventricular white matter, the basal ganglia and the thalamus (Kaplan & Sadock 2024). These are more common in bipolar I disorder and among older adults, and they appear to reflect atherosclerotic change, illustrating the deleterious interaction of aging and recurrent affective episodes (Kaplan

& Sadock 2024). This is the imaging anchor of the vascular depression hypothesis, the proposal that cerebrovascular disease predisposes to, precipitates or perpetuates some late-life depressive syndromes, supported by the high prevalence of hyperintensities in late-onset depression and the tie between hyperintensity burden and executive dysfunction and poor antidepressant response (Kaplan & Sadock 2024). Non-specifically, ventricular enlargement, cortical atrophy and sulcal widening have also been reported in more severe recurrent affective illness (Kaplan & Sadock 2024).

GOOD TO REMEMBER

- **Hippocampal volume loss:** the most robust structural finding; proportional to episode number and duration, especially early-onset MDD; tied to cortisol and reduced BDNF/neurogenesis (Kaplan & Sadock 2024).
- **Prefrontal and cingulate volume loss:** reduced medial orbital cortex and anterior cingulate volume; morphological change in neurons and glia across hippocampus, amygdala and PFC (New Oxford 2020).
- **White-matter hyperintensities:** increased subcortical/periventricular hyperintensities, more common in bipolar I and late-life depression, reflecting atherosclerotic change; the imaging basis of the vascular depression hypothesis (Kaplan & Sadock 2024).
- **Non-specific atrophy:** ventricular enlargement, cortical atrophy and sulcal widening in severe recurrent illness (Kaplan & Sadock 2024).

29.3 Functional findings: cortical hypofunction over limbic hyperactivity

The activation pattern. PET and fMRI convert the structural picture into a functional one, and it splits cleanly. The most widely replicated PET finding in depression is decreased anterior brain metabolism, generally more pronounced on the left, with reduced cerebral blood flow and glucose metabolism in the dorsolateral prefrontal cortex that is severity-dependent and correlates with impaired executive problem-solving, reduced abstraction and difficulty inhibiting negative affect (Kaplan & Sadock 2024). This **hypofrontality** reverses in concert with the shift from depression into hypomania (Kaplan & Sadock 2024). Against this cortical hypoactivity sits limbic overactivity: increased glucose metabolism in limbic regions, particularly in severe recurrent depression with a family history, correlating with intrusive rumination, and increased metabolic activity in the amygdala that behaves as an independent dysfunction from the DLPFC hypometabolism and is reversible with effective pharmacotherapy (Kaplan & Sadock 2024). The amygdala is characteristically hyperreactive to negative stimuli, and resting-state connectivity is abnormally increased in the default-mode network (Kaplan & Sadock 2024). This dissociation, a hypoactive cognitive cortex sitting over a hyperactive limbic core, is exactly the substrate the circuit model formalises.

left > right	DLPFC down	amygdala up
ANTERIOR HYPOMETABOLISM (PET) IN DEPRESSION	SEVERITY-DEPENDENT, EXECUTIVE DEFICITS	HYPERREACTIVE TO NEGATIVE STIMULI

29.4 The limbic-cortical circuit model: the two compartments

The Mayberg synthesis. The limbic-cortical circuit model organises these findings into two reciprocally related, functionally opposed compartments (Mayberg 1997; Kaplan & Sadock

2024; New Oxford 2020). The *dorsal compartment* is cortical and cognitive: the dorsolateral and dorsal anterior cingulate cortex and the dorsomedial prefrontal cortex, the machinery of attention, executive control and the top-down regulation of affect, and it is **hypoactive** in depression. The *ventral compartment* is limbic-paralimbic and vegetative: the subgenual cingulate, amygdala, hippocampus, insula and hypothalamus, the machinery of the somatic and autonomic features of mood, and it is **hyperactive** in depression. The core proposition is a **dorsal-ventral imbalance**: the depressed state is a failure of the cortical dorsal compartment to regulate an overactive limbic ventral compartment, mapping neatly onto the imaging dissociation of hypofrontality with amygdala hyperactivity. Recovery, on this account, is a re-normalisation of the balance, with dorsal metabolism rising and ventral limbic metabolism falling.

RULE **The limbic-cortical model frames depression as a dorsal-ventral imbalance with the subgenual cingulate as the hinge.** A hypoactive dorsal (cortical, cognitive) compartment fails to regulate a hyperactive ventral (limbic, vegetative) compartment.

29.5 The subgenual anterior cingulate as the regulatory hinge

Where the two compartments meet. The rostral and subgenual anterior cingulate cortex (the subgenual cingulate, Brodmann area 25) is the pivot of the model, the node that mediates between the dorsal cognitive and ventral limbic compartments and is proposed to be the site whose modulation lets one compartment shift the other (Mayberg 1997; Kaplan & Sadock 2024). Its practical importance is that it is a treatment target. On the observation that the subgenual cingulate cortex (Brodmann area 25) is metabolically *overactive* in treatment-resistant depression, deep brain stimulation was applied to Brodmann area 25 and produced a striking and sustained remission in some previously treatment-resistant patients in an open study (Mayberg 2005; New Oxford 2020). The example makes the model concrete: subgenual cingulate hyperactivity is both the imaging hinge of the dorsal-ventral imbalance and a stimulation target for correcting it. The stimulation technique itself belongs to the ECT and neurostimulation notes; here the point is the circuit logic.

PEARL

The subgenual cingulate is examinable in two directions at once. As a *marker*, its hyperactivity indexes the ventral-limbic overactivity of the depressed state. As a *target*, its overactivity in treatment-resistant depression is what motivated deep brain stimulation of Brodmann area 25 (Mayberg 2005). One region, two exam angles: the hinge of the model and a therapeutic node. Note the honest caveat, no randomised controlled trial has confirmed the deep-brain-stimulation antidepressant effect (New Oxford 2020).

29.6 Amygdala hyperreactivity and prefrontal hypofunction: the working core

The two-node shorthand. Stripped to its examinable minimum, the functional model is a two-node imbalance: **amygdala hyperreactivity** and **prefrontal hypofunction**. The amygdala over-responds to negative and threat-related stimuli and drives the negative processing bias of depression, the skew of attention and memory towards negative material that involves the amygdala, hippocampus, anterior cingulate and PFC (New Oxford 2020; Kaplan & Sadock 2024).

The dorsolateral and dorsomedial prefrontal cortex, normally exerting top-down control over the amygdala, is hypometabolic, so the brake is weakened and the limbic response goes unregulated (Kaplan & Sadock 2024). This is the microcosm of the whole dorsal-ventral story: a hyperactive ventral node (amygdala) released from a hypoactive dorsal node (prefrontal cortex). It is also the point of contact with the neurochemistry, since reduced prefrontal top-down control and heightened limbic reactivity are how the monoamine and glutamate accounts express themselves at the circuit level.

29.7 The limitation: group-level, overlapping, not diagnostic

Why none of this is a test. The decisive limitation, and the single most examined point, is that these findings are **group-level**, overlapping and not diagnostic at the individual level. They are mean differences between patient groups and controls in case-control designs, with distributions that overlap so heavily that no structural or functional measure separates a depressed person from a healthy one reliably enough to diagnose (New Oxford 2020). Imaging studies in psychiatry have often been too small and report effect sizes potentially inflated by post-hoc statistics and publication bias, so the field prefers pooled analyses of many comparable studies to any single scan (New Oxford 2020). Attempts to build imaging classifiers that predict diagnosis or treatment response in the individual patient have used modest samples, could not be tested on a fully held-out sample, and reached within-sample accuracies of only about 60% to 70%, short of clinical use (New Oxford 2020). The conclusion is firm: neuroimaging in mood disorder is a research and mechanistic tool, not a diagnostic test, and there is no scan that diagnoses depression.

TRAP **Do not read a scan as diagnostic of depression.** The structural and functional findings are group-level mean differences with overlapping distributions; no imaging measure diagnoses depression in the individual patient.

29.8 The findings and their limitations, at a glance

Mechanism handed to its limitation. The table lays the imaging story out in the standard neurobiology format for this block: each finding paired with the qualifier that keeps it honest, and the highlighted cells are the limitations the examiner tests.

DOMAIN	THE FINDING	THE LIMITATION / QUALIFIER
Structural: hippocampus	Reduced volume, proportional to episode number and duration, especially early-onset MDD	**Also present in first-episode and partly heritable; a group mean, overlapping, not diagnostic**
Structural: prefrontal / cingulate	Reduced medial orbital cortex and anterior cingulate volume; neuronal and glial change in PFC and amygdala	**Overlapping distributions; non-specific atrophy also in severe recurrent illness**
Structural: white matter	Increased subcortical/periventricular hyperintensities, more common in bipolar I and late-life depression	**Atherosclerotic and age-related; not specific to depression, basis of the vascular hypothesis only**

DOMAIN	THE FINDING	THE LIMITATION / QUALIFIER
Functional: cortex	Decreased anterior metabolism (left > right); DLPFC hypofunction, severity-dependent	**State-dependent, reverses into hypomania; not a diagnostic signature**
Functional: limbic	Amygdala hypermetabolism/hyperreactivity to negative stimuli; increased default-mode connectivity	**Independent of DLPFC change and reversible with treatment; a correlate, not a test**
Circuit: subgenual cingulate	Subgenual cingulate (BA25) overactive in treatment-resistant depression; the dorsal-ventral hinge and a DBS target (Mayberg 2005)	Open-study benefit only; no RCT has confirmed the DBS antidepressant effect

The neuroimaging story taught mechanism-with-limitation: each finding paired with the qualifier that keeps it out of the clinic; the highlighted cells are the limitations the examiner tests, above all that no scan is diagnostic at the individual level.

MNEMONIC

DVH: Dorsal down, Ventral up, Hinge is the subgenual cingulate

Dorsal compartment (dorsolateral and dorsal cingulate, dorsomedial PFC): cortical, cognitive, top-down control, **hypoactive** in depression. **V**entral compartment (subgenual cingulate, amygdala, hippocampus, insula, hypothalamus): limbic, vegetative, **hyperactive**. **H**inge: the subgenual anterior cingulate (Brodmann area 25) is the regulatory pivot and a deep-brain-stimulation target. And over the whole picture: imaging is not diagnostic.

INDIA

In Indian practice neuroimaging in mood disorder is used to exclude organic and structural causes of a mood presentation, for example the white-matter and vascular changes of a late-life depression, not to make or confirm the diagnosis of depression, which stays clinical and is consistent with the global position that no scan is diagnostic. Structural imaging is more accessible than functional imaging (PET and research fMRI remain largely research tools), so the everyday clinical use is the structural exclusion scan, not the circuit-level functional picture taught here.

GOOD TO REMEMBER

- **Limbic-cortical circuit model:** the Mayberg model of depression as a reciprocal dorsal-ventral imbalance; the dorsal (cortical, cognitive) compartment is hypoactive, the ventral (limbic, vegetative) compartment hyperactive (Mayberg 1997).
- **Subgenual anterior cingulate:** the rostral/subgenual cingulate (Brodmann area 25) is the regulatory hinge; its hyperactivity in treatment-resistant depression is a deep-brain-stimulation target (Mayberg 2005); the one eponym is Mayberg.
- **Two-node core:** amygdala hyperreactivity to negative stimuli plus prefrontal (DLPFC) hypofunction, a released limbic node under a weakened cortical brake.
- **Structural findings:** reduced hippocampal (episode-proportional), medial orbital and anterior cingulate volume; white-matter hyperintensities in bipolar I and late-life depression (Kaplan & Sadock 2024).
- **Functional findings:** decreased anterior/DLPFC metabolism (left > right, severity-dependent), amygdala hypermetabolism, increased default-mode connectivity (Kaplan & Sadock 2024).
- **The key limitation:** all findings are group-level, overlapping and not diagnostic at the individual level; imaging is a research and mechanistic tool, not a diagnostic test for depression (New Oxford 2020).

HOLD THIS

The limbic-cortical (Mayberg) model reads depression as a dorsal-ventral imbalance: a hypoactive dorsal cortical-cognitive compartment fails to regulate a hyperactive ventral limbic-vegetative compartment, with the subgenual cingulate (BA25) as the hinge and a DBS target, but every imaging finding is group-level and overlapping, so no scan diagnoses depression in the individual patient.

30 · Psychological theories of depression

Why this matters. Alongside the monoamine, HPA and neurotrophic accounts, the examiner expects a clean map of the **psychological theories of depression**: the cognitive, the learned-helplessness and the behavioural models, with a nod to the psychodynamic and interpersonal frames. These are not merely of historical interest, because each one names the mechanism it targets and so grounds a specific psychotherapy: beck's cognitive theory grounds cognitive therapy, learned helplessness and its attributional reformulation ground the reattribution work inside it, and the behavioural theory of lost reinforcement grounds behavioural activation. The single most rewarded move is to hold each model's core construct and the treatment it justifies, and to treat the models as complementary to the biological ones rather than in competition with them.

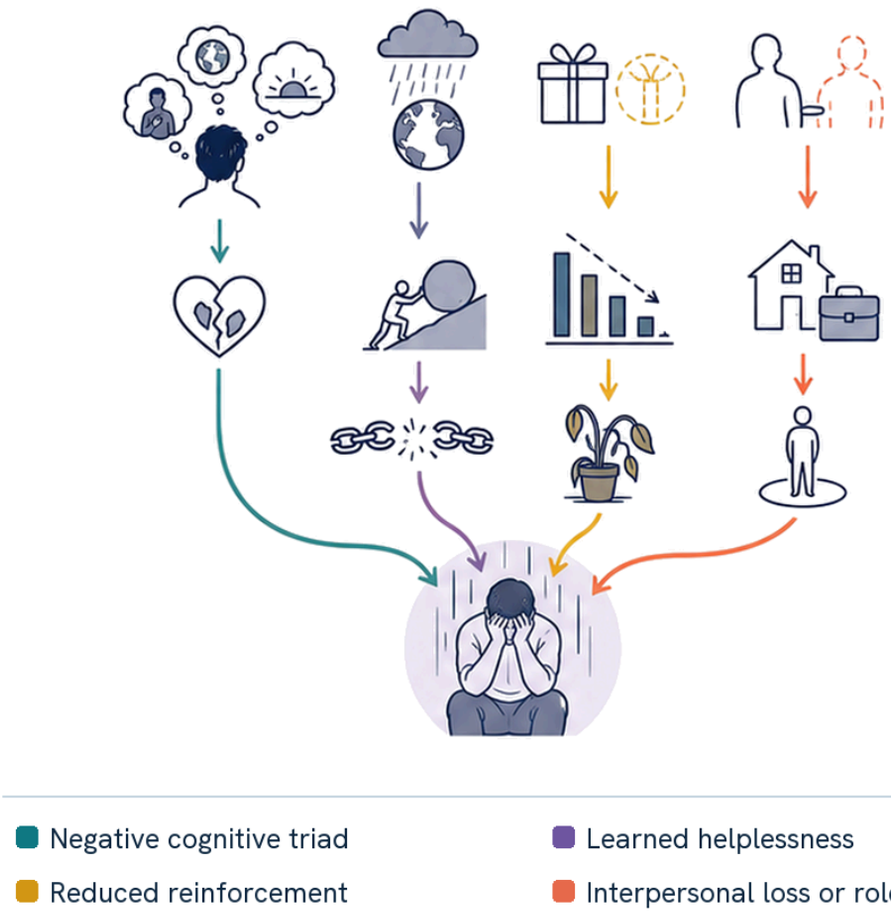

Fig 11.15 Four complementary psychological models of depression: negative beliefs about self, world and future; learned helplessness; reduced environmental reinforcement; and interpersonal loss, dispute or role transition.

This topic teaches the theories, the constructs they turn on, and the discriminating feature of each. The raw descriptive definitions of the mood symptoms and the rating scales are owned by the Psychometry, Assessment and Descriptive Psychopathology notes; the drug and neurostimulation treatments sit in the Mood disorders: pharmacotherapy notes and the ECT and neurostimulation notes; here the concern is the psychological mechanism and the psychotherapy it anchors.

30.1 Beck's cognitive theory: the cognitive triad

The central psychological model of depression is beck's cognitive theory, developed by Aaron T. Beck at the University of Pennsylvania from the late 1950s (Kaplan & Sadock 2024). Beck trained as a psychoanalyst and set out to test the psychoanalytic idea that depression was retroflected hostility; his studies did not support it, and he instead proposed that depression is associated with highly negative, distorted and dysfunctional thinking, the product of **biased information processing** rather than of unconscious drives (Kaplan & Sadock 2024). In his 1967 monograph he named the hallmark of clinical depression the cognitive triad: negatively biased

cognitions about **the self** ("I am worthless, inadequate"), **the world** and one's ongoing experience of it, including other people ("things are unfair, nothing works out"), and **the future** ("it is hopeless, nothing will change") (Kaplan & Sadock 2024; Tasman 2015). The depressed patient thinks of the self as powerless, interprets most events unfavourably in relation to the self, and believes the future to be hopeless, and this triad drives both the mood and the behaviour, with rumination on it exacerbating the symptoms and hopelessness about the future feeding suicidal ideation (Kaplan & Sadock 2024).

RULE **The cognitive triad is self, world and future, all viewed negatively.** Beck's whole model is that depression is a disorder of biased information processing, and this triad is the surface it produces.

30.2 Negative schemas and the systematic cognitive distortions

Beneath the surface triad, Beck's cognitive theory posits two deeper layers. The first is the negative schema, a hypothesised, relatively enduring mental structure that organises information and encodes the person's most central negative beliefs about the self, others and the world (Kaplan & Sadock 2024). These schemas develop in childhood out of the interaction of temperament and experience, then lie **latent** until activated by a matching stressor, at which point previously dormant dysfunctional beliefs become manifest and the person begins to see the self, the world and others through a negative lens (Kaplan & Sadock 2024). The second layer is the set of cognitive distortions, the systematic errors of logic through which the activated schema keeps confirming itself: **arbitrary inference** (a conclusion drawn without evidence), **selective abstraction** (focusing on one negative detail out of context), **overgeneralization** (a sweeping rule drawn from one event), **magnification and minimization** (over-weighting the negative, discounting the positive), **personalization** (relating external events to oneself without basis), and **dichotomous or all-or-nothing thinking** (Beck 1979; Tasman 2015). Negative automatic thoughts and these cognitive errors are demonstrably more common in depressed patients than in controls, which gives the model its empirical footing (Tasman 2015).

MNEMONIC

"A S>C: Arbitrary, Selective, Over-general, Magnify/Minimize, Personalize, Polarize."

The classic Beck cognitive distortions. Arbitrary inference (conclusion without evidence), Selective abstraction (one negative detail), Overgeneralization (one event becomes a rule), Magnification/Minimization (blow up the bad, shrink the good), Personalization (it must be about me), and dichotomous or Polarized all-or-nothing thinking. When a stem lists thinking errors and asks whose model, the answer is Beck.

30.3 How the cognitive theory grounds cognitive therapy

The reason the model earns its place is that it is directly operationalised into treatment. Because the theory locates the pathology in reversible cognitive content, cognitive therapy works by helping the patient **identify, test and modify** the biased thoughts and the schemas that generate

them: the automatic thoughts are examined against evidence, the distortions are labelled and challenged, and the therapy aims ultimately at the underlying negative schemas and the reversal of the cognitive triad (Kaplan & Sadock 2024). The first randomised controlled trial of cognitive therapy for depression (Rush et al. 1977) showed patients responding at least as well as those on pharmacotherapy and with fewer relapses, and later work confirmed efficacy in severe depression (Kaplan & Sadock 2024). The virtue of the model, and the point to state, is that it focuses on **reversible clinical dimensions**, helplessness, hopelessness and suicidal ideation, while providing a testable and practical psychotherapy.

RULE **The cognitive triad and the negative schemas are the target of cognitive therapy.** The therapy identifies, tests and modifies the biased thoughts and the schemas that generate them, aiming to reverse the triad.

The model's own limitation is worth holding: because it was built from retrospective study of already-depressed patients, it cannot prove that negative cognitions **cause** depression rather than being a symptom of it, and negative cognitions alone are unlikely to account for the sleep, appetite, autonomic and psychomotor disturbance of melancholic depression, where cognitive therapy is also less likely to succeed on its own (Kaplan & Sadock 2024). This is exactly why the psychological models are read as complementary to, not substitutes for, the biological ones.

GOOD TO REMEMBER

- **beck's cognitive theory:** depression as biased information processing; the discriminating construct is the **cognitive triad** of negative views of the self, the world and the future, underpinned by latent negative schemas and systematic cognitive distortions; the eponym to hold is **Aaron Beck** (triad described 1967), and it grounds **cognitive therapy**.
- **Negative schemas:** enduring childhood-formed mental structures holding core negative beliefs; the discriminating feature is that they lie **latent** until activated by a matching stressor.
- **Cognitive distortions:** systematic logical errors (arbitrary inference, selective abstraction, overgeneralization, magnification/minimization, personalization, dichotomous thinking) through which the schema confirms itself.

30.4 Learned helplessness and its reformulation into the hopelessness model

The second model is learned helplessness, which Kaplan and Sadock describe as, in some ways, an experimental analog of the cognitive model (Kaplan & Sadock 2024). It began with Martin Seligman's animal work in which dogs prevented from escaping inescapable shock later failed to escape even when escape became available; from the accumulation of such uncontrollable episodes Seligman postulated a learned trait, defining learned helplessness as the belief that it is futile to initiate personal action to reverse an aversive situation (Kaplan & Sadock 2024). Applied to depression, the person who has learned that their responses do not control outcomes stops trying, which maps onto the passivity, low hostility and self-blame of some depressions (Kaplan & Sadock 2024).

The original model could not explain **why** only some people who meet uncontrollable events become depressed, so it was reformulated. The human reformulation introduced attributional style, the characteristic way a person explains the causality, controllability and impact of events

(Abramson, Seligman & Teasdale 1978). People vulnerable to depression tend to explain bad events with attributions that are **internal** (personally controllable, "it is my fault"), **stable** (enduring, "it will always be so") and **global** (far-reaching, "it will affect everything") (Tasman 2015). This **depressive attributional style** was carried forward by Abramson, Metalsky and Alloy (1989) into the hopelessness model, which recast a theory-based **hopelessness depression** in which the internal, stable and global attribution for negative events, together with an expectation that desired outcomes will not occur, generates the hopelessness that is the proximal cause of the depressive symptoms (Abramson et al. 1989).

TRAP **The depressive attributional style is internal, stable and global for BAD events.** Do not swap the dimensions or attach them to good events; it is negative events explained as "my fault, permanent and pervasive" that mark vulnerability.

GOOD TO REMEMBER

- **learned helplessness (Seligman):** the belief that action is futile to change aversive circumstances, learned from uncontrollable events; the discriminating feature is the animal (inescapable-shock) origin and the resulting passivity; the eponym to hold is **Seligman**.
- **Depressive attributional style:** explaining bad events as **internal, stable and global**; this is the reformulated cognitive-vulnerability construct that marks who becomes depressed.
- **hopelessness depression (Abramson, Metalsky & Alloy 1989):** a theory-based subtype in which the depressive attributional style plus negative-outcome expectancy produces **hopelessness** as the proximal cause of symptoms.

30.5 The behavioural theory: Lewinsohn and lost reinforcement

The third model is the behavioural theory, developed by the psychologist Peter Lewinsohn and colleagues, which locates depression in a deficit of **response-contingent positive reinforcement**: depressive behaviour results from a low rate of reward that is contingent on the person's own actions (Kaplan & Sadock 2024). The rate falls for identifiable reasons, an environment that offers few rewarding opportunities, rewards delivered non-contingently (the gratis provision of undeserved rewards, which can itself lower self-esteem), or inadequate **social skills** that reduce the person's chances of eliciting reward from the environment (Kaplan & Sadock 2024). The reduced reinforcement lowers activity and mood, which further reduces engagement, closing a self-perpetuating loop. This is precisely the mechanism that grounds behavioural activation, the treatment that works by systematically re-scheduling access to rewarding, response-contingent activity to break the low-reinforcement cycle; behavioural activation is a recognised evidence-based psychotherapy for depression in its own right (Companion 2010; Kaplan & Sadock 2024). The model's own caveat is that a low rate of reinforced behaviour may in part **reflect** the psychomotor retardation of the depressive illness rather than cause it, so it too is a partial account (Kaplan & Sadock 2024).

RULE **Behavioural = lost reinforcement.** Lewinsohn's reduced response-contingent positive reinforcement is the deficit, and behavioural activation is the treatment that restores it.

GOOD TO REMEMBER

- **behavioural theory (Lewinsohn):** depression from a low rate of **response-contingent positive reinforcement**; the discriminating feature is the reward-deficit mechanism (few rewards, non-contingent rewards, poor social skills); the eponym to hold is **Lewinsohn**, and it grounds **behavioural activation**.

30.6 The psychodynamic and interpersonal frames

Two older frames complete the map. The **psychodynamic** account begins with Freud's 1917 paper Mourning and Melancholia, in which he drew attention to the resemblance between mourning and depression and argued that, just as mourning follows the death of a loved person, melancholia follows the loss of a loved **object**, which may be an actual person or an internal representation or abstraction (Freud 1917; Shorter Oxford 2018). The distinctive feature is the self-directed hostility: the depressed patient's self-reproach was read as a disguised reproach against the lost, ambivalently loved object, whose associated **hostility is turned back against the self** after the object is lost and internalised, so that depression arises where love and hostility (ambivalence) coexist (Shorter Oxford 2018). This is the classic examination phrase, depression as **loss and introjected anger**. The **interpersonal** frame, by contrast, does not commit to intrapsychic mechanism; it holds that depressive episodes arise and are maintained in the context of disturbed current relationships, grief, role disputes, role transitions and interpersonal deficits, and it grounds interpersonal psychotherapy as an evidence-based treatment (Companion 2010). Both are complementary lenses, not rivals to the cognitive and behavioural accounts.

TRAP **Do not treat the psychological models as mutually exclusive, or as rivals to the biological ones.** The cognitive, learned-helplessness, behavioural, psychodynamic and interpersonal frames are complementary, and they sit alongside the monoamine, HPA and neurotrophic accounts, not against them.

GOOD TO REMEMBER

- **Psychodynamic (Freud, Mourning and Melancholia 1917):** depression as **loss and introjected anger**; the discriminating idea is loss of an ambivalently loved object with hostility redirected against the self; the reference to hold is **Mourning and Melancholia**.
- **Interpersonal frame:** depression arising and maintained in disturbed current relationships (grief, role disputes, role transitions, interpersonal deficits); grounds interpersonal psychotherapy.

HOLD THIS

Three models, three targets, three therapies: **beck**'s **cognitive theory** (the cognitive triad of self, world and future, on negative schemas and cognitive distortions) grounds cognitive therapy; **learned helplessness** (Seligman), reformulated into the internal-stable-global depressive attributional style and the hopelessness model, grounds reattribution work; and the **behavioural theory** (Lewinsohn's lost response-contingent positive reinforcement) grounds behavioural activation, with the psychodynamic (loss and introjected anger) and interpersonal frames as complementary lenses to the biological accounts.

INDIA

Cognitive therapy and behavioural activation are the psychological treatments most widely delivered for depression in Indian practice because they are structured, manualised and briefer, which suits the high patient load of public psychiatry; the Indian Psychiatric Society clinical practice guideline for depression lists cognitive behaviour therapy, behavioural activation and interpersonal therapy among the recommended psychotherapies, and their theory bases are exactly the cognitive, behavioural and interpersonal models set out here.

Discriminate, apply and consolidate

31 · Apply: four worked vignettes

Why this matters. The mood block rewards recognition, not recitation. The examiner rarely asks "list the criteria for a hypomanic episode"; more often a short **vignette** is put in front of the candidate and the discrimination has to be made in a sentence: is this depression unipolar or bipolar, is this "depression" actually a mixed state, is this good spell a genuine hypomania, is this a melancholic or an atypical picture. This topic drills exactly that reflex. Each case is a compressed clinical scenario, then the reasoning that reads it, then the resolution, so that the criteria taught elsewhere in this chapter are exercised as they will actually be tested.

The four vignettes reuse only figures and criteria already established and verified in this chapter's own topics: the depressive-episode criteria (at least two weeks, five of nine, one cardinal), the hypomanic-episode criteria (at least four days DSM-5-TR, at least several days ICD-11, three or more DIGFAST symptoms, under the ceilings), the mixed-features rule (at least three non-overlapping opposite-pole symptoms), and the melancholic-versus-atypical split (loss of mood reactivity versus its preservation). Nosology is ICD-11 primary with DSM-5-TR cross-mapped. The deep pharmacology and the specific first-line agents are owned by the Mood disorders: pharmacotherapy notes and only pointed to here; the clinical suicide-risk assessment behind the mixed-state case belongs to the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

31.1 Vignette 1: the unipolar-versus-bipolar depression screen

An atypical, recurrent depression that hides a hypomania. The single most consequential act in assessing any depressed patient is deciding which of two illnesses is in front of you, because the wrong answer means an antidepressant given alone to someone who needed a mood stabiliser (Kaplan & Sadock 2024). The reflex the examiner tests is that *every* depression is screened for a past hypomanic episode before the label major depressive disorder is written, and that the screen leads first through **behavioural activation** (distinct sustained spells of unusual energy, reduced sleep need, racing vivid thinking, over-talkativeness noticed by others) and only then anchors the mood change to those spells (Kaplan & Sadock 2024). An atypical shape to the depression, early onset, recurrence, hypersomnia, hyperphagia and leaden heaviness, is itself a soft-bipolar signal that should raise the index of suspicion (Akiskal 2007).

RULE **Screen every depression for a past hypomanic episode before diagnosing unipolar disorder.** A single lifetime hypomania moves the patient into the bipolar column for life and away from antidepressant monotherapy.

TRAP **Do not start an antidepressant alone on an unscreened recurrent depression.** The atypical, early, recurrent picture is exactly the one most likely to be latent bipolar II; a missed hypomania makes antidepressant monotherapy the wrong first move.

WORKED EXAMPLE

Case: a 24-year-old woman presents with her third episode of low mood since age 18. Each episode runs with hypersomnia (she sleeps eleven hours), a leaden, weighed-down heaviness in her limbs, and carbohydrate craving with weight gain, and her mood still lifts when close friends visit. She denies ever being "manic" and asks for an antidepressant. *Reasoning.* The reactive mood plus reverse-vegetative signs read as atypical features, which carry a recognised affinity with the bipolar spectrum, so the atypical, early, recurrent shape mandates an explicit hypomania screen (DSM-5-TR; Akiskal 2007). Asked first about behavioural activation, she recalls two distinct spells, each five to six days, of needing only four hours of sleep, redecorating her flat overnight, talking so fast that friends teased her, and feeling unusually confident, changes her sister clearly noticed, with no marked impairment, no admission and no psychosis. Count it: elevated mood plus increased activity, over four days, with decreased need for sleep, pressured speech, grandiosity and goal-directed activity, four DIGFAST symptoms, observable and under all three ceilings. *Resolution.* That is a genuine hypomanic episode; with recurrent major depression the diagnosis is bipolar type II disorder, not unipolar depression, and the reflex to start an antidepressant alone is set aside for the guideline-anchored, phase-based plan owned by the bipolar-management topic and the Mood disorders: pharmacotherapy notes.

31.2 Vignette 2: the mixed-features presentation

An agitated, insomniac "depression" with racing thoughts. The most dangerous depression to mismanage is the one carrying manic admixtures, because the reflex to reach for an antidepressant is exactly wrong (Kaplan & Sadock 2024). The DSM-5-TR **with mixed features** specifier applies when full criteria are met for a depressive episode and **at least three** non-overlapping opposite-pole (manic) symptoms are present on most days: elevated or expansive mood, grandiosity, pressured speech or talkativeness, flight of ideas or racing thoughts, increased goal-directed activity or energy, risky pleasurable involvement, and decreased need for sleep (DSM-5-TR). The counting trap sits here: irritability, distractibility, psychomotor agitation and insomnia are **shared** across both poles and are deliberately excluded from the count, so an "agitated, insomniac" label alone does not make the specifier, the discriminating symptoms are the non-overlapping ones such as racing thoughts, pressured speech and grandiosity (DSM-5-TR). Mixed features flag bipolarity, predict a worse course and a poorer lithium response, and carry a raised suicide risk from the coupling of depressive hopelessness to manic drive; the formal risk assessment is owned by the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

RULE **Count only non-overlapping opposite-pole symptoms toward mixed features.** At least three of racing thoughts, pressured speech, grandiosity, elevated mood, increased activity, risky behaviour or decreased sleep need on most days; irritability, agitation, distractibility and insomnia do not count.

TRAP **Do not treat an agitated, mixed depression with an antidepressant alone.** Antidepressant monotherapy into a mixed depression can worsen the mixed and manic pole and raises the already-high suicide risk; screen every activated depression for mixed features first.

WORKED EXAMPLE

Case: a 31-year-old man is brought in with two weeks of profound low mood, hopelessness and passive death wishes, but he is agitated rather than slowed, sleeps only three hours a night, and his thoughts are "racing, too fast to hold", with pressured, over-fast speech and a fleeting sense that he could "fix everything overnight". *Reasoning.* The full depressive episode is present (low mood, hopelessness, suicidality, over two weeks). The examiner-tested move is to count only the non-overlapping manic symptoms: racing thoughts, pressured speech and the transient grandiose expansiveness are three qualifying opposite-pole symptoms, whereas his insomnia and agitation are shared symptoms and are set aside from the count (DSM-5-TR). This is a major depressive episode with mixed features, not a simple agitated depression. *Resolution.* Two consequences follow: the mixed features flag underlying bipolarity and mandate an antidepressant caution, so antidepressant monotherapy is avoided in favour of the mood-stabilising or atypical-antipsychotic-led plan owned by the bipolar-management topic; and the coupling of manic drive to depressive hopelessness raises the suicide risk sharply, so a structured safety assessment is done at once, cross-referred to the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

31.3 Vignette 3: recognising a bipolar II hypomania

A productive, over-active spell without marked impairment. The bipolar II diagnosis rests on documenting a single genuine hypomanic episode that the patient rarely volunteers, because the high is ego-syntonic and often welcomed (Kaplan & Sadock 2024). The threshold is precise: the manic symptom set at a lower altitude, lasting at least **four consecutive days** under DSM-5-TR (ICD-11 asks only for at least several days), with three or more DIGFAST symptoms (four if the mood is only irritable), an unequivocal, uncharacteristic change in functioning that is **observable by others**, and, decisively, staying under the three ceilings: **without marked impairment**, without psychotic features and without any need for hospitalisation (DSM-5-TR; ICD-11 CDDR). The counter-intuitive point the examiner rewards is that *productivity without impairment* does not exclude the diagnosis, it defines it: hypomania by definition does not cause marked impairment, so a genuinely productive four-day high with observable change is a hypomanic episode, and paired with major depression it makes bipolar type II disorder.

RULE **Hypomania is at least four days, observable, and under all three ceilings.** Being productive without marked impairment is what makes it hypomania rather than mania; with a major depressive episode, that yields bipolar type II.

TRAP **Do not upgrade the spell to "mania" or dismiss it as "just feeling well".** If it broke a ceiling it is mania (bipolar I); if it was a distinct four-day observable change without impairment, it is a hypomania and must be counted, not waved away as normal good mood.

WORKED EXAMPLE

Case: a 29-year-old teacher, seen for recurrent depression, describes a distinct four-day spell last year when she slept only four hours yet felt rested, prepared a term's worth of lesson plans in two nights, was unusually talkative and confident, and started three new projects. Colleagues remarked she was "on fire". She functioned well, was never admitted, had no delusions or hallucinations, and looks back on it fondly. *Reasoning.* Elevated mood with increased activity, four consecutive days, most of the day: the duration floor is met (at least four days DSM-5-TR). Within it, decreased need for sleep, more talkative than usual, inflated confidence and a marked increase in goal-directed activity are four DIGFAST symptoms, and the change was observable by others. Crucially, the productivity ran **without marked impairment**, without admission and without psychosis, so all three ceilings are intact, which keeps the episode hypomanic rather than manic. *Resolution.* This is a genuine hypomanic episode; with her recurrent major depressive episodes and no lifetime manic episode, the diagnosis is bipolar type II disorder (F31.81 DSM-5-TR; 6A61 ICD-11). The productive, unimpaired high is not a reason to discount the diagnosis, it is the diagnosis.

31.4 Vignette 4: the melancholic-versus-atypical differential

Two depressions told apart by mood reactivity and the vegetative signs. The organising axis across the depressive subtypes is **mood reactivity**: melancholic depression loses it, atypical depression keeps it (Kaplan & Sadock 2024). Melancholic depression (DSM-5-TR: with melancholic features) requires loss of pleasure or loss of reactivity (mood does not brighten even to good events) plus **three or more** of a distinct quality of depressed mood, AM-worse diurnal variation, early-morning awakening at least **two hours** early, marked psychomotor change, anorexia or weight loss, and excessive guilt (DSM-5-TR). Atypical depression (DSM-5-TR: with atypical features) is the mirror: preserved mood reactivity plus **two or more** of hyperphagia or weight gain, hypersomnia, leaden paralysis and long-standing interpersonal rejection sensitivity (DSM-5-TR). The management implication that the examiner wants is directional, not pharmacological in detail: the melancholic, more biological picture is the one classically responsive to somatic treatment and, at its severe or psychotic end, to ECT (the technique owned by the ECT and neurostimulation notes), while the atypical picture carries the historical MAOI-responsiveness and a bipolar-spectrum affinity that should prompt a hypomania screen; the specific first-line agents belong to the Mood disorders: pharmacotherapy notes.

RULE **Mood reactivity is the pivot: melancholic loses it, atypical keeps it.** Non-reactive mood with early-morning awakening and AM-worse variation reads melancholic; a mood that still brightens with reverse-vegetative signs reads atypical and prompts a bipolar screen.

TRAP **Do not read reversed vegetative signs as "not real depression".** Hypersomnia and hyperphagia are the core of a defined subtype (atypical depression) and a soft-bipolar red flag, not evidence against a mood disorder.

WORKED EXAMPLE

Case: two depressed patients, told apart on one axis. A 52-year-old woman has three weeks of severe low mood that does not lift even when her grandchildren visit, wakes at 4 AM (about two hours early), feels worst in the mornings, is visibly slowed, has lost 5 kg and voices intense guilt about being a burden. A 28-year-old man is also depressed, but his mood still brightens when friends call, he sleeps eleven hours, eats more than usual, describes his legs as leaden and has a lifelong hypersensitivity to rejection. *Reasoning.* The first patient shows non-reactive mood plus a distinct-quality mood, early-morning awakening, AM-worse diurnal variation, psychomotor retardation, weight loss and guilt, well over the three-of-six melancholic threshold: melancholic depression. The second shows preserved mood reactivity plus two reverse-vegetative features (hypersomnia, hyperphagia) with leaden paralysis and long-standing rejection sensitivity, meeting the two-of-four atypical threshold: atypical depression. *Resolution.* The management implication diverges on the axis: the melancholic, more biological picture is the one to consider for somatic treatment and, if severe or psychotic, for ECT; the atypical picture, with its reverse-vegetative signs, is a soft-bipolar signal that mandates a screen for a past hypomanic episode before committing to any antidepressant, with the drug-level detail deferred to the Mood disorders: pharmacotherapy notes.

31.5 The four moves, side by side

Read across the four vignettes and one common architecture appears: a presenting depression, a single decisive discriminator, and a management consequence that turns on it. The grid below is the revision object, each row a worked example collapsed to its trigger, its discriminator and what it changes.

VIGNETTE	PRESENTING PICTURE	THE ONE DISCRIMINATOR	WHAT IT CHANGES
1. Unipolar vs bipolar	Atypical, early, recurrent depression, patient wants an antidepressant	**A documented past hypomanic episode on behavioural-activation screening**	Reclassifies to bipolar II; away from antidepressant monotherapy
2. Mixed features	Agitated, insomniac "depression" with racing thoughts	**At least three non-overlapping manic symptoms (racing thoughts, pressured speech, grandiosity); insomnia and agitation excluded**	Mixed-features specifier; antidepressant caution; raised suicide risk assessed
3. Bipolar II hypomania	Productive, over-active four-day spell without impairment	**Four-plus days, observable change, under all three ceilings (no marked impairment, no psychosis, no admission)**	Genuine hypomania; with recurrent MDE, bipolar type II
4. Melancholic vs atypical	Two depressions, one non-reactive, one reactive	**Mood reactivity (lost in melancholic, preserved in atypical) plus the vegetative direction**	Somatic treatment/ECT vs bipolar screen; different management axis

The four worked vignettes reduced to trigger, discriminator and management consequence; the highlighted cells are the single discriminators the examiner tests.

PEARL

Every one of the four cases turns on the same underlying vigilance: the reflex to screen a depression for hidden bipolarity. Vignette 1 finds it in a past hypomania, vignette 2 in mixed features, vignette 3 in a recognised hypomanic spell, and vignette 4 in the atypical reverse-vegetative signal. The mood block is, at heart, a single repeated question asked four ways: is there bipolarity behind this depression (Kaplan & Sadock 2024)?

HOLD THIS

Four vignettes, one spine: read the discriminator in a sentence. Past hypomania on screening makes a recurrent atypical depression bipolar II (not antidepressant-alone); three non-overlapping manic symptoms in an agitated depression make it mixed features (antidepressant caution, high suicide risk); a productive four-day observable spell under all three ceilings is a hypomania (bipolar II); and mood reactivity separates melancholic from atypical depression and sets the management axis.

GOOD TO REMEMBER

- **Move 1, screen every depression for a past hypomanic episode:** ask behavioural activation first; a single documented hypomania reclassifies a recurrent atypical depression as bipolar II and steers away from antidepressant monotherapy; hold "ever high, then bipolar."
- **Move 2, count only non-overlapping symptoms for mixed features:** at least three opposite-pole symptoms (racing thoughts, pressured speech, grandiosity, elevated mood, increased activity, risky behaviour, decreased sleep need); irritability, agitation, distractibility and insomnia do not count; hold "mixed features raise suicide risk and forbid an antidepressant alone."
- **Move 3, keep the hypomania under the three ceilings:** at least four days (DSM-5-TR) or several days (ICD-11), observable, without marked impairment, psychosis or admission; productivity without impairment defines it; hold "four days, no ceiling broken, plus an MDE = bipolar II."
- **Move 4, split melancholic from atypical on mood reactivity:** melancholic loses reactivity (distinct-quality mood, early-morning awakening at least two hours early, AM-worse variation, psychomotor change, anorexia, guilt; three of six); atypical keeps it (hyperphagia, hypersomnia, leaden paralysis, rejection sensitivity; two of four); hold "reactivity is the pivot, and the vegetative signs run down in melancholic, up in atypical."

32 · Consolidate: mnemonic, retrieval and synthesis

The chapter is long, but it hangs on one spine that the examiner rewards over and over: name the mood **episode** first, split on **polarity**, then let the lifetime pattern name the disorder, and treat by **phase**. **Chain, do not list.** This topic closes the loop by turning the whole chapter into one memorable chain, a set of answer-free recall prompts, and a single map you can redraw on scrap paper before you walk into the hall.

Everything here is a compression of what the earlier topics taught in full. The raw descriptive definitions of the mood symptoms and the rating scales sit in the Psychometry, Assessment and Descriptive Psychopathology notes; the deep drug pharmacology and treatment-resistant algorithms sit in the Mood disorders: pharmacotherapy notes; the HPA-axis mechanics and monoamine pathway anatomy sit in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. Consolidation does not re-teach them; it wires them together.

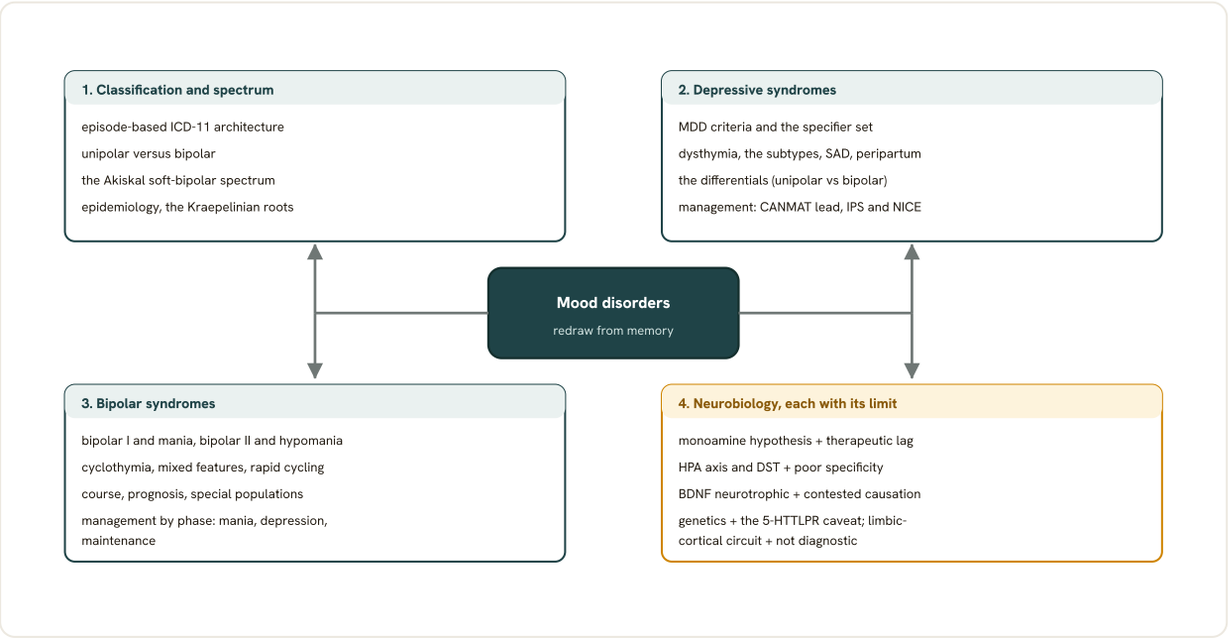

Fig 11.16 The whole-chapter synthesis map, to redraw from memory. Four branches hang off the mood-disorder core: the classification and the Akiskal spectrum; the depressive syndromes and their management; the bipolar syndromes and their phase-based management; and the neurobiology, where every hypothesis is held together with its limitation. Cover the branches and rebuild them.

32.1 The master mnemonic: one chain for the whole chapter

This is the pay-off of the Step-2 seed. The seed gave you the skeleton ("EPISODE first, then POLARITY; CLASSIFY, DEPRESS, then BIPOLAR; MANAGE by phase; MECHANISM with its limit"); here every letter is unpacked into the actual content, band by band, so that reciting the chain walks you through the entire chapter in order. Say it aloud until the branches fall out of the acronym without effort.

MNEMONIC

"EPISODE, then POLARITY → CLASSIFY · DEPRESS · BIPOLAR · MANAGE by phase · MECHANISM with its LIMIT"

Recite the chain as five linked bands, unpacking every letter.

EPISODE, then POLARITY (the two-beat core). **E**pisode: name the mood episode and check its threshold first, depressive (at least **two weeks**, five of nine, one cardinal symptom), manic (at least **one week** or any duration if hospitalised, the mood-and-energy gate, three DIGFAST or four if irritable-only), hypomanic (at least **four days**, same set, no marked impairment, no psychosis, no admission), or mixed (three non-overlapping opposite-pole symptoms). **P**olarity: split on the one question, has there ever been a hypomanic or manic episode; unipolar means depressions only, one lifetime hypomania or mania fixes bipolar for life.

CLASSIFY (band 1, the classification and the spectrum). **C**lassify the family episode-based, not by snapshot: ICD-11 primary, DSM-5-TR cross-mapped, ICD-10 flagged where exams still use it; the Kraepelinian dichotomy underneath. **L**adder the Akiskal soft-bipolar Akiskal spectrum before you enter type I: one-half (schizobipolar), I (mania), one-and-a-half (protracted hypomania), II (spontaneous hypomania with depression), two-and-a-half (cyclothymic depressions), III (antidepressant-mobilised hypomania), three-and-a-half (substance-linked bipolarity), IV (depression on a hyperthymic temperament); a heuristic for vigilance, not a coded nosology.

DEPRESS (band 2, the depressive syndromes and their management). **D**epressive episode and major depressive disorder, single versus recurrent. **E**ndophenotype specifiers: melancholic (loses mood reactivity), atypical (keeps reactivity, hyperphagia, hypersomnia, leaden paralysis, rejection sensitivity), psychotic (mood-congruent delusions), catatonic, peripartum, seasonal, anxious distress, mixed features. **P**ersistent depressive disorder (dysthymia, at least two years) and double depression. **R**eproductive and rhythm forms: premenstrual dysphoric disorder (prospective daily rating over two cycles), peripartum depression, seasonal affective disorder. **M**anage guideline-first (CANMAT lead): first-line a second-generation antidepressant or evidence-based psychotherapy, continuation 6 to 9 months after remission.

BIPOLAR (band 3, the bipolar syndromes and their management). **B**ipolar I (one manic episode ever). **I**I (a hypomanic plus a major depressive episode, never a manic one). **C**yclothymia (at least two years sub-threshold). **M**ixed features and **R**apid cycling (four or more episodes in twelve months). **P**hase-based management (CANMAT lead): acute mania stop the antidepressant and give lithium, valproate or an atypical; bipolar depression give quetiapine, lurasidone or lamotrigine (never an antidepressant alone); maintenance lithium leads.

MECHANISM with its LIMIT (band 4, the neurobiology, each hypothesis with its caveat). **M**onoamine, limited by the therapeutic lag (transmitters rise in hours, mood recovers over weeks). **E**ndocrine HPA and the dexamethasone suppression test, limited by poor specificity (mania, schizophrenia, dementia also non-suppress). **N**eurotrophic BDNF and neurogenesis, limited to a plasticity timescale that matches recovery, not a proven lesion. **G**ene-environment (the 5-HTTLPR-by-stress finding), limited by the replication controversy. Glutamate and inflammation each explain a subgroup only; the circuit (Mayberg dorsal-ventral, subgenual BA25) is group-level and diagnoses no individual.

RULE **Recite the chain, then hang the content on it.** The acronym is only a coat-hook: EPISODE and POLARITY are the two-beat core, then the four branches (classify, depress, bipolar, mechanism-with-limit) unpack in the fixed order the chapter taught.

TRAP **Do not stop at reciting letters.** A mnemonic you cannot unpack is worthless in the viva; if you can say "MENG" but cannot pair each hypothesis with its limitation, you have memorised a sound, not the neurobiology.

32.2 Retrieval practice, cover the answers

Reading is recognition; the exam is recall. The single most powerful study move at this stage is **active recall** under self-testing: **retrieval practice** forces the memory trace to reconstruct itself, which strengthens it far more than re-reading. Work the prompts below with the answers hidden, produce the full answer from memory, then check against the earlier topics. Do not peek; the effort of the failed retrieval is where the learning happens.

RETRIEVAL PRACTICE, COVER THE ANSWERS

Twelve to fifteen answer-free prompts across the five bands. Cover the answers, say each answer aloud in full, then verify against the topic it came from. The answers are deliberately not printed.

1. State the full depressive-episode criteria: duration, the number of symptoms, and the cardinal-symptom rule.
2. Give the manic-episode gate and the DIGFAST threshold, including the change when the mood is irritable only.
3. Define hypomania and list the three features whose presence would instead make the episode manic.
4. Name the single question that separates unipolar from bipolar, and why it must be asked of every depression.
5. Lay out the Akiskal soft-bipolar spectrum from one-half to IV, giving the one-line descriptor for each numbered type.
6. Contrast melancholic and atypical depression on the mood-reactivity discriminator and list two further features of each.
7. Define persistent depressive disorder by its duration rule and state what "double depression" means.
8. Give the diagnostic requirements for premenstrual dysphoric disorder, including the confirmation method and the symptom count.
9. Distinguish bipolar I from bipolar II by the one episode each absolutely requires and each absolutely excludes.
10. Define mixed features and rapid cycling, with the exact number in each definition.
11. For depression management, name the CANMAT first-line options and the continuation duration after remission, then state the Indian Psychiatric Society and NICE positions.
12. For bipolar management, give the phase-by-phase first-line choice for acute mania, bipolar depression and maintenance, and name the one agent never used alone in bipolar depression.
13. State the monoamine hypothesis and its single defining limitation.
14. State what the dexamethasone suppression test shows, the approximate non-suppression figure in depressed inpatients, and why it is not a diagnostic test.
15. Name the neurotrophic (BDNF) and the gene-environment (5-HTTLPR) hypotheses, each with the caveat that stops it being read as settled.

RULE **Test, do not re-read.** One cycle of answer-free retrieval practice beats three re-readings of the same page; schedule the prompts, do not just skim them.

32.3 The synthesis map to redraw from memory

The last consolidation move is spatial. Close the notes and draw the whole-chapter **synthesis map** from a blank centre labelled "Mood disorders", with four branches you **redraw from memory**: branch one, classification and the spectrum (the episode-then-polarity spine, the Kraepelinian dichotomy, ICD-11 versus DSM-5-TR, and the Akiskal ladder from one-half to IV); branch two, the depressive syndromes (major depressive disorder single and recurrent, the

specifiers, dysthymia and double depression, and the reproductive and seasonal forms); branch three, the bipolar syndromes (type I, type II, cyclothymia, mixed features and rapid cycling), each hung on its phase-based management; and branch four, the neurobiology, where you must write each hypothesis (monoamine, HPA and the dexamethasone suppression test, neurotrophic BDNF, gene-environment, glutamate and inflammation, the Mayberg circuit) paired with its own limitation, because a mechanism without its caveat is an exam error. If you can redraw all four branches with the management folded into the two clinical branches and every mechanism carrying its limit, the chapter is consolidated. This is Fig 11.12.

HOLD THIS

The whole chapter is one chain: name the EPISODE, split on POLARITY, then CLASSIFY, work the DEPRESSive then the BIPOLAR syndromes with their phase-based management, and finish on the neurobiology with every MECHANISM held to its LIMIT.

GOOD TO REMEMBER

- **The master chain:** "EPISODE, then POLARITY; CLASSIFY, DEPRESS, BIPOLAR; MANAGE by phase; MECHANISM with its LIMIT" is the whole chapter in one line; episode-then-polarity is the two-beat core.
- **Active recall:** retrieval practice with the answers covered strengthens memory far more than re-reading; the failed-retrieval effort is the learning.
- **The synthesis map:** four branches to redraw from memory, classification and spectrum, depressive syndromes, bipolar syndromes, neurobiology, with management folded into the clinical branches and each mechanism paired with its limitation (Fig 11.16).
- **The one discriminator:** a past hypomanic or manic episode is the single feature that reorders the entire grid from unipolar to bipolar; screen it in every depression.
- **The one management rule:** phase decides the drug, and an antidepressant is never given alone in a bipolar or mixed depression (CANMAT lead, with the Indian Psychiatric Society IPS guidelines and NICE concordant on stepped care).

Previously asked

The mood block is examined heavily and across the whole range: long diagnose-and-manage essays on major depression and on the bipolar disorders, a recurring interest in the bipolar spectrum and its soft forms, and a steady stream of short notes on the individual syndromes. The single most reliable long question is a full case of depression or of bipolar disorder taken from clinical features through differential diagnosis to management, so the criteria, the discriminators and the guideline-anchored plan in these notes are built to answer it. The genuine questions on record are grouped by band below. The individual drug pharmacology that several management questions also reward is developed in the Mood disorders: pharmacotherapy notes.

? HOW THIS TERRITORY IS ACTUALLY TESTED

Q **Classification and the bipolar spectrum.** The spectrum is a favourite: "bipolar spectrum disorder" has been asked as a 10-mark note, and the concept has twice carried a full 25-mark essay, once as "recent research in bipolar spectrum disorders with emphasis on soft bipolar disorders" and once as "the conceptual overview of bipolar spectrum disorder" paired with the management of treatment-refractory

bipolar II. Prepare the episode-based classification, the unipolar-versus-bipolar distinction and the detailed Akiskal soft-bipolar spectrum to be defined and drawn, and to open a bipolar essay. essay and short note, recurring

Q **Depressive syndromes.** "Define depressive disorder, describe the epidemiology of mood disorders, manage a case and add a note on suicide prevention" and "discuss the etiopathogenesis, clinical features and management of major depression" are the flagship 25-mark essays, so the depressive-episode criteria, the epidemiology and the subtypes must be exam-ready. "Dysthymia" has been asked as a 10-mark note, and the premenstrual and postpartum presentations recur as short notes. Prepare the criteria and specifiers, the subtypes keyed on their discriminators, and the guideline-anchored management. essay and short note, recurring

Q **Bipolar syndromes.** "Describe the clinical features and management of the various types of bipolar disorder" and "the clinical features, differential diagnosis and management of bipolar depression" are recurring 25-mark essays, and "the differential diagnosis and management of a patient with substance use and symptoms of mania" tests the manic differential. "Cyclothymia" and "rapid cycling bipolar disorder" are 10-mark notes. Prepare bipolar I and the manic episode, bipolar II and the hypomania threshold, mixed features, and the interleaved differential. essay and short note, recurring

Q **Management, guidelines-first.** Every long mood question ends in management, and "treatment of refractory mania", "the management of treatment-resistant depression" and "the management of resistant depression" have come as standalone questions. Prepare the CANMAT-led, phase-based plan for depression and for acute mania, bipolar depression and maintenance, and be able to state the Indian Psychiatric Society and NICE positions; the individual agents and the treatment-resistant algorithms are developed in the Mood disorders: pharmacotherapy notes. essay and short note, recurring

Q **Neurobiology and aetiology.** The etiopathogenesis of major depression is asked inside the long essay, and the monoamine and stress systems recur through the basic-science papers. Prepare the monoamine hypothesis with its limitations, the HPA axis and the dexamethasone suppression test, and the neurotrophic and circuit models, each with its evidence and its caveat, to supply the aetiology half of a depression or bipolar essay. essay component, recurring

Prepare this material to be defined, discriminated and managed, not just recited: the episode-based classification and the Akiskal spectrum, the criteria-anchored good-to-remember boxes, the interleaved differential and the guideline-anchored management topics in these notes are built to the way the block is examined. The individual drug pharmacology, the newer antidepressants and the treatment-resistant algorithms live in the Mood disorders: pharmacotherapy notes; the mood-with-psychotic-features boundary and catatonia live in the Other psychotic disorders, delusional syndromes and catatonia notes; the wider perinatal frame lives in the Perinatal/women's mental health and emergency psychiatry notes; and clinical suicide risk assessment lives in the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

Quick review

The whole subject in one table	
CLASSIFICATION	ICD-11 is episode-based: name the mood episode (depressive, manic, mixed, hypomanic), split on polarity (any lifetime manic or hypomanic episode makes it bipolar for life), then the lifetime pattern names the disorder. Qualify the current episode with severity and psychotic-symptom and specifier layers. ICD-11 primary, DSM-5-TR cross-mapped, ICD-10 (F-codes) still used in Indian settings.
ICD-11 CHANGES	Episode-based architecture; the mixed presentation is a qualifier on an episode (DSM-5-TR "with mixed features", at least three opposite-pole symptoms), never a free-standing disorder; ICD-11 retains a mixed episode, DSM-5 deleted it. Severity (mild/moderate/severe) and the without/with psychotic symptoms qualifier are now separate, so psychosis no longer forces a severe rating as it did in ICD-10.
UNIPOLAR VS BIPOLAR; AKISKAL	Unipolar has depressive episodes only; one lifetime manic or hypomanic episode makes it bipolar. Bipolar depression: earlier onset, more recurrent with shorter episodes, retarded and hypersomnic, antidepressant switch risk. Akiskal's soft spectrum (bipolar one-half through IV) shows bipolarity shading into apparent unipolar depression; screen every depression for a past hypomanic episode. Only bipolar I, II and cyclothymia are formal categories.
EPIDEMIOLOGY	Major depression: high lifetime prevalence, roughly two-to-one female preponderance, onset in the twenties to thirties. Bipolar I around one percent, roughly equal sex ratio, earlier onset (late teens to twenties). Both are leading causes of disability with elevated suicide and cardiometabolic mortality. Quote Indian NMHS figures, not Western ones.
MAJOR DEPRESSIVE DISORDER	At least two weeks, five or more of nine symptoms including a cardinal one (depressed mood or anhedonia), plus impairment. Nine symptoms across cardinal, cognitive (guilt, concentration, death/suicidality) and neurovegetative (sleep, appetite/weight, psychomotor, energy) clusters. Specifiers: melancholic, atypical, psychotic, catatonic, peripartum, seasonal, anxious distress, mixed features. Suicide is the key risk.
DYSTHYMIA AND SUBTYPES	Persistent depressive disorder: chronic low mood at least two years (one in youth); double depression is a major episode on top. Subtypes keyed by mood reactivity: melancholic loses it (early waking, anorexia, morning worsening), atypical keeps it (hypersomnia, hyperphagia, leaden paralysis, rejection sensitivity), psychotic adds mood-congruent delusions, catatonic adds catatonic signs.
SAD, PERIPARTUM, PMDD	Seasonal affective disorder: recurrent episodes with a regular seasonal onset and remission, often atypical, light therapy first-line. Peripartum depression: onset in pregnancy or within four weeks

The whole subject in one table	
	of delivery; screen with the Edinburgh scale; sertraline preferred in breastfeeding (CANMAT), ECT for severe or psychotic. PMDD: luteal-phase symptoms confirmed by prospective rating, SSRI first-line.
DEPRESSION MANAGEMENT	Guideline-first on locus (outpatient default; admit for suicide risk, psychosis, severe self-neglect or ECT), focus (acute aim remission; continuation 6 to 9 months at the acute dose; maintenance 2 years or more if recurrent) and modus. CANMAT first-line: a second-generation antidepressant or CBT/IPT/behavioural activation, combination superior; do not combine two antidepressants at initiation. rTMS/iTBS first-line, ECT for severe/psychotic/resistant. IPS names SSRIs first-line (Gautam 2017); psychotic depression needs antidepressant plus antipsychotic, or ECT.
BIPOLAR I AND THE MANIC EPISODE	One manic episode ever defines bipolar I. Manic episode: elevated, expansive or irritable mood plus increased activity or energy, at least one week (or any duration if hospitalised), with three or more DIGFAST symptoms (four if only irritable), marked impairment, sometimes psychosis. Over the lifetime more time is spent depressed than manic.
BIPOLAR II AND HYPOMANIA	A hypomanic episode plus a major depressive episode, no manic episode ever. Hypomania: at least four days (several days ICD-11), an observable change, but without marked impairment, without psychosis and without hospitalisation. Any of those three makes it a mania. Never diagnose bipolar II without a documented hypomanic episode.
CYCLOTHYMIA, MIXED, RAPID CYCLING	Cyclothymia: at least two years of sub-threshold highs and lows. Mixed features: at least three opposite-pole symptoms in one episode, a qualifier, high suicide risk, antidepressant caution (dysphoric mania, agitated depression). Rapid cycling: four or more episodes of any polarity in twelve months, commoner in women and bipolar II, driven by antidepressants and hypothyroidism; withdraw the antidepressant.
BIPOLAR COURSE AND POPULATIONS	Recurrent and lifelong with inter-episode recovery but residual sub-syndromal and cognitive impairment; mixed and rapid-cycling course predict worse outcome; high suicide and cardiometabolic mortality. Special populations: require clear episodicity before diagnosing paediatric bipolar (versus DMDD), exclude an organic or vascular cause in new late-life mania, and manage the high postpartum relapse risk (avoid valproate in women of childbearing potential).
BIPOLAR MANAGEMENT	By phase (CANMAT/ISBD 2018). Acute mania: stop any antidepressant; first-line lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone or cariprazine, or an atypical plus lithium/divalproex if severe; lithium acute level 0.8 to 1.2. Bipolar depression: quetiapine, lurasidone, lithium or lamotrigine, never an antidepressant alone. Maintenance: lithium leads (level 0.6 to 1.0),

The whole subject in one table	
	plus psychoeducation, LAI if non-adherent. IPS (Shah 2017) and NICE broadly agree.
THE MOOD DIFFERENTIAL	Polarity (a past hypomania or mania) is the master discriminator: screen every depression. MDD versus persistent depressive disorder versus adjustment by duration and threshold and stressor. Melancholic versus atypical by mood reactivity. Bipolar I versus II versus cyclothymia by mania versus hypomania versus sub-threshold. Mixed features versus an agitated depression by the count of opposite-pole symptoms.
NEUROBIOLOGY: MONOAMINE AND HPA	Monoamine hypothesis: a functional deficiency of serotonin, noradrenaline and dopamine; the therapeutic lag and the failure of depletion to depress healthy controls are the key limitations, so it is the trigger for slower plasticity changes. HPA axis overactive with blunted feedback; the dexamethasone suppression test shows non-suppression (fair sensitivity in melancholic/psychotic depression, poor specificity), so it is not a clinical diagnostic test.
NEUROBIOLOGY: PLASTICITY, GENES, CIRCUITS	Neurotrophic hypothesis: stress lowers BDNF and hippocampal neurogenesis, antidepressants and ECT restore them over weeks (matching the lag), but the evidence is associative. Glutamate/NMDA (rapid ketamine effect) and inflammation (raised cytokines) explain a subgroup. Bipolar is highly heritable (roughly 60 to 85 percent), depression moderately (35 to 40 percent), polygenic; the 5-HTTLPR by stress interaction is the classic but contested example. Limbic-cortical model: dorsal-cortical hypoactive, ventral-limbic hyperactive, subgenual cingulate the hinge, not diagnostic. Psychological: Beck's cognitive triad, learned helplessness and hopelessness, Lewinsohn's lost reinforcement.

References

The content is grounded in the standard clinical, psychopharmacology and guideline sources (the source hierarchy below), which anchor the settled facts on the criteria, the syndromes and the neurobiology; the nosology follows ICD-11 (CDDR) primary with DSM-5-TR cross-mapped, and the management is guideline-first (CANMAT leading, with the Indian Psychiatric Society and the British Association for Psychopharmacology). Every diagnostic criterion, duration threshold, epidemiological number, mechanism-with-its-limitation and guideline recommendation has been checked against these sources. Each journal PMID here was verified against PubMed this build, matched on title, first author and year; any identifier that did not resolve to the cited paper was corrected or dropped rather than guessed. The classic conceptual sources that seed the models (Kraepelin, Leonhard, Beck 1967, Freud's Mourning and Melancholia 1917, Abramson, Seligman and Teasdale 1978, Lewinsohn, and Mayberg's limbic-cortical model) are cited in the prose by author and year.

SOURCE HIERARCHY (CLINICAL, PSYCHOPHARMACOLOGY AND NOSOLOGY TEXTS)

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PART V

V

Mood Disorders: Pharmacotherapy, Antidepressants, Mood Stabilisers, Lithium

Treating mood disorder: the antidepressants, the mood stabilisers, and lithium, with the rules for using each.

PAPER II

Mood disorders: pharmacotherapy

Four sections · one complete notes document

This material closes the mood block, gathering into one document the drug treatment of the depressive and bipolar disorders. The first band is **antidepressant pharmacotherapy**: the classification of the antidepressants and the action of each class at the synapse, the SSRIs, SNRIs, tricyclics, monoamine oxidase inhibitors, mirtazapine, bupropion and the newer multimodal agents with their pharmacology, adverse effects and interactions, serotonin syndrome and the discontinuation syndrome, the rapid-acting glutamatergic agents ketamine and esketamine, and how to choose an antidepressant and manage the phases of an acute depressive episode. The second band is **mood stabilisers and lithium**: lithium in depth, its mechanism, initiation, dosing, monitoring, toxicity and every organ-system effect and interaction and its use in pregnancy, then valproate, carbamazepine, lamotrigine and the antipsychotics used as mood stabilisers, and the guideline-anchored choice of stabiliser across acute mania and maintenance. The third band is **treatment resistance, augmentation and the special populations**: treatment-resistant depression and its staging, the augmentation ladder, depression in the elderly, the suicide-risk and pharmacological angle, ECT and neuromodulation and the psychotherapies in the algorithm, and the dedicated management of bipolar depression, bipolar mixed episodes and bipolar maintenance. The examinable skill is the safe, guideline-anchored choice and monitoring of every mood drug: which agent for which patient and phase, at what dose and serum level, with which adverse effect and interaction watched, and when to escalate.

HOW TO USE THESE NOTES

Read the four bands as one continuous account of how mood disorder is treated with medicines. The **antidepressant** band teaches each class at the synapse and then every agent with its dose range, its signature adverse effect and its key interaction, ending with how to choose and how to run the phases of treatment. The **mood stabiliser** band gives lithium the depth it carries in the examination, its therapeutic window, its monitoring schedule, its toxicity and its organ effects, then valproate, carbamazepine, lamotrigine and the atypicals, and the guideline choice of stabiliser by phase. The **treatment resistance** band teaches the augmentation ladder and the special populations and closes with three dedicated bipolar-management topics: bipolar depression, bipolar mixed episodes and maintenance. Every management recommendation is guideline-anchored, led by the CANMAT guidelines with the Indian Psychiatric Society, BAP and NICE positions stated, on the where-to-treat, target-by-phase, modes-of-treatment spine; every named agent ends with a **Good to remember** box giving the mechanism, the signature adverse effect or interaction, and the one dose or first-line indication. Figures declare one axis and code it in colour: **petrol** marks structure and the neutral case, **coral** marks the trap or the danger, and **marigold** highlights the number to hold. Several boundaries are worth stating up front: the mood-disorder classification, the depressive and bipolar clinical syndromes and the guideline-anchored management plan are taught in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes and are cross-referenced here rather than repeated; the monoamine pathway anatomy, the receptor systems and CYP metabolism live in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the technique of electroconvulsive therapy and of rTMS, VNS and DBS lives in the ECT and neurostimulation notes, and only their place in the algorithm is taught here; the full clinical suicide risk assessment lives in the Somatic-symptom, sexual, impulse-control disorders and suicide notes; the wider emergency and perinatal frames live in the Perinatal/women's mental health and emergency psychiatry notes; and the psychotherapy technique lives in the Psychotherapies, clinical assessment, MSE and nosology notes. This is doctor-facing revision, so the full technical vocabulary is used, brand names lead with the Indian brand, and every dose, serum level, monitoring interval, teratogenicity fact and first-line recommendation is verified against a source or omitted and flagged.

Antidepressant pharmacotherapy

1 . Classifying the antidepressants and the treatment algorithm

This is the opening map of the whole pharmacotherapy block. Two schemas orient everything that follows: a **class map** of the antidepressants and mood stabilisers ordered by what each drug does at the synapse, and a phase-based **treatment algorithm** that tells you which agent, in which phase, on which line. Get both in your head first and every later topic (the SSRIs, lithium and its monitoring, valproate, the mood-stabiliser and antidepressant-selection topics, the emergencies, treatment resistance) becomes a slot to fill, not a list to memorise cold.

The board rewards a resident who reasons in two moves: **first** name the drug by its primary synaptic action, **then** place the patient in a phase and polarity and treat accordingly. Lead with

the CANMAT guidelines (CANMAT 2016 for depression, CANMAT 2018 for bipolar disorder), then state the Indian Psychiatric Society (IPS) position and where the BAP and NICE agree. The mood classification, the depressive and bipolar syndromes, the criteria and the guideline-anchored management PLAN are owned by, and cross-referred to, the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; this block owns the pharmacology, the doses, the monitoring and the algorithm.

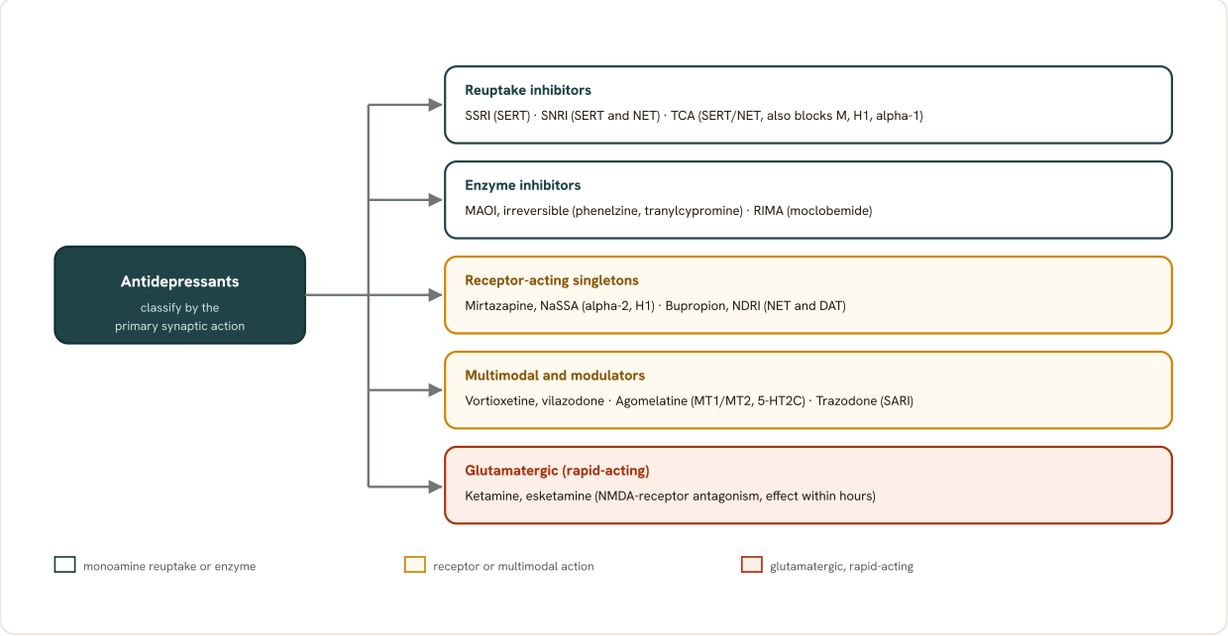

Fig 12.1 The antidepressants classified by their primary synaptic action, which predicts both tolerability and the dangerous interactions. The reuptake inhibitors (SSRI, SNRI, TCA) and the enzyme inhibitors (MAOI, RIMA) act on the monoamine supply; the receptor-acting singletons (mirtazapine, bupropion) and the multimodal and modulator agents (vortioxetine, agomelatine, trazodone) act at specific receptors; and the glutamatergic agents (ketamine, esketamine) act at the NMDA receptor with an effect within hours.

1.1 The organising principle: classify by mechanism, then treat by phase

Two schemas, in order. The **classification of antidepressants** is by **primary synaptic action**: which transporter or receptor the drug primarily hits, and therefore which monoamine it raises and which adverse effects and interactions follow. That single fact predicts most of the tolerability profile and most of the dangerous interactions. The **treatment algorithm** is the second schema: once the drug is classified, the patient is treated by **phase** (acute to remission, then continuation, then maintenance) and by **polarity** (unipolar depression versus bipolar disorder, which are treated with different classes). The monoamine pathway anatomy, the receptor systems and the CYP metabolism that sit underneath the mechanisms are cross-referred to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

RULE **Classify an antidepressant by its synaptic action, then treat by phase.** Mechanism predicts the adverse-effect and interaction set; phase and polarity dictate the agent.

TRAP **Treating every depression the same regardless of phase or polarity.** A bipolar depression treated as a unipolar depression, or a patient stopped at response instead of remission, is the classic examinable error.

1.2 The class map: antidepressants by primary action

The **class map** groups every antidepressant by what it primarily does at the synapse (Stahl 2021; Maudsley 2021). The reuptake-inhibitor families come first, then the receptor-acting families, then the enzyme inhibitors, then the multimodal and glutamatergic agents. The SSRIs (selective serotonin reuptake inhibitors: escitalopram, sertraline, fluoxetine, paroxetine, citalopram, fluvoxamine) block the serotonin transporter (SERT). The SNRIs (serotonin-noradrenaline reuptake inhibitors: venlafaxine, desvenlafaxine, duloxetine) block both SERT and the noradrenaline transporter (NET). The tricyclic antidepressants (amitriptyline, imipramine, clomipramine, nortriptyline) block SERT and NET but additionally antagonise muscarinic, histamine H1 and alpha-1 receptors, which is why they carry the anticholinergic, sedative, orthostatic and cardiotoxic burden and are dangerous in overdose. The monoamine oxidase inhibitors (MAOIs: phenelzine, tranylcypromine as irreversible; moclobemide as the reversible RIMA) inhibit the enzyme that degrades monoamines, raising serotonin, noradrenaline and dopamine, and carry the tyramine (cheese) and serotonergic interaction hazards. The receptor-acting singletons are the NaSSA mirtazapine (a noradrenergic and specific serotonergic antidepressant: alpha-2 autoreceptor and heteroreceptor antagonist plus H1 blockade) and the NDRI bupropion (a noradrenaline-dopamine reuptake inhibitor with no direct serotonergic action). The multimodal and serotonin-modulator agents are vortioxetine (SERT inhibition plus 5-HT1A agonism and 5-HT3/5-HT7 antagonism), agomelatine (melatonin MT1/MT2 receptor agonist plus 5-HT2C antagonist) and trazodone (a serotonin antagonist and reuptake inhibitor, SARI). The glutamatergic agents are ketamine and its S-enantiomer esketamine, NMDA-receptor antagonists that act rapidly and outside the monoamine framework.

CLASS	PROTOTYPE AGENTS	PRIMARY SYNAPTIC ACTION	SIGNATURE TO HOLD
SSRI	escitalopram, sertraline, fluoxetine, paroxetine, citalopram, fluvoxamine	**Selective SERT (serotonin transporter) blockade**	First-line for tolerability and overdose safety
SNRI	venlafaxine, desvenlafaxine, duloxetine	**SERT plus NET (noradrenaline transporter) blockade**	Dose-dependent blood-pressure rise (venlafaxine)
Tricyclic (TCA)	amitriptyline, imipramine, clomipramine, nortriptyline	**SERT/NET blockade plus muscarinic, H1, alpha-1 antagonism**	Anticholinergic load, cardiotoxic, lethal in overdose
MAOI (irreversible)	phenelzine, tranylcypromine	**Irreversible inhibition of monoamine oxidase**	Tyramine (cheese) reaction, serotonergic interactions

CLASS	PROTOTYPE AGENTS	PRIMARY SYNAPTIC ACTION	SIGNATURE TO HOLD
RIMA	moclobemide	**Reversible inhibition of MAO-A**	Far lower tyramine risk than irreversible MAOIs
NaSSA	mirtazapine	**Alpha-2 autoreceptor/heteroreceptor antagonism plus H1 blockade**	Sedation, appetite and weight gain; useful with insomnia
NDRI	bupropion	**Noradrenaline and dopamine reuptake inhibition**	Activating, no sexual dysfunction; lowers seizure threshold
Multimodal (serotonin modulator)	vortioxetine	**SERT inhibition plus 5-HT1A agonism, 5-HT3/5-HT7 antagonism**	Nausea commonest; pro-cognitive claims
Melatonergic	agomelatine	**MT1/MT2 agonist plus 5-HT2C antagonist**	Sleep-promoting; monitor liver function
SARI	trazodone	**5-HT2 antagonism plus weak SERT inhibition**	Sedating; priapism risk; used for insomnia
Glutamatergic	ketamine, esketamine	**NMDA-receptor antagonism**	Rapid action; dissociation and blood-pressure rise

Fig 12.1 in prose: the antidepressant class map keyed to primary synaptic action. The highlighted mechanism cell is the fact that predicts each class's tolerability and its dangerous interactions.

GOOD TO REMEMBER

- **SSRIs:** block SERT selectively; first-line for MDD; hold escitalopram **10 to 20 mg/day** as the type case (CANMAT 2016).
- **SNRIs:** block SERT and NET; venlafaxine raises blood pressure dose-dependently; hold venlafaxine **75 to 225 mg/day** (CANMAT 2016).
- **TCAs:** block SERT/NET but add muscarinic, H1 and alpha-1 antagonism, so anticholinergic, sedating and cardiotoxic; lethal in overdose; second-line (CANMAT 2016).
- **MAOIs:** inhibit monoamine oxidase; signature hazard is the tyramine (cheese) reaction and serotonergic interactions; reserved third-line (CANMAT 2016).
- **Mirtazapine (NaSSA):** alpha-2 antagonist plus H1 blockade; signature is sedation and weight gain; first-line, useful with insomnia; hold **15 to 45 mg/day** (CANMAT 2016).
- **Bupropion (NDRI):** noradrenaline-dopamine reuptake inhibitor; activating, spares sexual function, lowers seizure threshold; first-line; hold **150 to 300 mg/day** (CANMAT 2016).
- **Vortioxetine (multimodal):** SERT inhibition plus receptor modulation; nausea commonest; first-line; hold **10 to 20 mg/day** (CANMAT 2016).
- **Agomelatine (melatonergic):** MT1/MT2 agonist plus 5-HT2C antagonist; sleep-promoting; monitor LFTs; first-line; hold **25 to 50 mg/day** (CANMAT 2016).
- **Trazodone (SARI):** 5-HT2 antagonist with weak reuptake inhibition; sedating, priapism risk; second-line, common as a hypnotic (CANMAT 2016).
- **Ketamine/esketamine (glutamatergic):** NMDA antagonists; rapid antidepressant and anti-suicidal effect; monitor blood pressure and dissociation; adjunct in treatment resistance (CANMAT 2016).

PEARL

The whole tolerability story of the tricyclics is off-target receptor blockade, not the reuptake inhibition. Muscarinic antagonism gives the dry mouth, constipation and urinary hesitancy; H1 gives the sedation and weight gain; alpha-1 gives the postural drop; and sodium-channel blockade gives the overdose cardiotoxicity. The SSRIs are "clean" precisely because they do none of this.

1.3 The mood stabilisers alongside the class map

The class map does not stop at the antidepressants. The bipolar arm of this block is built on the **mood stabilisers**: lithium (the archetype, with anti-manic, prophylactic and specific anti-suicide effect), the anticonvulsants valproate (sodium valproate and divalproex), carbamazepine (and its keto-analogue oxcarbazepine) and lamotrigine (the depression-predominant stabiliser), and the atypical antipsychotics used as mood stabilisers (quetiapine, olanzapine, aripiprazole, risperidone, asenapine, cariprazine, lurasidone). Each is a slot expanded later: lithium initiation, monitoring and toxicity, the valproate topic and its teratogenicity, the lamotrigine titration and the stabiliser-selection topic all belong downstream. The deep antipsychotic pharmacology, including the receptor profiles and the extrapyramidal and metabolic adverse effects, is cross-referred to the Schizophrenia: management, antipsychotics and adverse effects notes.

GOOD TO REMEMBER

- **Lithium:** the archetypal mood stabiliser; first-line for acute mania and maintenance with specific anti-suicide evidence; hold maintenance level **0.6 to 1.0 mmol/L** (CANMAT 2018).
- **Valproate/divalproex:** broad-spectrum anticonvulsant stabiliser; first-line for acute mania; signature hazard is teratogenicity (neural tube defects), so avoid in women of childbearing potential; hold serum **50 to 100 microg/mL** (CANMAT 2018).
- **Carbamazepine:** anticonvulsant stabiliser; signature is enzyme induction, hyponatraemia and the HLA-B*1502 Stevens-Johnson risk in at-risk Asian ancestry; second-line (CANMAT 2018).
- **Lamotrigine:** the depression-predominant stabiliser; first-line for bipolar depression and maintenance; signature hazard is the rash, so titrate slowly; target a minimum of **200 mg/day** starting at 25 mg (CANMAT 2018).
- **Atypical antipsychotics as stabilisers:** quetiapine, olanzapine, aripiprazole, risperidone, asenapine, cariprazine, lurasidone; first-line across mania, bipolar depression and maintenance; signature is metabolic burden (CANMAT 2018).

1.4 The treatment algorithm: the LOCUS-FOCUS-MODUS spine

Every management plan in this block runs on one spine. **LOCUS** is *where*: outpatient (or the day care centre) is the default, and admission is reserved for high suicide risk, psychotic features, severe self-neglect, or the need for inpatient-level treatment such as ECT. **FOCUS** is *the target by phase*: what you are trying to achieve right now. **MODUS** is *the modes of treatment*: which pharmacological and psychological modes each guideline recommends first. This is not a mnemonic for its own sake; it is the order in which a board answer is constructed. Decide the locus, name the phase, then list the guideline-first modes for that phase. The full clinical suicide risk assessment and safety planning that set the admission threshold are cross-referred to the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

RULE **LOCUS then FOCUS then MODUS orders every plan.** Where to treat, which phase you are targeting, then which mode is first-line for that phase.

1.5 FOCUS for depression: acute, continuation, maintenance

The unipolar depression skeleton is three phases (CANMAT 2016; BAP 2015; Gautam et al. 2017). The **acute** phase runs from the outset to **remission** (not merely response): start one first-line second-generation antidepressant, review every **1 to 2 weeks**, and judge the trajectory by **2 to 4 weeks**, optimising the dose or switching if there is no improvement. The **continuation** phase then holds the same agent at the **acute treatment dose** for **6 to 9 months** after remission, to lock in the remission and prevent relapse. The **maintenance** phase extends treatment to **2 years or longer** for recurrent or high-risk illness to prevent recurrence, with CBT or MBCT as the psychological relapse-prevention modes. The individual phase-by-phase management plan, the augmentation and the psychotherapy detail are owned by the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; here it is the orienting skeleton only.

1 to 2 wk	2 to 4 wk	6 to 9 mo	2 years+
ACUTE REVIEW INTERVAL	JUDGE ACUTE RESPONSE TRAJECTORY	CONTINUATION AFTER REMISSION	MAINTENANCE IF RECURRENT

1.6 FOCUS for bipolar disorder: mania, depression, maintenance

The bipolar skeleton is a different triad because the classes are different (CANMAT 2018; Grover and Avasthi 2017). **Acute mania** is treated with lithium, quetiapine, divalproex, aripiprazole, asenapine, paliperidone, risperidone or cariprazine as first-line monotherapy, or an atypical antipsychotic plus lithium or divalproex in severe presentations; any antidepressant is discontinued. **Bipolar depression** is treated with quetiapine, lurasidone (with or without lithium/divalproex), lithium, lamotrigine or the olanzapine-fluoxetine combination as first-line, and is *not* treated with an antidepressant alone. **Bipolar maintenance** continues the agent that worked acutely, with lithium, quetiapine, divalproex, lamotrigine, asenapine or aripiprazole as first-line monotherapy and a maintenance lithium level of **0.6 to 1.0 mEq/L**. Each limb is expanded later in the block; here it is the skeleton that sits beside the depression skeleton.

TRAP **Giving an antidepressant alone in a bipolar depression.** It risks a manic switch and rapid cycling; the first-line agents are quetiapine, lurasidone, lithium, lamotrigine or the olanzapine-fluoxetine combination (CANMAT 2018).

1.7 The Indian Psychiatric Society, BAP and NICE positions

The Indian Psychiatric Society Clinical Practice Guidelines are the Indian reference and the guideline most likely named in Indian postgraduate examinations. For depression, the **IPS guidelines** (Gautam et al. 2017) name the SSRIs as first-line on tolerability and overdose safety, with TCAs, mirtazapine, bupropion and venlafaxine as further options, and continue treatment after remission with a maintenance phase for recurrent illness. For bipolar disorder, the IPS guidelines (Grover and Avasthi 2017) direct that antidepressants are not used as monotherapy in bipolar depression, prefer bupropion and avoid paroxetine if an antidepressant is added, and name lithium and valproate as the best-evidenced maintenance agents. The BAP and NICE converge on the same spine: SSRIs and other newer agents are first-line for depression because they are better tolerated and safer in overdose (BAP 2015), and NICE names lithium as the first-line long-term treatment for bipolar disorder (NICE 2014). Where the IPS position on a specific point could not be confirmed against the parsed library it is flagged rather than invented.

INDIA

Every drug in this block is available in India; this chapter names no brand, and the Indian brand for each agent, Indian brand first, is given in the individual drug topics that follow (for example escitalopram, sertraline, lithium carbonate, sodium valproate, lamotrigine, quetiapine). The Indian Psychiatric Society Clinical Practice Guidelines are the guideline to cite first in Indian postgraduate examinations: Gautam et al. for depression and Grover and Avasthi for bipolar disorder. Lithium remains a mainstream first-line mood stabiliser in Indian practice, and ECT is widely available and heavily used for severe, psychotic, suicidal or treatment-resistant mood illness across Indian teaching hospitals.

1.8 The master mnemonic: chaining the chapter

One master **mnemonic** chains the four movements of this block so nothing is dropped: the antidepressant classes, then lithium and the mood stabilisers, then the emergencies, then

treatment resistance. Hold it as **"A SNoM LiVeS, then CALM the STORM, then climb the LADDER"**, unpacked below. It is a scaffold, not the content: each capitalised beat is a downstream topic.

MNEMONIC

A-SNoM-Li-VeS then CALM the STORM then the LADDER

The four movements of the pharmacotherapy block. **Antidepressant classes** (A): SSRI, SNRI, NaSSA/NDRI, MAOI, Multimodal (A SNoM). **Mood stabilisers**: Lithium, Valproate, lamotrigine and the Stabiliser antipsychotics (LiVeS). **Emergencies**: serotonin syndrome and lithium toxicity (CALM the STORM). **Treatment resistance**: the switch-augment-combine-neuromodulate ladder (the LADDER). Classify first (A SNoM LiVeS), then know what goes wrong (CALM the STORM), then know the next step when first-line fails (the LADDER).

MOVEMENT	WHAT IT HOLDS	WHERE IT IS EXPANDED
Antidepressant classes	SSRI, SNRI, TCA, MAOI, NaSSA, NDRI, multimodal, SARI, glutamatergic	**The SSRI, SNRI, TCA/MAOI and newer-agent topics in this block**
Lithium and mood stabilisers	Lithium, valproate, carbamazepine, lamotrigine, atypicals	**Lithium initiation/monitoring/toxicity, valproate, lamotrigine, stabiliser-selection topics**
Emergencies	Serotonin syndrome, lithium toxicity	**The emergencies topics in this block; wider acute management cross-referred to the Perinatal/women's mental health and emergency psychiatry notes**
Treatment resistance	Switch, augment, combine, neuromodulate	**The treatment-resistant-depression ladder topic**

The master mnemonic mapped to the four downstream movements of the block; each highlighted cell names where that movement is taught in full.

GOOD TO REMEMBER

- **Classify by mechanism:** name the antidepressant by its primary synaptic action (SERT, NET, receptor, enzyme, NMDA) before you prescribe.
- **The phases are acute, continuation, maintenance:** aim remission, then hold at the acute dose, then extend for recurrence.
- **LOCUS-FOCUS-MODUS orders every plan:** decide where, name the phase, list the guideline-first modes for that phase.
- **Polarity matters:** unipolar depression and bipolar disorder use different classes; do not give an antidepressant alone in bipolar depression.
- **Guideline order:** lead with CANMAT, then state the Indian Psychiatric Society, BAP and NICE positions.

WORKED EXAMPLE

A 30-year-old man presents with a moderate depressive episode, no psychosis, no active suicidal plan and no history of mania. Working the two schemas: the class map says a first-line second-generation antidepressant (an SSRI such as escitalopram), classified as a SERT blocker; the algorithm says LOCUS outpatient, FOCUS the acute phase aiming at remission, MODUS one first-line agent with measurement-based review at 2 weeks and a trajectory judgement by 2 to 4 weeks. On reaching remission by month 3, the continuation phase holds the same agent at the same dose for 6 to 9 months. Had the same man reported a past manic episode, polarity would flip the plan entirely: the class map moves to the mood stabilisers and the bipolar-depression first-line agents, and an antidepressant alone would be a trap.

HOLD THIS

Classify the antidepressant by its primary synaptic action, then treat by phase (acute to remission, continuation 6 to 9 months at the acute dose, maintenance 2 years or longer if recurrent) and by polarity (unipolar and bipolar use different classes), on the LOCUS-FOCUS-MODUS spine, leading with CANMAT.

2 . Selective serotonin reuptake inhibitors

The **selective serotonin reuptake inhibitor** class is the first-line antidepressant group and the single most-prescribed drug family in psychiatry, so the board expects the mechanism, the individual agents with their doses, and the whole adverse-effect set at your fingertips. The organising truth the examiner rewards: the members of the **ssri** class are broadly equal in antidepressant efficacy and differ mainly in **half-life**, **cytochrome interactions** and **adverse-effect emphasis**, not in how well they lift mood (Maudsley 2021; Stahl 2021). This topic teaches the pharmacology; the guideline-anchored choice of which antidepressant, and the discontinuation and serotonin-syndrome detail, are cross-referred where relevant.

Learn each agent by its one distinguishing feature (the long half-life of **fluoxetine**, the QTc ceiling of **escitalopram**, the discontinuation burden of **paroxetine**), then hang the shared class adverse effects on top. The dosing anchors are verified against Stahl's Prescriber's Guide and the Maudsley (Stahl 2021; Maudsley 2021); the monoamine-pathway anatomy and cytochrome metabolism underneath all of this belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

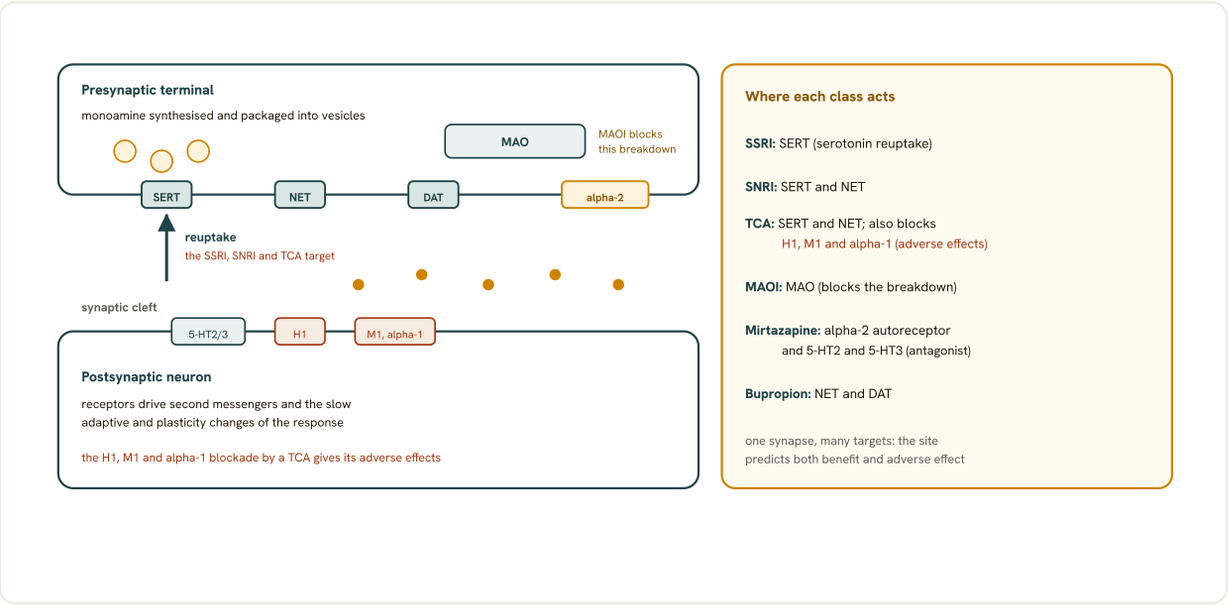

Fig 12.2 The monoamine synapse and where each antidepressant class acts. The reuptake transporters (SERT, NET, DAT) and the enzyme MAO clear the monoamine, and the post-synaptic and autoreceptors shape the signal. The SSRIs block SERT; the SNRIs block SERT and NET; the TCAs block both and, off-target, H1, M1 and alpha-1 (their adverse effects); the MAOIs block MAO; mirtazapine blocks the alpha-2 autoreceptor and 5-HT2/5-HT3; and bupropion blocks NET and DAT. The site of action predicts both the benefit and the adverse-effect profile.

2.1 Mechanism: SERT blockade, then receptor adaptation

The acute action. Every SSRI blocks the presynaptic serotonin transporter (**SERT**, the SLC6A4 protein), the pump that clears serotonin from the synapse back into the neuron. Blocking SERT raises **synaptic serotonin**, which is the immediate pharmacological effect and happens within hours of the first dose (Stahl 2021). Yet the antidepressant benefit does not appear for weeks, and that gap is the key teaching point.

The therapeutic lag. The initial rise in serotonin first stimulates somatodendritic 5-HT1A autoreceptors at the cell body, which shut down neuronal firing and blunt the expected increase in serotonin in the projection fields. Only with continued dosing do these autoreceptors **desensitise and downregulate**, after which firing resumes, serotonin release in the forebrain rises, and downstream postsynaptic receptor adaptation delivers the mood effect. This slow receptor adaptation, not the transporter block itself, is why the clinical response takes about 2 to 4 weeks to build (Stahl 2021; Companion 2010).

RULE **SERT block is immediate; the antidepressant effect is not.** The therapeutic lag reflects 5-HT1A autoreceptor desensitisation, so give an adequate trial before judging efficacy.

2.2 The class as a whole: what "selective" and "equal efficacy" mean

Selective. The SSRIs are highly potent and selective inhibitors of SERT with little direct action on noradrenaline or dopamine transporters and, unlike the tricyclics, little affinity for muscarinic, histaminergic or alpha-adrenergic receptors, which is why they are far safer in overdose and better tolerated (Companion 2010). Sertraline is the partial exception, with a mild dopamine reuptake effect at the top of its range.

Equal efficacy, different profiles. Head-to-head, no SSRI is convincingly more effective than another for major depression; the choice is driven by half-life, cytochrome interactions, and the adverse-effect emphasis of each drug (Maudsley 2021). That single sentence answers most "which SSRI and why" viva questions.

2.3 The individual agents: doses and distinguishing features

Six agents matter. The table gives the verified adult dose range with the unit in the header; the prose gives the one feature that makes each one examinable. All start at or near the minimum effective dose and are given once daily (fluvoxamine often divided).

SSRI (INDIAN BRAND)	DOSE (MG/DAY)	HALF-LIFE	DISTINGUISHING FEATURE	KEY CYP EFFECT
Fluoxetine (Fludac)	**20 to 80**	Parent 2 to 3 days; norfluoxetine ~2 weeks	Longest half-life, activating, self-tapering on stopping	Inhibits CYP2D6 and CYP3A4
Sertraline (Serta, Daxid)	50 to 200	~26 hours	**Broadest first choice; mild dopamine effect; prominent GI upset/diarrhoea**	Weak CYP2D6 inhibitor
Escitalopram (Nexito, S-Citadep)	10 to 20	27 to 32 hours	**Cleanest, fewest interactions; dose-dependent QTc**	Minimal CYP effect
Citalopram	20 to 40	~33 hours	Racemate of escitalopram; QTc cap at 40 (20 in the elderly / 2C19 inhibition)	Weak CYP2D6 inhibitor
Paroxetine (Pexep)	20 to 50	~21 hours (short)	**Anticholinergic, weight gain, worst discontinuation, avoid in pregnancy**	Potent CYP2D6 inhibitor
Fluvoxamine	100 to 300	~13 to 22 hours	OCD workhorse; sedating; no active metabolite	Potent CYP1A2 inhibitor

The six SSRIs with verified adult dose ranges (Stahl 2021), half-lives and the one feature each is tested on; the highlighted cell is the board discriminator for that drug. Doses are for adult depression.

Fluoxetine (Fludac). The prototype. Its very long half-life (parent 2 to 3 days, active metabolite norfluoxetine about 2 weeks) means it effectively self-tapers and rarely causes a discontinuation syndrome, but also means a 5-week washout before an MAOI. It is the most **activating** SSRI and inhibits both CYP2D6 and CYP3A4 (Stahl 2021).

Sertraline (Serta or Daxid). The pragmatic broadest first choice with the widest evidence base and a mild dopamine-reuptake effect at higher doses; its signature adverse effect is

gastrointestinal, especially diarrhoea. It is only a weak CYP inhibitor, which helps in the medically complex or polypharmacy patient (Maudsley 2021).

Escitalopram (Nexito or S-Citadep) and citalopram. Escitalopram is the S-enantiomer of citalopram and the **cleanest** SSRI, with the fewest cytochrome interactions; 10 mg of escitalopram is roughly comparable to 20 mg of citalopram (Stahl 2021). Both carry a **dose-dependent QTc** prolongation: citalopram must not exceed **40 mg/day** (and 20 mg in the elderly or with a CYP2C19 inhibitor), and escitalopram is capped at **20 mg/day**.

Paroxetine (Pexep). The most troublesome of the group: a short half-life with no active metabolite, so it has the **worst discontinuation** syndrome; the most **anticholinergic** SSRI (dry mouth, constipation); the most weight gain; a potent CYP2D6 inhibitor; and the one SSRI specifically to **avoid in pregnancy** (see 2.7).

Fluvoxamine. Positioned mainly for OCD, sedating rather than activating, with no active metabolite. Its defining pharmacological hazard is potent **CYP1A2 inhibition**, which raises levels of theophylline, clozapine, caffeine and duloxetine (Stahl 2021).

GOOD TO REMEMBER

- **Fluoxetine (Fludac):** longest half-life (norfluoxetine ~2 weeks), activating, CYP2D6/3A4 inhibitor; dose **20 to 80 mg/day**.
- **Sertraline (Serta or Daxid):** broadest first choice, mild dopamine effect, GI/diarrhoea; dose **50 to 200 mg/day**.
- **Escitalopram (Nexito or S-Citadep):** cleanest, fewest interactions, dose-dependent QTc; dose **10 to 20 mg/day** (max 20).
- **Citalopram:** escitalopram's racemate; QTc cap at **40 mg/day** (20 in elderly); dose **20 to 40 mg/day**.
- **Paroxetine (Pexep):** short half-life, anticholinergic, weight gain, worst discontinuation, avoid in pregnancy; dose **20 to 50 mg/day**.
- **Fluvoxamine:** OCD agent, strong CYP1A2 inhibitor, sedating; dose **100 to 300 mg/day**.

2.4 The class adverse-effect set: GI, sexual, activation

Gastrointestinal. Nausea, loose stools and dyspepsia are the commonest early adverse effects, driven by gut 5-HT3 stimulation; they are usually dose-related and settle over the first 1 to 2 weeks. Sertraline is the most likely to cause diarrhoea (Maudsley 2021).

Sexual dysfunction. sexual dysfunction (use "sexual dysfunction") is very common with all SSRIs (reduced desire, delayed orgasm or anorgasmia, and erectile or ejaculatory difficulty) and is the leading cause of covert non-adherence, so ask about it directly rather than waiting for the patient to volunteer it (Maudsley 2021). Management options include dose reduction, switching to a lower-risk agent (bupropion, mirtazapine or agomelatine), a drug holiday, or adding sildenafil/tadalafil. Do not dismiss it: an unasked, untreated sexual side effect is a classic reason a patient silently stops an effective antidepressant.

Early activation and anxiety. A jittery, agitated worsening of anxiety and insomnia can occur in the first days, most with the activating fluoxetine; in anxiety disorders start at half the usual dose

and titrate up. Emergent agitation, especially in a young person, also raises the question of an unmasked bipolar state (Maudsley 2021).

TRAP **Dismissing or never asking about sexual dysfunction.** It is very common, patient-limiting, and the commonest silent cause of SSRI non-adherence; ask directly and act.

2.5 Hyponatraemia, bleeding and QTc: the systemic risks

Hyponatraemia and SIADH. All SSRIs can cause hyponatraemia through the syndrome of inappropriate antidiuretic hormone secretion, and the risk is greatest in the **elderly**, in women, in low body weight, and with co-prescribed diuretics; it is a first-month risk (Maudsley 2021; Stahl 2021). In an older patient who becomes confused, drowsy, unsteady or has a seizure after starting or increasing an SSRI, check the sodium before anything else.

Bleeding. By depleting platelet serotonin, SSRIs impair platelet aggregation and raise the risk of gastrointestinal and other bleeding, and this risk is amplified when combined with **NSAIDs** or antiplatelet or anticoagulant drugs; co-prescribe gastroprotection where an NSAID or antiplatelet cannot be avoided (Maudsley 2021).

QTc. Citalopram and escitalopram cause a dose-dependent QTc prolongation, which is the reason for the hard dose ceilings above; caution with other QT-prolonging drugs, hypokalaemia and pre-existing cardiac disease.

TRAP **Missing SSRI-induced hyponatraemia in an older patient.** New confusion, falls, unsteadiness or a seizure weeks into an SSRI is hyponatraemia until the sodium proves otherwise.

2 to 4 wk	40	20
THERAPEUTIC LAG TO RESPONSE	CITALOPRAM QTC CEILING (MG/DAY)	ESCITALOPRAM MAXIMUM (MG/DAY)

2.6 The paediatric suicidality signal and serotonin syndrome

Paediatric suicidality. A small but real increase in suicidal ideation and behaviour (not completed suicide) is seen with antidepressants in children, adolescents and young adults up to about age 25, prompting a boxed warning and close monitoring in the early weeks; the same reanalyses show a reduction in suicidality with antidepressants in adults over 65 (Stahl 2021). The message is monitoring in the young, not avoidance: untreated depression is itself a suicide risk. The full clinical suicide risk assessment and safety planning are owned by the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

Serotonin syndrome. Combining an SSRI with another serotonergic drug, above all an MAOI (including moclobemide), tramadol, triptans, linezolid or another serotonergic antidepressant, can precipitate serotonin syndrome, the triad of neuromuscular excitation (clonus, hyperreflexia, tremor), autonomic instability and altered mental state. An adequate washout is mandatory when switching to or from an MAOI, and the long half-life of fluoxetine means a 5-week gap. The acute recognition and emergency management of serotonin syndrome are cross-referred to the Perinatal/women's mental health and emergency psychiatry notes.

RULE **Never co-prescribe an SSRI with an MAOI.** Leave 14 days after an MAOI, and 5 weeks after fluoxetine before starting one, to avoid serotonin syndrome.

2.7 CYP interactions and the discontinuation caveat

Cytochrome interactions in brief. The clinically important inhibitors are the ones to memorise: fluoxetine and paroxetine are potent CYP2D6 inhibitors (fluoxetine also inhibits CYP3A4), and fluvoxamine is a potent CYP1A2 inhibitor. Practical consequences: paroxetine reduces the efficacy of tamoxifen (a CYP2D6-activated pro-drug); fluoxetine raises clozapine and TCA levels; fluvoxamine markedly raises theophylline, clozapine and caffeine levels. Sertraline, escitalopram and citalopram are comparatively clean, which is why escitalopram or sertraline is preferred in the medically complex patient (Maudsley 2021; Stahl 2021).

Discontinuation caveat. Stopping an SSRI abruptly, especially a short-half-life agent, produces a discontinuation syndrome (flu-like symptoms, insomnia, nausea, imbalance, sensory "electric-shock" disturbances and hyperarousal). Paroxetine is the worst offender and fluoxetine essentially exempt because it self-tapers. Always taper; the full discontinuation-and-withdrawal detail is cross-referred to the Perinatal/women's mental health and emergency psychiatry notes.

INDIA

SSRIs are the most-prescribed antidepressants in Indian practice and all six are cheap and freely available as generics and branded generics. Lead with the Indian brand: escitalopram is sold as Nexito or S-Citadep, sertraline as Serta or Daxid, fluoxetine as Fludac, and paroxetine as Pexep; citalopram and fluvoxamine are marketed generically and by brand. Escitalopram and sertraline are the workhorse first-line agents in Indian outpatient departments, and monthly cost is low (a month of a generic SSRI typically costs a small fraction of a single private consultation), which matters for adherence in a largely out-of-pocket health system.

WORKED EXAMPLE

A 72-year-old woman on a thiazide for hypertension is started on an SSRI for a moderate depressive episode. Ten days later she is brought in confused, unsteady and drowsy. Rather than escalating the antidepressant or reaching for an antipsychotic, the first action is a serum sodium, which is 122 mmol/L: SSRI-induced hyponatraemia from SIADH, compounded by the diuretic and her age. The SSRI is stopped, sodium corrected cautiously, and a lower-risk strategy planned. Missing the sodium here is the classic examined error.

PEARL

Match the SSRI to the patient by its non-efficacy features: the anxious or agitated patient may do better away from activating fluoxetine; the medically complex, polypharmacy patient suits clean escitalopram or sertraline; the patient likely to miss doses should avoid short-half-life paroxetine because of its discontinuation burden. The efficacy is broadly the same; the fit is not.

MNEMONIC

FINISH

SSRI discontinuation syndrome, worst with paroxetine: **F**lu-like symptoms, **I**nsomnia, **N**ausea, **I**mbalance, **S**ensory disturbances (the "electric shocks"), **H**yperarousal. Taper slowly; fluoxetine self-tapers.

HOLD THIS

SSRIs are first-line and equally effective, differing in half-life, CYP interactions and adverse-effect emphasis: fluoxetine long and activating, paroxetine short with the worst discontinuation and avoided in pregnancy, escitalopram cleanest with a QTc ceiling, fluvoxamine a CYP1A2 inhibitor for OCD; watch for sexual dysfunction, hyponatraemia in the elderly, NSAID-associated bleeding, and never combine with an MAOI.

3 · Serotonin-noradrenaline reuptake inhibitors

Why this matters. The **serotonin-noradrenaline reuptake inhibitor** (SNRI) class is the most heavily examined second-generation antidepressant group after the SSRIs, and it is where a resident must marry a clean synaptic mechanism to a small set of dose-dependent adverse effects. Every SNRI blocks both the serotonin transporter (SERT) and the noradrenaline transporter (NET), but the noradrenergic action is not free at every dose: with venlafaxine it emerges only as the dose is raised, which is exactly why the blood-pressure rise, the sweating and the urinary effects track dose. The class also carries the single most feared antidepressant discontinuation problem, the venlafaxine withdrawal syndrome.

The examinable skill is threefold: to state the dual SERT and NET mechanism and its dose-dependence, to name and dose each agent (venlafaxine, desvenlafaxine, duloxetine, milnacipran and levomilnacipran) with its signature adverse effect, and to place the class in the algorithm, a common second step after an SSRI, or a first-line choice where depression is comorbid with neuropathic pain. The monoamine-transporter pharmacology and CYP metabolism that underpin this class are developed in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

3.1 The mechanism: dual SERT and NET blockade with a noradrenergic action that emerges at higher dose

The class name says the mechanism: an SNRI inhibits reuptake at both the serotonin transporter and the noradrenaline transporter, combining two therapeutic actions in one molecule (Stahl 2021; Kaplan & Sadock 2024). What distinguishes the newer SNRIs from the older dual-acting tricyclics is **selectivity**: they have essentially no affinity for muscarinic, histaminergic or alpha-adrenergic receptors, which is why they are far better tolerated than clomipramine or amitriptyline while sharing the dual-reuptake logic (Kaplan & Sadock 2024). The crucial teaching point is that the two actions are not equipotent at every dose. For venlafaxine the affinity for SERT is much greater than for NET, so at the lowest therapeutic dose the drug behaves as a de-facto SSRI, and NET is only reliably engaged as the dose climbs; Stahl frames this as serotonergic actions present at low doses with noradrenergic actions "progressively enhanced as dose

increases" (Stahl 2021). This ascending dose-response is the conceptual spine of the whole topic: the noradrenergic benefits and the noradrenergic adverse effects both arrive together, at higher dose.

RULE **An SNRI is an SSRI at low dose and a dual agent higher up.** The noradrenergic action, and every noradrenergic adverse effect, appears as you push the dose, so dose determines the pharmacology.

3.2 Venlafaxine: the dose-dependent noradrenergic effect and the ascending dose-response

Venlafaxine (Venlor) is a bicyclic phenylethylamine, the prototype SNRI, approved for major depressive disorder, generalised anxiety disorder, social anxiety disorder and panic disorder (Kaplan & Sadock 2024). Its pharmacology is textbook dose-dependence: it acts as a serotonergic agent at the minimum effective dose of **75 mg/day**, whereas the noradrenaline transporter is consistently engaged only at a dose of about **225 mg/day** (Kaplan & Sadock 2024). CANMAT lists venlafaxine as a first-line SNRI for MDD at **75 to 225 mg/day** (CANMAT 2016). The immediate-release form has a short elimination half-life of roughly **4 hours** (its active metabolite O-desmethylvenlafaxine about **10 hours**), and this short half-life is what drives the discontinuation problem covered below (Kaplan & Sadock 2024). The extended-release capsule allows once-daily dosing but does not lengthen the elimination half-life, so it does not abolish the withdrawal risk (Kaplan & Sadock 2024).

WORKED EXAMPLE

A patient on venlafaxine 75 mg/day for depression has partial response with no side effects. Because 75 mg is essentially a serotonergic dose, uptitration towards 150 to 225 mg/day recruits the noradrenergic action and can improve response, but from about 150 mg upward you must begin checking blood pressure, because the noradrenergic effect that helps also raises blood pressure.

3.3 Venlafaxine: the dose-dependent blood-pressure rise and the monitoring rule

The signature venlafaxine adverse effect is a **dose-dependent rise in blood pressure**, a direct consequence of dose-dependent noradrenergic reuptake blockade. With the immediate-release formulation, sustained hypertension was dose-related, rising from about **3 to 7 percent** at doses of 100 to 300 mg/day and to about **13 percent** at doses greater than 300 mg/day (Kaplan & Sadock 2024). Capping the extended-release dose largely attenuated the signal, but the prescribing rule stands: when higher doses are used, monitoring of blood pressure is recommended (Kaplan & Sadock 2024). The Maudsley makes the class point plainly, that the SNRIs venlafaxine and duloxetine are associated with dose-dependent increases in blood pressure (Maudsley 2021). This is the load-bearing SNRI prescribing principle: blood pressure is checked, and checked again, as the dose is raised.

3 to 7	13	75 to 225
SUSTAINED HYPERTENSION AT 100 TO 300 MG/DAY (PERCENT)	SUSTAINED HYPERTENSION ABOVE 300 MG/DAY (PERCENT)	FIRST-LINE VENLAFAXINE RANGE (MG/DAY)

RULE **Venlafaxine's noradrenergic effect and blood-pressure rise are dose-dependent, so monitor blood pressure at higher doses.** Check a baseline and recheck as you titrate past the low serotonergic range.

3.4 Venlafaxine: the short half-life and the marked discontinuation syndrome

Venlafaxine is one of the antidepressants most commonly associated with a discontinuation syndrome, a direct consequence of its short half-life (Kaplan & Sadock 2024). On rapid taper or abrupt cessation, and even after a few missed doses, patients develop dizziness, nausea, insomnia, nervousness, sweating, anorexia, diarrhoea, somnolence and sensory disturbances (the "electric shock" or "brain zap" paraesthesiae) (Kaplan & Sadock 2024). Because the extended-release formulation does not change the elimination half-life, switching to it does not reduce the discontinuation potential (Kaplan & Sadock 2024). The Maudsley notes that antidepressants with noradrenergic effects tend to have more severe withdrawal, and names venlafaxine, desvenlafaxine, duloxetine and paroxetine as the agents most often implicated (Maudsley 2021). Management is prevention: warn the patient not to stop abruptly, and taper slowly, reducing the daily dose by no more than about **75 mg each week** when longer-term treatment must be stopped; a few bridging doses of fluoxetine can smooth the final step (Kaplan & Sadock 2024).

TRAP **Stopping venlafaxine abruptly precipitates a severe discontinuation syndrome.** The short half-life means even missed doses can trigger it; never stop it suddenly, taper by no more than about 75 mg per week.

GOOD TO REMEMBER

- **Venlafaxine (Venlor):** dual SERT and NET reuptake inhibitor, noradrenergic action emerges with dose; signature effect is a dose-dependent blood-pressure rise (monitor at higher doses) plus a marked discontinuation syndrome from its short half-life; hold 75 to 225 mg/day, serotonergic at 75, NET engaged near 225.

3.5 Desvenlafaxine: the active metabolite, less CYP-dependent

Desvenlafaxine is O-desmethylvenlafaxine, the principal active metabolite of venlafaxine, formed from the parent drug by CYP2D6 (Stahl 2021; Kaplan & Sadock 2024). Because it is already the downstream metabolite, its systemic exposure is **less dependent on CYP2D6 conversion** than venlafaxine's, so its plasma levels are more predictable across the genetic polymorphisms of that enzyme (Stahl 2021). It has relatively greater noradrenaline reuptake inhibition than venlafaxine but remains more potent at SERT (Stahl 2021). The minimum therapeutic dose is **50 mg/day**, and controlled trials showed no greater efficacy at higher doses; CANMAT lists it as a first-line SNRI for MDD at **50 to 100 mg/day** (Kaplan & Sadock 2024; CANMAT 2016). Note the Maudsley caveat that desvenlafaxine was not marketed in the UK at the time of writing, so it appears in guidelines as an option rather than a mainstream UK agent (Maudsley 2021).

GOOD TO REMEMBER

- **Desvenlafaxine:** the active O-desmethyl metabolite of venlafaxine, less CYP2D6-dependent so more predictable levels; relatively more noradrenergic than venlafaxine but still SERT-predominant; hold a minimum effective dose of 50 mg/day (first-line range 50 to 100 mg/day).

3.6 Duloxetine: the neuropathic-pain and stress-incontinence indications

Duloxetine (Duzela) inhibits both SERT and NET, and because it has lower affinity for NET than for SERT, doses higher than **60 mg/day** are needed to reliably obtain a central noradrenergic effect (Stahl 2021; Kaplan & Sadock 2024). CANMAT lists duloxetine as a first-line SNRI for MDD at **60 mg/day** (CANMAT 2016). Its distinguishing feature is a set of pain and urological indications that flow from noradrenergic action on descending spinal pathways and on urethral sphincter tone: it is specifically used for **diabetic and other neuropathic pain**, for fibromyalgia, and for **stress urinary incontinence** in women because it increases urethral tone (Tripathi 2019; Kaplan & Sadock 2024). This makes duloxetine the natural first-line antidepressant when depression coexists with a chronic pain syndrome. Its blood-pressure effect is smaller than venlafaxine's and, curiously, does not appear to be dose-dependent, with only about a 1 percent greater risk of sustained hypertension than placebo (Kaplan & Sadock 2024).

INDIA

Duloxetine is widely stocked in India under several brands (Duzela among them); the internationally recognised innovator brand is Cymbalta. When comorbid neuropathic pain drives the choice, duloxetine is often the pragmatic first antidepressant on an Indian formulary because it treats both targets with one drug.

3.7 Duloxetine: the hepatotoxicity caution and key interactions

The specific safety caution for duloxetine is **hepatotoxicity**: the Maudsley references a drug-induced liver injury case series, and the drug should be avoided in patients with significant hepatic impairment or substantial alcohol use, with liver function monitored if there is concern (Maudsley 2021). Metabolically, duloxetine is a CYP1A2 and CYP2D6 substrate: its levels are about 30 percent lower in smokers (CYP1A2 induction) and rise about four-fold with potent CYP1A2 inhibitors such as fluvoxamine and some fluoroquinolone antibiotics, so co-prescription with fluvoxamine is a notable interaction to avoid (Kaplan & Sadock 2024). As with all serotonergic agents, a lethal interaction with monoamine oxidase inhibitors is expected, and the MAOI washout rules must be followed; the acute serotonin-syndrome frame that this interaction can trigger is developed in the Perinatal/women's mental health and emergency psychiatry notes.

TRAP **Co-prescribing duloxetine with fluvoxamine multiplies its level roughly four-fold.** Fluvoxamine is a potent CYP1A2 inhibitor; the combination, and heavy alcohol use, both stack onto duloxetine's hepatotoxicity risk.

GOOD TO REMEMBER

- **Duloxetine (Duzela):** dual SERT and NET inhibitor, doses above 60 mg needed for a central noradrenergic effect; signature niche is neuropathic pain, fibromyalgia and stress urinary incontinence, with a hepatotoxicity caution (avoid in hepatic impairment or heavy alcohol use); hold a first-line dose of 60 mg/day.

3.8 Milnacipran and levomilnacipran in brief

Milnacipran is a dual reuptake inhibitor that, unlike venlafaxine, is preferentially noradrenergic, roughly twice as potent at NET as at SERT; it behaves as a preferential NE uptake inhibitor at its minimum therapeutic dose of **50 mg twice daily** and recruits more serotonergic action as the dose rises to its maximal recommended **200 mg/day** for fibromyalgia (Kaplan & Sadock 2024). In many countries it is licensed for major depressive disorder, but in the United States it is approved only for fibromyalgia (Kaplan & Sadock 2024). Consistent with its noradrenergic bias, its notable adverse effects, at rates higher than an SSRI, are dizziness, sweating and urinary hesitancy (Kaplan & Sadock 2024). Levomilnacipran is the more active enantiomer, developed as a separate once-daily antidepressant for MDD; like the others it must never be given close to an MAOI (Kaplan & Sadock 2024).

GOOD TO REMEMBER

- **Milnacipran:** the preferentially noradrenergic SNRI (about twice as potent at NET as SERT), signature effects sweating and urinary hesitancy; hold a minimum therapeutic dose of 50 mg twice daily (maximum 200 mg/day, licensed mainly for fibromyalgia).
- **Levomilnacipran:** the more active enantiomer of milnacipran, marketed as a once-daily SNRI antidepressant for MDD; never combine with an MAOI.

3.9 The class adverse-effect profile: the noradrenergic signature

Beyond the shared serotonergic effects (nausea, which is more frequent than with SSRIs, sexual dysfunction, headache), the examinable SNRI signature is the **noradrenergic** cluster, all traceable to NET blockade: **sweating**, a rise in **blood pressure**, increased pulse, and **urinary** effects (hesitancy). With venlafaxine these are dose-dependent, tracking the emergence of noradrenergic action at higher dose; milnacipran, being preferentially noradrenergic, shows the sweating and urinary signal even at usual dose (Kaplan & Sadock 2024). Layered on top is the discontinuation liability, most marked for venlafaxine because of its short half-life. Holding these together, the class is well tolerated but demands two things of the prescriber that SSRIs do not: blood-pressure monitoring as the dose rises, and a deliberate, slow taper on stopping.

PEARL

Every noradrenergic SNRI adverse effect, sweating, raised blood pressure, urinary hesitancy, is the same pharmacology (NET blockade) seen from a different organ. If you remember "sweat, pressure, pee" you have reconstructed the class side-effect profile from first principles.

3.10 Adverse-effect comparison across the agents

AGENT (BRAND)	USUAL DOSE (MG/DAY)	NE VS 5-HT BALANCE	SIGNATURE ADVERSE EFFECT / CAUTION
Venlafaxine (Venlor)	75 to 225	SERT > NET; NET recruited with dose	**Dose-dependent blood-pressure rise; marked discontinuation syndrome**
Desvenlafaxine	50 to 100	More NET than venlafaxine, still SERT-predominant	Less CYP2D6-dependent, more predictable levels
Duloxetine (Duzela)	60 (up to 120)	SERT > NET; NET needs >60 mg	**Hepatotoxicity caution; neuropathic pain and stress incontinence indications**
Milnacipran	100 (50 twice daily), max 200	NET > SERT (preferentially noradrenergic)	Sweating, urinary hesitancy; mainly fibromyalgia
Levomilnacipran	40 to 120	Noradrenergic-leaning enantiomer	Once-daily; MAOI contraindication

SNRI agents compared on dose, transporter balance and the single adverse effect or caution to hold for each; blood-pressure monitoring and slow taper apply across the class.

3.11 The place in therapy: a common second step after an SSRI, or first-line with comorbid pain

In the guideline algorithm the SNRIs sit as core options for major depressive disorder. CANMAT names venlafaxine (75 to 225 mg/day), duloxetine (60 mg/day) and desvenlafaxine (50 to 100 mg/day) as **first-line** SNRI agents for MDD, individualising the choice to the patient (CANMAT 2016). The commonest practical use is as a **second step after an SSRI**: when a first-line SSRI fails on efficacy grounds, a switch to an SNRI is a standard next move, and CANMAT directs that for a non-improver at 2 to 4 weeks you increase the dose if tolerated and switch to another agent if tolerability is the problem (CANMAT 2016). The BAP similarly reserves maximised-efficacy agents including venlafaxine at 150 mg or more for more severely ill patients, and NICE positions SNRIs among the alternatives after an initial SSRI (Malhi 2015 for the BAP position on severity; NICE 2014). The other clear first-line indication is **comorbid pain**: duloxetine is the natural first choice when depression coexists with neuropathic pain, fibromyalgia or stress urinary incontinence. For the Indian Psychiatric Society position, kb-search did not return a confirmable IPS depression recommendation on SNRI sequencing in the parsed library, so the specific IPS line could not be confirmed and is flagged rather than invented; the guideline-anchored management plan for depression as a whole is developed in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

RULE **An SNRI is a standard second step after a failed SSRI, and first-line when pain is comorbid.** Venlafaxine, duloxetine and desvenlafaxine are all CANMAT first-line SNRIs; duloxetine also treats the pain.

COMMON TRAP

Do not treat a bipolar depression with an SNRI as monotherapy. As with any antidepressant, using it alone in bipolar depression risks a switch into mania or mixed states; the SNRI place in therapy described here is for unipolar depression, and the bipolar-depression algorithm belongs in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

HOLD THIS

Every SNRI blocks SERT and NET, but venlafaxine's noradrenergic action, and its blood-pressure rise, are dose-dependent (SSRI-like at 75 mg, NET engaged near 225 mg), so monitor blood pressure as you titrate and never stop it abruptly (short half-life, severe discontinuation syndrome).

MNEMONIC

"VDD-ML": Venlafaxine, Desvenlafaxine, Duloxetine, Milnacipran, Levomilnacipran

The five SNRIs in rough order of exam weight. Venlafaxine carries blood pressure and discontinuation; Desvenlafaxine is its less-CYP-dependent metabolite; Duloxetine owns pain and stress incontinence with a liver caution; Milnacipran and Levomilnacipran are the noradrenergic-leaning, fibromyalgia-associated tail.

4 . Tricyclic antidepressants

The **tricyclic antidepressants** (the **TCAs**) are the oldest effective antidepressant class, and although second-generation agents have displaced them from first line, they remain firmly on the exam because their pharmacology is the teaching template for the whole antidepressant syllabus: a wanted reuptake action bundled with three unwanted receptor blockades that generate the entire adverse-effect picture, and a cardiotoxicity that makes them lethal in overdose. On a guideline reading they are a **second-line** option for major depression (CANMAT 2016) and have specific evidence in treatment-resistant depression and, for clomipramine, in obsessive-compulsive disorder.

Why the class still matters. A resident must be able to say, in one breath, why a TCA works (reuptake blockade), why it is unpleasant (muscarinic, H1 and alpha-1 blockade), and why it kills (quinidine-like sodium-channel blockade in the myocardium). The receptor systems behind these actions are laid out in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the guideline-anchored place of the class within the depression algorithm is in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

4.1 Mechanism: reuptake blockade plus three off-target blockades

The wanted action. TCAs block the presynaptic serotonin transporter (SERT) and the noradrenaline transporter (NET), raising synaptic monoamine availability, exactly the shared final pathway of the SSRIs and SNRIs (Stahl 2021). **The unwanted actions.** Unlike the selective

agents, TCAs simultaneously block three off-target receptors, and this promiscuity, not the reuptake action, drives almost every adverse effect: **muscarinic (antimuscarinic)** blockade gives the anticholinergic set, **histamine H1** blockade gives sedation and weight gain, and **alpha-1 adrenergic** blockade gives orthostatic hypotension (Stahl 2021, Kaplan and Sadock 2024). A fourth, separate action, blockade of fast cardiac sodium channels, is what makes overdose dangerous and is covered in 4.6.

Muscarinic (M1) blockade
dry mouth, constipation, blurred vision, urinary hesitancy, tachycardia, cognitive slowing, delirium in the elderly

Histamine H1 blockade
sedation, drowsiness and appetite-driven weight gain

Alpha-1 adrenergic blockade
orthostatic (postural) hypotension, dizziness and reflex tachycardia

Fast sodium-channel blockade
the quinidine-like membrane-stabilising effect on the myocardium, dormant at therapeutic dose but lethal in overdose

4.2 Tertiary versus secondary amines

The structural distinction that predicts tolerability. **Tertiary amine** TCAs (amitriptyline, imipramine, clomipramine, doxepin, trimipramine) are more potent at all the off-target receptors and are therefore more anticholinergic, more sedating and more hypotensive. Their demethylated **secondary amine** metabolites and drugs (nortriptyline from amitriptyline, desipramine from imipramine) are relatively more noradrenergic and, crucially, **less anticholinergic and better tolerated** (Kaplan and Sadock 2024). Nortriptyline in particular has the least orthostatic hypotension of the class and desipramine is the least anticholinergic, which is why the secondary amines are preferred in the elderly.

RULE **Secondary before tertiary in the frail.** If a TCA is unavoidable in an older or medically compromised patient, choose a secondary amine (nortriptyline, desipramine): same reuptake efficacy, lighter anticholinergic and orthostatic load.

AGENT (INDIAN BRAND)	AMINE CLASS	SIGNATURE FEATURE	DOSE (MG/DAY)
Amitriptyline (Tryptomer)	tertiary	**most sedating and cardiotoxic; also pain and migraine prophylaxis**	75 to 200
Imipramine (Depsonil)	tertiary	the original TCA; childhood enuresis	75 to 200
Clomipramine (Anafranil)	tertiary	**most serotonergic; OCD**	up to 250
Nortriptyline	secondary	**best-tolerated; therapeutic window 50 to 150 ng/mL**	75 to 150
Desipramine	secondary	least anticholinergic	100 to 200

Tertiary amines are more sedating, anticholinergic and hypotensive; secondary amines are better tolerated and preferred in the elderly.

4.3 Amitriptyline: the sedating prototype

The workhorse tertiary amine. Amitriptyline (Tryptomer) is strongly serotonergic and noradrenergic but also the most anticholinergic, sedating and cardiotoxic, and it is one of the leading single-drug causes of death by overdose (Kaplan and Sadock 2024). Its sedation and analgesic action make it a standard low-dose agent for **chronic pain** and **migraine prophylaxis**, well below antidepressant doses. Antidepressant dosing runs up through the usual antidepressant range of **75 to 200 mg/day**, and up to 300 mg/day only under specialist supervision (Companion 2010), taken at night to exploit the sedation.

4.4 Imipramine and clomipramine

Imipramine, the original and the enuresis drug. Imipramine (Depsonil) was the first tricyclic; beyond depression it retains a niche use in childhood nocturnal **enuresis**, where the antidepressants (unlike anxiolytics) reduce bed-wetting (Shorter Oxford 2018). **Clomipramine, the serotonergic one.** Clomipramine (Anafranil) is the **most serotonergic** TCA and is the tricyclic with first-line-strength efficacy in obsessive-compulsive disorder (Lopez-Ibor, 1967; Shorter Oxford 2018): conventional TCAs are ineffective in OCD, clomipramine is the exception. Its OCD dosing climbs to a maximum around **250 mg/day** (Maudsley 2021). Because it is the most serotonergic, clomipramine carries the highest serotonin-syndrome risk of the class if combined with an MAOI or another serotonergic drug.

> **COMMON TRAP**
>
> Reaching for a "plain" TCA (amitriptyline, imipramine) for obsessive-compulsive disorder. Only **clomipramine**, the most serotonergic tricyclic, works in OCD; the others are essentially inactive against obsessions and compulsions.

4.5 Nortriptyline: best-tolerated, with a therapeutic window

The monitorable secondary amine. Nortriptyline is the best-tolerated TCA (least orthostatic hypotension, relatively low anticholinergic burden) and is the one TCA with a genuine

therapeutic window: efficacy tracks a plasma level of roughly **50 to 150 ng/mL**, and levels above the window are associated with loss of response and rising toxicity, so plasma-level monitoring is meaningfully used to guide dosing (Kaplan and Sadock 2024, Maudsley 2021). The average dose needed to reach about 100 ng/mL is near **75 mg/day** but varies widely, which is exactly why the level, not just the dose, is checked.

WORKED EXAMPLE

A 70-year-old with recurrent depression needs a TCA after two SSRIs failed. You choose nortriptyline (a secondary amine, least orthostatic), get a baseline ECG, start low, titrate every few days, and draw a plasma level after 5 to 7 days on a steady dose, aiming for the **50 to 150 ng/mL** window rather than pushing the milligram dose blind.

4.6 The adverse-effect set and the cardiotoxicity

The everyday adverse effects follow directly from the three off-target blockades in 4.1: anticholinergic effects (dry mouth, constipation, blurred vision, urinary retention, precipitation of narrow-angle glaucoma, delirium in the elderly), sedation, weight gain, and orthostatic hypotension, which is in fact the single most common reason for stopping a TCA (Kaplan and Sadock 2024). **The cardiotoxicity** is separate and more dangerous. TCAs have a **quinidine-like** (type 1A antiarrhythmic) membrane-stabilising action: by blocking fast cardiac sodium channels they slow intraventricular conduction, which shows on the ECG as **QRS widening** and QT prolongation and, at higher exposure, as ventricular arrhythmia and heart block (Kaplan and Sadock 2024). A pre-existing conduction delay, or a QTc of 450 msec or greater, is a contraindication, and an ECG should precede TCA use in the elderly or the cardiac patient.

50 to 150	450	75 to 200
NORTRIPTYLINE THERAPEUTIC WINDOW (NG/ML)	QTC CONTRAINDICATION THRESHOLD (MSEC)	CLASS ANTIDEPRESSANT RANGE (MG/DAY)

4.7 Key interactions

The two that matter for the exam. The most dangerous is the **TCA plus MAOI** combination: adding a large dose of a tricyclic to a patient already on a monoamine oxidase inhibitor can precipitate a serotonin syndrome or a fatal hypertensive reaction, so an adequate washout is mandatory (Kaplan and Sadock 2024). The second is **pharmacokinetic**: TCAs are cleared by cytochrome P450, and CYP2D6 inhibitors, notably fluoxetine, paroxetine, duloxetine and bupropion, raise TCA plasma levels (fluoxetine roughly triples desipramine levels), pushing an otherwise safe dose toward cardiotoxic territory. Enzyme inducers such as carbamazepine do the reverse and can make a therapeutic level unattainable. The CYP machinery is detailed in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

TRAP **Co-prescribing a 2D6 inhibitor with a TCA and not rechecking the level.** Adding fluoxetine or paroxetine to a stable TCA can several-fold raise the tricyclic level and tip a well-tolerated dose into QRS-widening toxicity.

4.8 Overdose: the reason TCAs are feared

A small multiple of the daily dose can be lethal. Because the target population is depressed and at risk of self-harm, overdose lethality is the defining safety problem of the class: a tricyclic overdose of about **10 times the daily dose** can be fatal, and death is most often from cardiac toxicity, with seizures and respiratory depression also occurring (Kaplan and Sadock 2024). The mortality risk with TCAs in overdose is many-fold higher than with SSRIs. The **toxidrome** combines the anticholinergic picture (hot, dry, dilated, delirious, tachycardic, ileus, retention) with central nervous system depression and **seizures**, and the cardiac picture of a **wide QRS**, ventricular arrhythmia and **hypotension**.

The management headline. Secure the airway, get an urgent **ECG**, and give intravenous **sodium bicarbonate** for QRS widening (and for significant arrhythmia or hypotension): serum alkalinisation and a sodium load counteract the quinidine-like sodium-channel block. The rest is supportive, activated charcoal if early, benzodiazepines for seizures, fluids and pressors for hypotension. The full acute-emergency detail, including the wider poisoning and serotonin-syndrome frame, is in the Perinatal/women's mental health and emergency psychiatry notes.

HOLD THIS

A TCA overdose of about ten times the daily dose can be fatal, kills mainly through quinidine-like cardiotoxicity (wide QRS, arrhythmia, hypotension) plus seizures, and the antidote to the widened QRS is intravenous sodium bicarbonate.

4.9 Where the TCAs sit in the guidelines

Second-line, weighed against overdose risk. CANMAT (CANMAT 2016) places TCAs (amitriptyline, clomipramine and others) as a **second-line** monotherapy for major depression, behind the SSRIs and SNRIs, precisely because the newer agents are safer in overdose and better tolerated. The BAP (Cleare, 2015) makes the same point at guideline level, choose antidepressants that are better tolerated and safer in overdose first, and reserves TCAs and MAOIs for when first-line treatment has failed, while noting that TCAs have evidence for **superior efficacy in treatment-resistant depression** where serum levels can guide dosing. The place of the class in the wider stepped algorithm is set out in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

INDIA

TCAs remain widely and cheaply available in India: amitriptyline as Tryptomer, imipramine as Depsonil, clomipramine as Anafranil. Low cost keeps them in real-world use, which makes the overdose-lethality counselling in 4.8 and the prescribing rule below all the more important where supply and follow-up may be limited.

RULE **Weigh suicide risk before you prescribe.** TCAs are effective but dangerous in overdose (cardiotoxic), so assess suicide risk first and prefer a safer agent, or dispense small quantities, in anyone at risk.

TRAP **Handing an actively suicidal patient a large quantity of a TCA.** A month's supply of amitriptyline is a lethal stockpile; this is the classic, avoidable prescribing error of the class.

MNEMONIC

TCA overdose: the 3 Cs plus Seize

Convulsions (seizures), **C**oma (CNS depression), **C**ardiotoxicity (wide QRS, arrhythmia, hypotension), on a background of anticholinergic delirium. QRS widening is answered by sodium bicarbonate.

GOOD TO REMEMBER

- **TCA class:** SERT and NET reuptake blockade drives efficacy; muscarinic, H1 and alpha-1 blockade drives the adverse effects; second-line for depression, dangerous in overdose.
- **Tertiary vs secondary amine:** secondary amines (nortriptyline, desipramine) are less anticholinergic and better tolerated; prefer them in the elderly.
- **Amitriptyline (Tryptomer):** sedating, most anticholinergic and cardiotoxic tertiary amine; also used for chronic pain and migraine prophylaxis; antidepressant range 75 to 200 mg/day.
- **Imipramine (Depsonil):** the original TCA; niche use in childhood nocturnal enuresis.
- **Clomipramine (Anafranil):** the most serotonergic TCA; first-line-strength for OCD, up to about 250 mg/day; highest serotonin-syndrome risk with MAOIs.
- **Nortriptyline:** best-tolerated (least orthostatic); therapeutic window 50 to 150 ng/mL, so plasma-level monitoring guides dosing.
- **Cardiotoxicity:** quinidine-like sodium-channel block, QRS widening, arrhythmia; ECG before use, avoid if QTc 450 msec or more.
- **Overdose:** about 10 times the daily dose can be fatal; discriminator is a wide QRS; first management step is ECG plus intravenous sodium bicarbonate.

5 . Monoamine oxidase inhibitors

The **monoamine oxidase inhibitors** (the **MAOIs**) were the first effective antidepressants, and although they have been pushed to a late line by their diet and interaction hazards, they remain firmly on the exam for two reasons: the **tyramine (cheese) reaction** and the **serotonergic interaction** are the most examinable drug-safety stories in the whole antidepressant syllabus, and the class retains a real place in atypical and treatment-resistant depression. A resident must be able to say, in one breath, why they work (they block monoamine breakdown), why the diet matters (dietary tyramine is normally destroyed by gut MAO-A), and why they must never be co-prescribed with a serotonergic drug without a washout.

Why the class still matters. The monoamine oxidase enzyme and the monoamine pathways it acts on are laid out in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the guideline-anchored place of the class within the depression algorithm is in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes. Here the teaching is the pharmacology: the mechanism, the agents, the tyramine reaction, the drug interactions and the mandatory washout intervals.

5.1 Mechanism: irreversible non-selective inhibition of MAO

The target. Monoamine oxidase is the mitochondrial enzyme that oxidatively deaminates the monoamines. It exists as two isoforms: **MAO-A** preferentially metabolises serotonin, noradrenaline and dietary tyramine, and **MAO-B** preferentially metabolises phenylethylamine, while both isoforms handle dopamine and tyramine (Stahl 2021, Companion 2010). **The action.** The classical agents produce **irreversible non-selective inhibition of MAO-A and MAO-B**, so monoamine breakdown is blocked and synaptic serotonin, noradrenaline and dopamine all rise, which is the antidepressant action. Because the inhibition is irreversible, the effect persists until new enzyme is synthesised, which takes about two weeks and is precisely why the washout intervals in 5.6 are so long (Kaplan and Sadock 2024).

RULE **Irreversible means think in weeks, not half-lives.** Enzyme activity returns only as new MAO is made (about two weeks), so the drug's danger outlasts its plasma clearance.

5.2 The agents: irreversible, reversible and transdermal

The irreversible non-selective agents. Phenelzine, tranylcypromine and isocarboxazid are the classical irreversible MAOIs. Phenelzine and isocarboxazid are hydrazines (with a small hepatotoxicity risk); tranylcypromine is a non-hydrazine with an amphetamine-like structure and can be activating (Kaplan and Sadock 2024). **The reversible agent.** Moclobemide is a **reversible inhibitor of MAO-A** (a RIMA), and this is its defining safety advantage: because tyramine can competitively displace it from the enzyme, moclobemide is much safer for the tyramine reaction and does not require adherence to a low-tyramine diet at normal doses (Shorter Oxford 2018). **The transdermal agent.** Transdermal selegiline (a patch) delivers drug systemically for antidepressant effect while, at the lowest patch strength, largely sparing gut MAO-A, so the lowest dose does not require dietary restriction; the higher patch strengths do (Kaplan and Sadock 2024).

AGENT	TYPE	SIGNATURE POINT	DOSE (MG/DAY)
Phenelzine	irreversible non-selective	**hydrazine; most weight gain of the class**	45 to 90
Tranylcypromine	irreversible non-selective	**amphetamine-like, activating**	20 to 60
Isocarboxazid	irreversible non-selective	hydrazine; least used	20 to 60
Moclobemide	**reversible MAO-A (RIMA)**	much safer for tyramine; no strict diet	300 to 600
Selegiline (transdermal)	patch	lowest strength spares gut MAO-A, no diet	see monograph

Phenelzine 45 to 90 and tranylcypromine 20 to 60 mg/day per CANMAT (2016); moclobemide 300 to 600 mg/day per CANMAT (2016).

GOOD TO REMEMBER

- **Phenelzine:** irreversible non-selective MAOI; signature is the tyramine (cheese) reaction and most weight gain of the class; hold the dose **45 to 90 mg/day** and that it is a third-line antidepressant.
- **Tranylcypromine:** irreversible non-selective MAOI, amphetamine-like and activating; signature is the hypertensive tyramine reaction; hold the dose **20 to 60 mg/day**.
- **Isocarboxazid:** irreversible non-selective hydrazine MAOI; signature is the same tyramine and serotonergic hazard; hold that it is third-line and least used.
- **Moclobemide:** reversible inhibitor of MAO-A (a RIMA); signature is that it is much safer for the tyramine reaction and needs no strict diet; hold the dose **300 to 600 mg/day** as a second-line agent (CANMAT 2016).
- **Transdermal selegiline:** patch delivery; signature is that the lowest strength spares gut MAO-A and needs no diet, higher strengths do; hold this as its whole reason for existing.

5.3 The tyramine reaction: the cheese reaction and hypertensive crisis

The mechanism. Dietary **tyramine** is a sympathomimetic amine normally broken down by gut and hepatic MAO-A before it reaches the circulation. On an irreversible MAOI that first-pass breakdown is abolished, so ingested tyramine passes into the circulation and drives a surge of noradrenaline release from sympathetic nerve terminals, producing a **hypertensive crisis** (Kaplan and Sadock 2024). This is the historical **cheese reaction**, first traced by Blackwell at the Maudsley to certain cheeses. **The clinical picture.** A tyramine crisis presents with a severe throbbing occipital headache, palpitations, nausea, vomiting, sweating and a dangerously raised blood pressure, and can progress to arrhythmia, stroke and intracranial haemorrhage (Kaplan and Sadock 2024).

WORKED EXAMPLE

A patient stable on phenelzine eats a mature cheddar and salami platter with a glass of red wine, and within the hour develops a pounding occipital headache, sweating and a blood pressure of 210/130. This is a tyramine-driven hypertensive crisis. The management headline is to treat it as a hypertensive emergency with a rapid-acting agent to lower the pressure, for example intravenous phentolamine, with the wider acute management set out in the Perinatal/women's mental health and emergency psychiatry notes.

The foods to avoid. The high-tyramine foods a patient on an irreversible MAOI must avoid include aged cheeses, aged and cured or fermented meats, improperly stored or spoiled meat, poultry or fish, broad (fava) bean pods, Marmite and other yeast extracts, sauerkraut, soy sauce and soybean condiments, and tap or draught beer (Kaplan and Sadock 2024). Fresh foods and moderate amounts of most everyday items are safe; it is the aged, cured, fermented and spoiled that concentrate tyramine.

MNEMONIC

AGED foods bite the MAOI patient

Aged cheese, Aged and cured meats, Alcohol (tap beer, some wines); Gone-off (spoiled) meat, poultry or fish; broad bEans (fava pods) and yeast extract; Draught beer and soy or fermented (sauerkraut) condiments. The unifying theme is anything Aged, fermented, cured or spoiled, because that is where tyramine accumulates.

5.4 The serotonergic interaction and serotonin syndrome

The most dangerous drug combination. Combining an MAOI with a serotonergic drug can precipitate a potentially fatal serotonin syndrome: the MAOI blocks serotonin breakdown while the second drug raises serotonin further, and the two together can produce runaway serotonergic activity (Stahl 2021, Kaplan and Sadock 2024). The offending drugs are the **SSRIs, SNRIs and clomipramine and other TCAs**, and among analgesics the classic culprits are **tramadol** and **pethidine (meperidine)**, both of which have serotonergic activity and are absolutely contraindicated with an MAOI (Kaplan and Sadock 2024). The clinical triad of serotonin syndrome is neuromuscular excitation (clonus, hyperreflexia, tremor, rigidity), autonomic instability (fever, tachycardia, sweating, diarrhoea) and altered mental state (agitation, confusion), detailed in the Perinatal/women's mental health and emergency psychiatry notes.

The sympathomimetic interaction. Separately, combining an MAOI with a **sympathomimetic** drug, amphetamines, methylphenidate, cocaine, and the sympathomimetic amines in some cold and cough remedies (pseudoephedrine, phenylephrine), produces the same noradrenaline-surge **hypertensive crisis** as the tyramine reaction, by the same final mechanism of unopposed pressor amine (Stahl 2021).

GOOD TO REMEMBER

- **Serotonin syndrome (the discriminator):** the triad is neuromuscular (clonus, hyperreflexia, rigidity), autonomic (fever, tachycardia, sweating) and mental-state (agitation, confusion) change; clonus and hyperreflexia are the features that distinguish it from neuroleptic malignant syndrome. First step: stop all serotonergic drugs and give supportive care.
- **The forbidden co-prescriptions:** never give an MAOI with an SSRI, SNRI, clomipramine, tramadol or pethidine (serotonin syndrome), nor with a sympathomimetic (hypertensive crisis).

5.5 The washout periods when switching

Why washout is non-negotiable. Because irreversible MAO inhibition lasts until new enzyme is made, an adequate **washout** must be observed in both directions when switching between an MAOI and a serotonergic drug, or a serotonin syndrome or hypertensive reaction can result even after the drug itself has cleared (Kaplan and Sadock 2024). **The intervals.** Allow at least **two weeks** after stopping an irreversible MAOI before starting a serotonergic drug (to let new enzyme regenerate), and at least **one week** (about five half-lives) after stopping most SSRIs and SNRIs before starting an MAOI, or two weeks after a tricyclic. The important exception is **fluoxetine**: because of its very long-acting active metabolite norfluoxetine, allow a longer

washout of about **five weeks** after stopping fluoxetine before starting an MAOI (Maudsley 2021, Kaplan and Sadock 2024).

2	1	5
OFF AN MAOI BEFORE A SEROTONERGIC DRUG (WEEKS)	OFF MOST SSRIS/SNRIS BEFORE AN MAOI (WEEKS)	OFF FLUOXETINE BEFORE AN MAOI (WEEKS)

RULE **Never combine an MAOI with a serotonergic drug, and observe the washout both ways.** At least two weeks off an MAOI before a serotonergic drug, and about five weeks off fluoxetine before an MAOI.

TRAP **Starting an SSRI too soon after an MAOI, or missing dietary tyramine counselling.** The commonest lethal errors are ignoring the washout when switching and failing to counsel the patient on the tyramine-rich foods to avoid.

5.6 Where the MAOIs sit in the guidelines

A later-line option. The MAOIs are reserved for **atypical depression** and **treatment-resistant depression** once better-tolerated, safer agents have failed. CANMAT (CANMAT 2016) places the irreversible agents, phenelzine **45 to 90 mg/day** and tranylcypromine **20 to 60 mg/day**, as **third-line** antidepressants, and moclobemide **300 to 600 mg/day**, the reversible MAO-A inhibitor, as a **second-line** option (CANMAT 2016). The BAP (Cleare, 2015) makes the same point at guideline level, reserve older TCAs and MAOIs for when first-line treatment has failed, and initiate an MAOI only with expertise in treating mood disorders. For the Indian Psychiatric Society position, the IPS depression guidance (Gautam et al., 2017) prioritises SSRIs and other second-generation agents first line and does not foreground the MAOIs; the specific IPS line-position for MAOIs could not be confirmed and is therefore not stated here. In pregnancy the MAOIs are to be avoided (CANMAT 2016). The place of the class in the wider stepped algorithm is set out in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

INDIA

The irreversible MAOIs (phenelzine, tranylcypromine) are little used in routine Indian practice and are not widely stocked, which is itself protective against the diet and interaction hazards. Where an MAOI is considered, it belongs in specialist hands for atypical or treatment-resistant depression, with explicit tyramine counselling and a documented washout when switching from or to a serotonergic drug.

HOLD THIS

Irreversible non-selective MAOIs (phenelzine, tranylcypromine, isocarboxazid) block tyramine breakdown, so aged, cured and fermented foods cause a hypertensive crisis, and a serotonergic drug causes serotonin syndrome; allow at least two weeks off an MAOI before a serotonergic drug and about five weeks off fluoxetine before an MAOI.

6 . Mirtazapine and bupropion

Two atypical antidepressants that a resident reaches for when an **SSRI is the wrong fit**. Each is a CANMAT Level-1 first-line agent for major depression, yet each is prescribed for its side-effect signature as much as its efficacy: mirtazapine (the **nassa**) is sedating and appetite-boosting, so it suits the depressed patient who cannot sleep and will not eat; bupropion (the **ndri**) is activating and pro-sexual, so it suits the fatigued, apathetic patient and the one whose SSRI killed libido. The mirror-image profiles are the exam point. The one hard caveat is bupropion's dose-dependent lowering of the **seizure threshold**.

Framing. This pair sits next to the SSRI and SNRI monographs; for how they slot into the guideline-anchored selection algorithm see the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes. For the receptor systems and CYP metabolism they act on, see the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. Verify every dose and the seizure caveat: a wrong one is a prescribing error.

6.1 Mirtazapine: the NaSSA mechanism

Noradrenergic and specific serotonergic antidepressant. Mirtazapine (brand Mirtaz; generic mirtazapine) is a nassa that works without any reuptake blockade (Stahl 2021). It antagonises the **alpha-2 adrenergic autoreceptor** on noradrenergic neurons, removing the noradrenaline brake and so raising noradrenaline release; and it antagonises the **alpha-2 heteroreceptor** sitting on serotonin neurons, which disinhibits and raises serotonin release. On top of this dual monoamine boost it blocks **5-HT2A, 5-HT2C and 5-HT3** serotonin receptors and the **H1 histamine** receptor (Stahl 2021, Maudsley 2021). The receptor set explains the whole clinical picture below.

RULE **Reroute, don't block.** Mirtazapine raises noradrenaline and serotonin by antagonising alpha-2 auto- and heteroreceptors, not by inhibiting a reuptake pump, so it carries none of the SSRI serotonergic-tone side effects.

6.2 Mirtazapine: dose and the paradox of low doses

15 to 45 mg at night. Start **15 mg** in the evening, titrate every 1 to 2 weeks to a usual maximum of **45 mg/day** (Stahl 2021, CANMAT 2016). The counter-intuitive teaching point: **sedation and the antihistamine load are worse at the LOWER dose**. At 7.5 to 15 mg the H1 blockade dominates; as the dose climbs, the rising noradrenergic drive partly offsets the histaminergic sedation, so sedation may not worsen and can even ease (Stahl 2021). Breaking a 15 mg tablet to give 7.5 mg can therefore increase, not reduce, drowsiness.

PEARL

If a patient complains mirtazapine is too sedating at 15 mg, the fix is often to go UP, not down: 30 mg is frequently less sedating than 15 mg because added noradrenergic tone counters the H1 effect (Stahl 2021).

6.3 Mirtazapine: the adverse-effect profile that is the selling point

Sedation and appetite gain, with clean serotonergic tolerability. The signature effects are **sedation** (H1 antagonism) and **increased appetite and weight gain** (H1 plus 5-HT2C antagonism), both of which are the reason to choose it in a depressed patient with insomnia and poor appetite (Stahl 2021, Maudsley 2021). Because it does not raise synaptic serotonin by reuptake blockade and it antagonises 5-HT2 and 5-HT3, it has **minimal sexual dysfunction** (5-HT2 sparing) and **minimal GI upset or nausea** (5-HT3 blockade, the same mechanism as ondansetron). Rare but examinable: dizziness, abnormal dreams, dry mouth, and a rare risk of low white cell count, so flu-like symptoms warrant a blood count (Stahl 2021).

RECEPTOR ACTION	CLINICAL CONSEQUENCE
Alpha-2 auto- and heteroreceptor antagonism	**antidepressant effect (raises noradrenaline and serotonin)**
H1 histamine block	**sedation and weight gain (both worse at low dose)**
5-HT2C block	appetite and weight gain
5-HT2A block	minimal sexual dysfunction; may aid sleep
5-HT3 block	minimal nausea and GI upset (anti-emetic)

Each mirtazapine side effect maps to a specific receptor it blocks (Stahl 2021).

15 to 45	20 to 40
MIRTAZAPINE DOSE (MG/DAY)	MIRTAZAPINE HALF-LIFE (HOURS)

6.4 Mirtazapine: where it fits, and the interaction to hold

First-line for depression with insomnia and weight loss; a favoured add-on. CANMAT lists mirtazapine 15 to 45 mg/day as a Level-1 first-line antidepressant for major depression, singling out the patient with sleep disturbance (CANMAT 2016). It is a metabolised substrate of CYP2D6, 3A4 and 1A2 with no significant pharmacokinetic interactions of its own (Stahl 2021), which makes it an easy combination partner: added to an SNRI it forms the dual-action combination Stahl nicknames "California rocket fuel", and CANMAT rates mirtazapine or mianserin 30 to 60 mg/day added to an antidepressant as a second-line adjunct (CANMAT 2016). The one dangerous interaction to hold: like all monoaminergic antidepressants it can precipitate serotonin syndrome with an MAOI, so allow a 14-day washout after stopping an MAOI (Stahl 2021). For the acute management of serotonin syndrome see the Perinatal/women's mental health and emergency psychiatry notes.

GOOD TO REMEMBER

- **Mirtazapine (Mirtaz), mechanism:** NaSSA, alpha-2 auto- and heteroreceptor antagonist raising noradrenaline and serotonin, plus 5-HT2/5-HT3 and H1 block, no reuptake inhibition.
- **Mirtazapine, signature effect:** sedation and weight gain (worse at LOWER dose), with minimal sexual dysfunction and minimal nausea.
- **Mirtazapine, one to hold:** 15 to 45 mg/day at night, CANMAT first-line for depression with insomnia and poor appetite; 14-day washout with MAOIs (serotonin syndrome).

6.5 Bupropion: the NDRI mechanism

Norepinephrine-dopamine reuptake inhibitor. Bupropion (brand Bupron; generic bupropion, formerly amfebutamone) is an ndri that blocks the noradrenaline transporter and the dopamine transporter, raising noradrenaline and dopamine neurotransmission (Stahl 2021). Because the prefrontal cortex largely lacks dopamine transporters and clears dopamine via the noradrenaline pump, blocking that pump also lifts prefrontal dopamine. It has essentially **no direct serotonergic action**, which is why its side-effect profile is the mirror image of the SSRIs: it is **activating**, not sedating. It is also a CYP2D6 inhibitor, a fact that matters for interactions (Stahl 2021).

MNEMONIC

DA-NO-BUP

bupropion boosts DA and NA and has NO serotonin action, hence NO weight gain, NO sexual dysfunction, and NO sedation; but it does lower the seizure threshold.

6.6 Bupropion: dose and formulations

Three formulations, one first-line depression range. CANMAT lists bupropion **150 to 300 mg/day** as a Level-1 first-line NDRI for major depression (CANMAT 2016). The formulation determines the dosing schedule and the single-dose ceiling, which exists precisely to cap the seizure risk (Stahl 2021):

FORMULATION	RANGE (MG/DAY)	SCHEDULE	MAX SINGLE DOSE (MG)
Immediate-release (IR)	225 to 450	3 divided doses	**150**
Sustained-release (SR)	200 to 450	2 divided doses	**200**
Extended-release (XL)	150 to 450	once daily	450

Splitting the dose and capping the single dose limits the peak concentration that drives seizures (Stahl 2021).

6.7 Bupropion: the indications, including smoking cessation

Depression, SSRI-adjunct, and nicotine dependence. Beyond monotherapy for major depression, bupropion is the antidepressant of choice as an **adjunct for SSRI-induced sexual dysfunction** and for residual **fatigue, cognitive slowing and apathy** ("SSRI poop-out"), because it adds dopaminergic and noradrenergic drive without serotonergic burden (Stahl 2021). It is separately licensed for **smoking cessation** (as sustained-release bupropion, marketed for that indication as Zyban): begin it 1 to 2 weeks before the quit date, titrating to 150 mg twice daily, and it reduces craving (Stahl 2021).

RULE **Match the deficit to the drug.** Mirtazapine helps depression with insomnia and weight loss; bupropion helps depression with fatigue and sexual dysfunction. Choose by the residual-symptom profile.

6.8 Bupropion: low sexual dysfunction, low weight gain

The tolerability edge. Because it lacks serotonergic action, bupropion causes **little or no sexual dysfunction** and **little or no weight gain** (indeed it is weight-neutral to weight-reducing), and it is less likely to induce hypomania than some antidepressants (Stahl 2021). This is why it is the go-to switch or add-on for the SSRI-treated patient troubled by anorgasmia, low libido or antidepressant-associated weight gain. The trade-off is activation: insomnia, agitation, dry mouth, tremor and, at the extreme, the seizure risk that dominates its contraindications.

6.9 Bupropion: the seizure threshold caveat and contraindications

Dose-dependent lowering of the seizure threshold. The one caveat every examiner wants: bupropion lowers the **seizure threshold** in a **dose-dependent** way (Stahl 2021, Maudsley 2021). It is therefore **contraindicated in a current or past seizure disorder**; in a **current or past eating disorder** (anorexia or bulimia, where electrolyte disturbance and low body weight amplify the risk, the historical signal coming from high-dose immediate-release use in low-weight anorexia); and in a patient **abruptly discontinuing alcohol, sedatives or an anticonvulsant**, since withdrawal itself lowers the threshold (Stahl 2021). Also avoid with an MAOI and within 14 days of stopping one (hypertensive risk), and use caution combining with nicotine replacement (hypertension) (Stahl 2021).

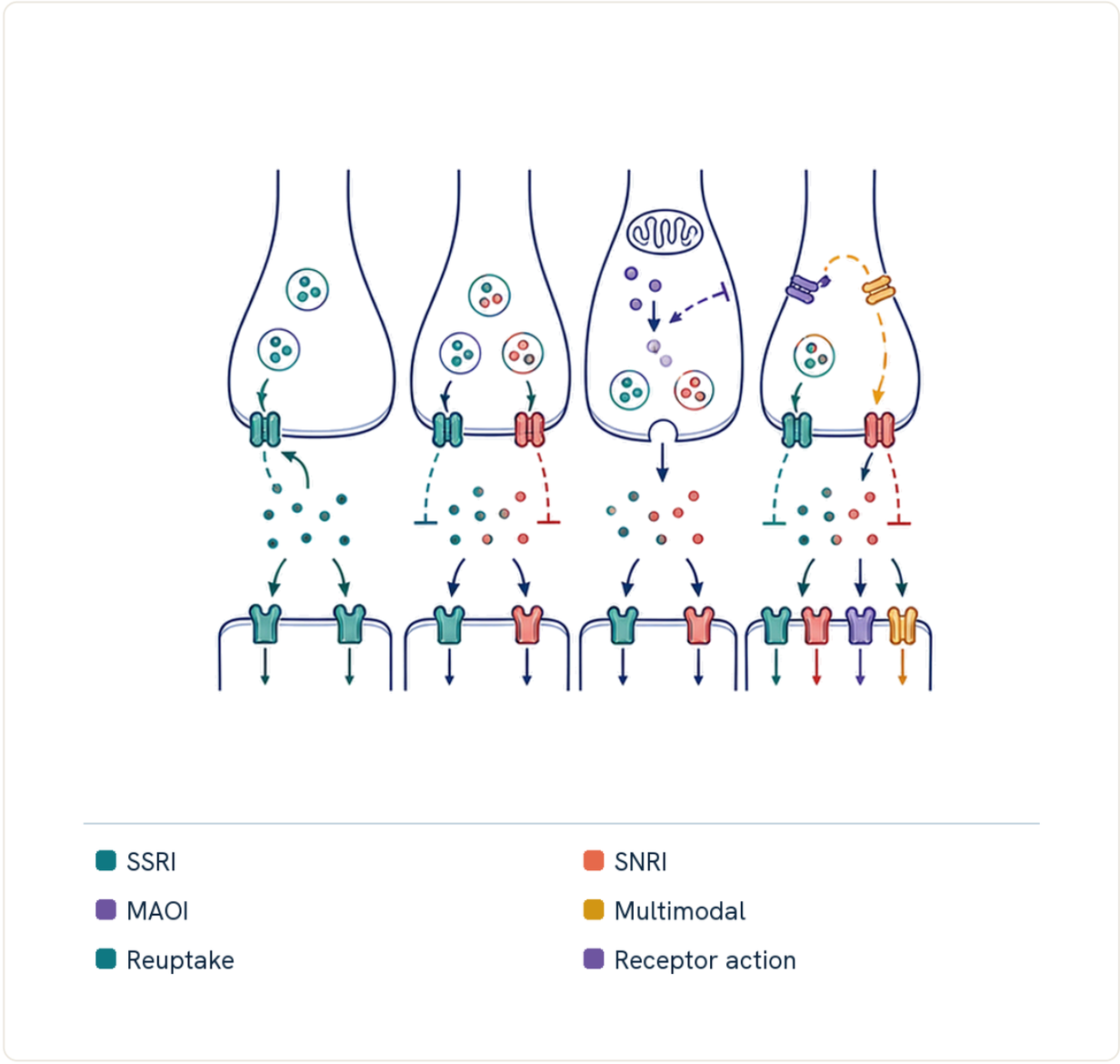

Fig 12.3 Antidepressant mechanism families at the synapse: selective serotonin reuptake inhibition, dual serotonin-noradrenaline reuptake inhibition, monoamine-oxidase inhibition and multimodal transporter-receptor action.

TRAP **The forbidden prescription.** Prescribing bupropion to a patient with a seizure disorder or an eating disorder, or during alcohol/sedative withdrawal, is the classic error: each independently lowers the seizure threshold that bupropion also lowers.

COMMON TRAP

"Low sexual dysfunction" makes bupropion tempting for the SSRI patient with a bulimia history, but the eating-disorder contraindication is absolute. Screen for a current or past eating disorder before any bupropion prescription.

INDIA

Bupropion (Bupron) and mirtazapine (Mirtaz) are both widely available in India. The Indian Psychiatric Society guidance on bipolar disorder notes that where an antidepressant must be used, bupropion is preferred over paroxetine (IPS guidelines); the Indian Psychiatric Society depression CPG (Gautam et al.) endorses second-generation antidepressants including these agents as first-line, though a mirtazapine- or bupropion-specific first-line row for depression could not be confirmed from the guideline database and is stated here at class level only.

GOOD TO REMEMBER

- **Bupropion (Bupron), mechanism:** NDRI, blocks noradrenaline and dopamine reuptake, activating, no serotonergic action, a CYP2D6 inhibitor.
- **Bupropion, signature caveat:** dose-dependent lowering of the seizure threshold, contraindicated in seizure disorders, eating disorders and abrupt alcohol/sedative withdrawal.
- **Bupropion, one to hold:** 150 to 300 mg/day, CANMAT first-line for depression and adjunct for SSRI-induced sexual dysfunction and fatigue; licensed (SR) for smoking cessation, started 1 to 2 weeks before the quit date.

HOLD THIS

Mirtazapine (NaSSA, alpha-2 antagonist) sedates and grows appetite with clean sexual and GI tolerability, best for depression with insomnia and weight loss; bupropion (NDRI) activates with no sexual dysfunction or weight gain, best for fatigue and SSRI-induced sexual dysfunction and for smoking cessation, but its dose-dependent lowering of the seizure threshold forbids it in seizure and eating disorders.

7 . Newer and multimodal antidepressants

A compact fold covering the agents that sit outside the SSRI, SNRI, TCA and MAOI classes yet keep appearing in exams because each carries one signature receptor mechanism and one signature caveat. The theme is **receptor engineering beyond simple reuptake**: two **multimodal** agents that add direct receptor actions to serotonin reuptake block, one melatonergic agent that resets the body clock, one sedating serotonin modulator repurposed for sleep, and one frankly atypical drug with a glutamate-and-opioid mechanism. Learn each as mechanism plus the one adverse effect the examiner is hunting for.

Framing. These are the "others" beside the SSRI and SNRI monographs; for how each slots into the guideline-anchored selection algorithm see the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes. For the serotonin receptor subtypes and CYP metabolism these agents act on, see the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. Two facts are CRITICAL and verified below: agomelatine needs scheduled liver function monitoring, and trazodone causes priapism.

7.1 Vortioxetine and vilazodone: the multimodal serotonin modulators

An SSRI backbone plus direct receptor actions. Both are serotonin modulator antidepressants that block the serotonin transporter (SERT), the same pump the SSRIs act on, but add clinically meaningful action at specific 5-HT receptor subtypes (Stahl 2021, K&S 2024). Vortioxetine

(generic vortioxetine) is the fuller **multimodal** agent: SERT reuptake inhibitor, full agonist at 5-HT1A, partial agonist at 5-HT1B, and antagonist at 5-HT3, 5-HT7 and 5-HT1D (K&S 2024). Vilazodone (generic vilazodone) is narrower: an SSRI combined with 5-HT1A partial agonism, the same 5-HT1A property that makes buspirone anxiolytic, which is why Stahl files it as a SPARI (serotonin partial agonist reuptake inhibitor) (Stahl 2021). The added receptor actions are what differentiate the tolerability and, for vortioxetine, the cognitive signal.

RULE **Reuptake plus receptor.** A multimodal serotonin modulator does two things at once, block SERT and directly hit a named 5-HT receptor; the direct receptor action is what sets its side-effect profile apart from a plain SSRI.

7.2 Vortioxetine: dose, the pro-cognitive signal, and dose-dependent nausea

10 to 20 mg once daily, a first-line multimodal agent. CANMAT lists vortioxetine **10 to 20 mg/day** as a Level-1 first-line antidepressant for major depression (CANMAT 2016). PET occupancy of SERT reaches about 80% only at the 20 mg dose, so 10 to 20 mg is the effective band (K&S 2024). Its distinctive claims: a **pro-cognitive signal**, an improvement in processing speed, attention and executive function that trials suggest is partly independent of the antidepressant effect (attributed to its 5-HT7 and 5-HT3 antagonism and 5-HT1A agonism); a comparatively **lower rate of sexual dysfunction** than SSRIs; and a favourable cardiac profile with no meaningful effect on QT (Maudsley 2021, K&S 2024). The dominant adverse effect is **dose-dependent nausea**, driven by its serotonergic load, usually early and transient. It is a CYP2D6 substrate with a long **66-hour** half-life, so a strong 2D6 inhibitor roughly doubles levels and calls for a dose reduction, and a 14-day gap is needed before starting an MAOI (Stahl 2021, K&S 2024).

WORKED EXAMPLE

A depressed accountant with prominent complaints of "brain fog", slowed thinking and SSRI-related anorgasmia is a rational fit for vortioxetine 10 mg/day, uptitrated to 20 mg: the pro-cognitive signal targets the cognitive complaint and the lower sexual-dysfunction rate addresses the anorgasmia. Warn about early nausea and take it after food if needed (Stahl 2021, K&S 2024).

7.3 Vilazodone: dose, titration and the GI trade-off

20 to 40 mg once daily, titrated slowly with food. CANMAT places vilazodone **20 to 40 mg/day** as a second-line antidepressant, started at 10 mg and titrated up over about 2 weeks, taken **with food** to ensure absorption (CANMAT 2016, K&S 2024). The 5-HT1A partial agonism gives a relatively lower rate of sexual dysfunction and weight gain than pure reuptake blockers, but the price is **gastrointestinal**: diarrhoea and nausea are the commonest adverse effects, which is exactly why the slow titration and food rule exist, to blunt the GI burden (K&S 2024). It has no clinically significant effect on cardiac conduction. Head-to-head network meta-analyses find no clear efficacy advantage of vilazodone or vortioxetine over older antidepressants, which keeps vilazodone in the second line (Maudsley 2021).

10 to 20	20 to 40	66
VORTIOXETINE (MG/DAY)	VILAZODONE (MG/DAY)	VORTIOXETINE HALF-LIFE (HOURS)

GOOD TO REMEMBER

- **Vortioxetine, mechanism:** multimodal serotonin modulator, SERT reuptake inhibitor plus 5-HT1A agonist and 5-HT3/5-HT7 antagonist; a pro-cognitive signal.
- **Vortioxetine, signature effect and one to hold:** dose-dependent nausea and lower sexual dysfunction; CANMAT first-line 10 to 20 mg/day, CYP2D6 substrate, 66-hour half-life.
- **Vilazodone, mechanism:** an SSRI plus 5-HT1A partial agonism (SPARI); lower sexual dysfunction, but GI diarrhoea and nausea.
- **Vilazodone, one to hold:** CANMAT second-line 20 to 40 mg/day, titrate from 10 mg over 2 weeks and take with food.

7.4 Agomelatine: the melatonergic agonist that resets the body clock, and its liver caveat

An MT1/MT2 agonist and 5-HT2C antagonist. Agomelatine (generic agomelatine) is the uniquely **melatonergic** antidepressant: it is an agonist at the melatonin receptors **MT1** (mt1) and **MT2** (mt2), using the older M1/M2 nomenclature in some texts, and an antagonist at the serotonin **5-HT2C** (5-ht2c) receptor (K&S 2024, Stahl 2021). The MT1/MT2 agonism resynchronises circadian rhythm, restoring sleep architecture, while the 5-HT2C antagonism disinhibits frontocortical noradrenaline and dopamine, giving the antidepressant effect. CANMAT lists agomelatine **25 to 50 mg/day** at bedtime as a first-line agent, singled out for depression **with sleep disturbance**, and it has a low rate of sexual dysfunction, weight gain and discontinuation symptoms (CANMAT 2016). The defining caveat is **hepatotoxicity**: dose-related transaminase rises, and rare hepatitis and hepatic failure, mostly in the first months (Maudsley 2021).

The one monitoring rule. Agomelatine mandates **liver function monitoring**: check LFTs at baseline and again at 3, 6, 12 and 24 weeks after starting, and at every dose increase, then as clinically indicated; **stop the drug if transaminases rise above 3 times the upper limit of normal**; and it is **contraindicated in hepatic impairment** including cirrhosis and active liver disease (Maudsley 2021). It is a CYP1A2 substrate, so a strong 1A2 inhibitor such as fluvoxamine or ciprofloxacin markedly raises levels and is contraindicated.

25 to 50	0, 3, 6, 12, 24	3x ULN
AGOMELATINE (MG/DAY)	LFT WEEKS AFTER STARTING	TRANSAMINASE STOP THRESHOLD

RULE **Agomelatine needs baseline and follow-up liver function tests.** LFTs at baseline, then 3, 6, 12 and 24 weeks and at each dose increase; stop if transaminases exceed 3 times the upper limit of normal.

TRAP **Forgetting the LFTs.** Starting agomelatine without baseline liver function monitoring, or omitting the follow-up bloods, is the classic error; the same trap in reverse is missing high-dose trazodone priapism below.

GOOD TO REMEMBER

- **Agomelatine, mechanism:** melatonergic MT1 and MT2 agonist plus 5-HT2C antagonist that resynchronises circadian rhythm; CANMAT first-line 25 to 50 mg/day, especially with sleep disturbance.
- **Agomelatine, signature caveat and one to hold:** hepatotoxicity, so liver function monitoring at baseline and 3, 6, 12, 24 weeks; stop if transaminases exceed 3x ULN; contraindicated in hepatic impairment.

7.5 Trazodone: the sedating SARI, and the priapism caveat

A serotonin antagonist/reuptake inhibitor used low-dose for sleep. Trazodone (generic trazodone) is a SARI serotonin modulator: a potent 5-HT2A antagonist with weak serotonin reuptake inhibition and, crucially, **alpha-1 adrenergic** and H1 histamine antagonism (K&S 2024). At full antidepressant doses CANMAT rates it a second-line agent at **150 to 300 mg/day**, but in practice it is used far more often at **low dose (25 to 100 mg at night) for insomnia**, where the H1 and 5-HT2A block deliver sedation without the dependence of a benzodiazepine (CANMAT 2016, K&S 2024). The signature caveat is priapism: the alpha-1 antagonism that also causes its orthostatic hypotension can produce prolonged, painful erection, a urological emergency requiring immediate attention (K&S 2024). It is a CYP3A4 substrate, so a strong 3A4 inhibitor raises levels.

TRAP **The priapism warning omitted.** Prescribing trazodone, even low-dose for sleep, without counselling a male patient that a prolonged or painful erection is a medical emergency needing urgent care is the classic trazodone error.

PEARL

Trazodone's alpha-1 antagonism is the common thread: it explains the orthostatic hypotension AND the priapism. The mnemonic is that trazodone can "drop the pressure and raise the wrong thing" (K&S 2024).

GOOD TO REMEMBER

- **Trazodone, mechanism:** SARI serotonin modulator, 5-HT2A antagonist with weak SERT block plus alpha-1 and H1 antagonism; sedating, hence widely used low-dose (25 to 100 mg) for insomnia.
- **Trazodone, signature caveat and one to hold:** priapism (alpha-1 antagonism), a urological emergency; antidepressant dose 150 to 300 mg/day, CANMAT second-line.

7.6 Tianeptine: the glutamatergic, opioid-modulating atypical antidepressant

A mechanism unlike any other antidepressant. Tianeptine (generic tianeptine) is a genuinely atypical antidepressant whose action is **glutamatergic** rather than classically monoaminergic: it potentiates AMPA-receptor function and promotes synaptic plasticity, reversing stress-induced hippocampal remodelling, and (paradoxically for an antidepressant) it enhances rather than blocks serotonin reuptake (New Oxford 2020). More recently it has been shown to act as a **mu-opioid receptor agonist**, which is now thought to underlie much of its acute effect (New Oxford 2020). It is dosed at **25 to 50 mg/day** and is not marketed in many countries, including the UK

and USA (Maudsley 2021). The examinable concern that flows directly from the opioid mechanism is **abuse potential**: at supratherapeutic doses tianeptine behaves as an opioid, and misuse and dependence have been reported.

RULE **Glutamate and opioid, not just monoamine.** Tianeptine's antidepressant action rests on AMPA/glutamatergic modulation plus mu-opioid agonism; that opioid action is exactly why it carries abuse potential.

GOOD TO REMEMBER

- **Tianeptine, mechanism:** atypical glutamatergic antidepressant, AMPA-receptor potentiator that promotes synaptic plasticity and enhances serotonin reuptake, plus mu-opioid receptor agonism.
- **Tianeptine, signature concern and one to hold:** abuse potential from its opioid action; dose 25 to 50 mg/day; not marketed in many countries.

INDIA

Among these agents, agomelatine and vortioxetine are marketed in India; low-dose trazodone is in routine use for insomnia. A specific Indian brand for vortioxetine (sometimes cited as Vortioxa) could not be confirmed from the parsed reference library, so the generic name is used here rather than an unverified brand. The Indian Psychiatric Society depression CPG (Gautam et al.) endorses newer second-generation antidepressants as first-line at class level, but an IPS agent-specific first-line row for these particular molecules could not be confirmed from the guideline database and is stated at class level only.

COMMON TRAP

Treating this whole group as interchangeable SSRIs. They are not: agomelatine demands scheduled LFTs, trazodone risks priapism, and tianeptine has genuine abuse liability. Each carries a caveat an SSRI does not.

HOLD THIS

Vortioxetine (multimodal, SERT plus 5-HT1A agonism and 5-HT3/5-HT7 antagonism, pro-cognitive, dose-dependent nausea, 10 to 20 mg/day first-line) and vilazodone (SSRI plus 5-HT1A partial agonism, GI-heavy, 20 to 40 mg/day) are the multimodal serotonin modulators; agomelatine (melatonergic MT1/MT2 agonist and 5-HT2C antagonist, 25 to 50 mg/day) resets the body clock but needs liver function monitoring at baseline and 3, 6, 12, 24 weeks with a stop at transaminases above 3x ULN; trazodone (sedating SARI) is used low-dose for insomnia and can cause priapism; tianeptine is a glutamatergic, mu-opioid-agonist atypical with abuse potential.

8 . Serotonin syndrome and the NMS differential

Of all the complications an antidepressant can cause, **serotonin syndrome** is the one the exam asks about most reliably, because it is the drug-safety story that ties the whole antidepressant syllabus together: it is what happens when serotonergic drive is pushed too hard, usually by a combination of agents, and the single most dangerous combination, an MAOI plus a serotonergic drug, is exactly the interaction taught in the monoamine oxidase inhibitor topic. A resident must

be able to recite the triad, name the diagnostic criteria (the **hunter criteria**), give the first management step, and, above all, separate it cleanly from **neuroleptic malignant syndrome**, its dopamine-blocker mimic.

Why the differential is the whole point. Serotonin syndrome and neuroleptic malignant syndrome are both hyperthermic, rigid, autonomically unstable, altered-consciousness emergencies, and they are constantly confused. The examiner rewards the candidate who can name the one discriminator that tells them apart. The pharmacology of the serotonergic and dopaminergic pathways is in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the wider acute management of both syndromes (cooling, sedation, restraint, the medical emergency frame) is set out in the Perinatal/women's mental health and emergency psychiatry notes. Here the teaching is recognition, criteria, first management and the differential.

Discriminator	Serotonin syndrome serotonergic excess	Neuroleptic malignant syndrome dopamine blockade
Onset speed	over hours, rapid	over days, slower
Trigger drug	a serotonergic drug or combination SSRI plus MAOI, tramadol, linezolid	a dopamine blocker (antipsychotic), or abrupt dopamine-agonist withdrawal
Neuromuscular the pivot	clonus, hyperreflexia, tremor, myoclonus	lead-pipe rigidity, bradyreflexia
Bowel sounds	hyperactive	normal or reduced
Pupils	dilated (mydriasis)	normal
Course	resolves within about a day if stopped	evolves over days, slow recovery
Specific drug	cyproheptadine	dantrolene, bromocriptine
First step	stop the serotonergic agent	stop the antipsychotic

Fig 12.4 Serotonin syndrome versus neuroleptic malignant syndrome. The pivot is the neuromuscular sign: clonus and hyperreflexia point to serotonin syndrome, lead-pipe rigidity with hyporeflexia to NMS. Serotonin syndrome comes on over hours from a serotonergic combination, resolves fast once the drug is stopped and responds to cyproheptadine; NMS comes on over days from a dopamine blocker, evolves slowly and is treated with dantrolene or bromocriptine.

8.1 Pathophysiology: serotonergic excess, usually from a combination

The mechanism. Serotonin syndrome is a state of excessive serotonergic activity at central and peripheral serotonin receptors, chiefly the postsynaptic 5-HT2A and 5-HT1A receptors, produced by drugs that raise synaptic serotonin (Shorter Oxford 2018, Stahl 2021). It is extremely rare with a single agent at a recommended dose and is almost always the product of a **combination** of serotonergic drugs, or of an overdose (Kaplan and Sadock 2024). **The most dangerous combination.** The classic and most lethal pairing is an **MAOI plus a serotonergic drug**: the MAOI blocks serotonin breakdown while the second agent, an SSRI, an SNRI, clomipramine, tramadol or pethidine, drives serotonin higher, and together they produce runaway 5-HT toxicity (Shorter Oxford 2018, Stahl 2021). Other precipitants added to an SSRI

include a second serotonergic antidepressant, lithium, tryptophan, triptans, linezolid, methylene blue and the recreational drug ecstasy.

RULE **Serotonin syndrome is usually a combination, and MAOI-plus-serotonergic is the deadliest.** A single serotonergic drug at a normal dose rarely does it; two together, above all an MAOI, is the danger.

8.2 The clinical triad: neuromuscular, autonomic, mental-state

The three-part picture. Serotonin syndrome presents as a triad, and holding the triad is the fastest route to recognition (Shorter Oxford 2018, Stahl 2021). The first arm is **neuromuscular excitation**: clonus (spontaneous, inducible and ocular clonus, the single most characteristic sign), hyperreflexia, myoclonus, tremor and rigidity, and the neuromuscular findings are typically more prominent in the lower limbs. The second arm is **autonomic instability**: hyperthermia, tachycardia, diaphoresis, **mydriasis** (dilated pupils) and hyperactive bowel sounds with diarrhoea. The third arm is **altered mental state**: agitation, restlessness, anxiety and, in severe cases, confusion progressing to coma. Onset is **rapid, over hours** of the offending exposure.

clonus	hours	3
MOST CHARACTERISTIC NEUROMUSCULAR SIGN	TYPICAL ONSET AFTER THE TRIGGER	ARMS OF THE TRIAD (NEUROMUSCULAR, AUTONOMIC, MENTAL)

MNEMONIC

The three A's plus the clonus

Think Agitation (mental state), Autonomic instability (hyperthermia, tachycardia, diaphoresis, mydriasis, hyperactive bowel sounds) and Augmented neuromuscular activity (clonus, hyperreflexia, tremor, rigidity). The one sign that clinches it and that NMS does not share is clonus with hyperreflexia.

8.3 Diagnostic criteria: the hunter criteria and the older Sternbach criteria

The Hunter criteria. The hunter criteria (the Hunter Serotonin Toxicity Criteria, Dunkley et al. 2003) are the more specific and now-preferred diagnostic rule. In a patient who has taken a serotonergic agent, the diagnosis is made if any one of the following is present: spontaneous clonus; inducible clonus plus agitation or diaphoresis; ocular clonus plus agitation or diaphoresis; tremor plus hyperreflexia; or hypertonia plus a temperature above 38 degrees Celsius plus ocular or inducible clonus (Kaplan and Sadock 2024). The recurring anchors, clonus, agitation, diaphoresis, tremor and hyperreflexia, are why clonus and hyperreflexia are the exam discriminators. **The older Sternbach criteria.** The **Sternbach criteria** (Sternbach 1991) are the original, broader rule: a recent addition or dose increase of a serotonergic agent plus at least three of a list of features (agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhoea, incoordination, fever, mental-state change), with other causes and a recent neuroleptic excluded. Sternbach is more sensitive but less specific than Hunter.

TRAP **Treating serotonin syndrome as a diagnosis of exclusion only.** It is a clinical diagnosis anchored on clonus in a patient on a serotonergic drug; there is no confirmatory blood test, so waiting for one wastes time.

8.4 Management: stop the drug, support, benzodiazepines, cyproheptadine

The first and most important step. Stop all serotonergic agents immediately; if a 5-HT syndrome develops, all serotonergic medication should be withdrawn at once (Shorter Oxford 2018). **Supportive care.** Give supportive care with intravenous fluids, continuous monitoring and active **cooling** for hyperthermia, which is the feature that kills; the wider acute emergency frame, aggressive cooling, sedation and the management of severe hyperthermia, is set out in the Perinatal/women's mental health and emergency psychiatry notes. **Benzodiazepines.** Use a benzodiazepine (for example lorazepam or diazepam) to control agitation, tremor and the neuromuscular hyperactivity and to reduce the hyperadrenergic state. **The specific antidote.** In moderate-to-severe cases give cyproheptadine, a 5-HT2A antagonist, as the serotonin-antagonist antidote (Maudsley 2021, Kaplan and Sadock 2024); it is given orally, a common regimen being an initial 12 mg then 2 mg every two hours if symptoms continue, to a ceiling around 32 mg in 24 hours. Most cases resolve within about 24 hours of stopping the trigger and starting supportive care.

WORKED EXAMPLE

A patient on phenelzine is inadvertently started on tramadol for back pain and within hours becomes agitated and sweaty, with a temperature of 39 degrees Celsius, dilated pupils, a tachycardia of 130, brisk reflexes and sustained ankle clonus. This is serotonin syndrome from an MAOI-serotonergic combination. Stop both drugs at once, cool the patient and give intravenous fluids, sedate with a benzodiazepine, and give cyproheptadine as the serotonin antagonist. The Hunter criteria are met by the spontaneous clonus alone.

GOOD TO REMEMBER

- **Serotonin syndrome (the feature):** serotonergic excess, usually a combination and most dangerously an MAOI plus a serotonergic drug; the triad is neuromuscular excitation (clonus, hyperreflexia, tremor, rigidity), autonomic instability (hyperthermia, tachycardia, diaphoresis, mydriasis, hyperactive bowel sounds) and altered mental state (agitation); onset is rapid over hours.
- **Hunter criteria (the discriminator):** in a patient on a serotonergic agent, diagnose on clonus (spontaneous, inducible or ocular) with agitation or diaphoresis, or tremor plus hyperreflexia; clonus and hyperreflexia are the signs that separate it from NMS.
- **Cyproheptadine (the first management after stopping the drug):** a 5-HT2A antagonist used as the serotonin-antagonist antidote in moderate-to-severe cases; the management sequence is stop the serotonergic agents, support and cool, benzodiazepine for agitation, then cyproheptadine.

8.5 The differential from neuroleptic malignant syndrome

Why they are confused. Serotonin syndrome and neuroleptic malignant syndrome share hyperthermia, muscular rigidity, autonomic instability and altered consciousness, and 5-HT neurotoxicity is occasionally confused with NMS at the bedside (Shorter Oxford 2018, Maudsley

2021). What separates them is the **trigger, the neuromuscular sign and the tempo**. Serotonin syndrome follows a serotonergic drug, comes on **rapidly over hours**, and is defined by **clonus** and **hyperreflexia** with hyperactive bowel sounds and mydriasis. Neuroleptic malignant syndrome follows a **dopamine-blocker** (an antipsychotic or another dopamine antagonist such as metoclopramide), comes on **slowly over days**, and is defined by **lead-pipe rigidity** with **hyporeflexia**, normal-to-sluggish bowel sounds, and a marked rise in creatine kinase, often above 1000 units per litre (Maudsley 2021). The one discriminator to carry into the exam is **clonus and hyperreflexia (serotonin syndrome) versus lead-pipe rigidity and hyporeflexia (NMS).**

FEATURE	SEROTONIN SYNDROME	NEUROLEPTIC MALIGNANT SYNDROME
Trigger	a serotonergic drug (SSRI, SNRI, MAOI combination, tramadol)	a dopamine-blocker (antipsychotic, metoclopramide)
Onset / tempo	rapid, over hours	slow, over days
Neuromuscular sign (the discriminator)	**clonus and hyperreflexia**	**lead-pipe rigidity and hyporeflexia**
Pupils	mydriasis	normal
Bowel sounds	hyperactive, diarrhoea	normal or reduced
Creatine kinase	usually mild rise	marked rise, often above 1000 units per litre
Resolution	fast, often within about 24 hours of stopping the drug	slow, over days to weeks
Specific agent	cyproheptadine (5-HT2A antagonist)	bromocriptine and dantrolene

The serotonin-syndrome versus NMS grid: clonus and hyperreflexia against lead-pipe rigidity is the one discriminator (Shorter Oxford 2018, Maudsley 2021).

RULE **Clonus and hyperreflexia point to serotonin syndrome; lead-pipe rigidity points to NMS.** A serotonergic trigger over hours with brisk clonus is serotonin syndrome; a dopamine-blocker over days with lead-pipe rigidity and a high CK is NMS.

TRAP **Missing serotonin syndrome after an MAOI-serotonergic combination, or confusing it with NMS.** The commonest errors are failing to recognise 5-HT toxicity when an MAOI meets a serotonergic drug, and mislabelling clonus-with-hyperreflexia as NMS.

INDIA

Tramadol and pethidine are widely and casually co-prescribed for pain in Indian practice, so the highest-risk everyday scenario is a patient on an antidepressant (or, worse, an MAOI) who is given tramadol for a musculoskeletal complaint. Cyproheptadine is freely available in India as an oral antihistamine (commonly stocked as Ciplactin or Practin), which makes the antidote easy to obtain when moderate-to-severe serotonin syndrome is recognised.

GOOD TO REMEMBER

- **The one discriminator:** clonus and hyperreflexia mean serotonin syndrome; lead-pipe rigidity and hyporeflexia mean neuroleptic malignant syndrome.
- **Serotonin syndrome:** serotonergic trigger, rapid onset over hours, clonus, hyperreflexia, mydriasis, hyperactive bowel sounds, usually mild CK rise; first step stop the drug, then support/cool, benzodiazepine, cyproheptadine.
- **Neuroleptic malignant syndrome:** dopamine-blocker trigger, slow onset over days, lead-pipe rigidity, hyporeflexia, marked CK rise (often above 1000 units per litre); stop the antipsychotic, support, benzodiazepine, then bromocriptine and dantrolene.

HOLD THIS

Clonus and hyperreflexia after a serotonergic drug (rapid, over hours) is serotonin syndrome; lead-pipe rigidity and hyporeflexia after a dopamine-blocker (slow, over days) with a high CK is neuroleptic malignant syndrome, and the first step in serotonin syndrome is to stop the serotonergic agents and give cyproheptadine.

9 . Antidepressant discontinuation syndrome

When an antidepressant taken continuously for at least a few weeks is stopped or reduced, a recognisable cluster of somatic and psychological symptoms can emerge within a few days. This is **antidepressant discontinuation syndrome**, and the examiner tests three things: that you can name the cluster (the **finish** mnemonic), that you can predict who is at risk (the short-half-life agents), and that you can tell it apart from a true relapse of depression. Getting the last point wrong is the classic clinical error, because the fix for discontinuation is a slower taper and reassurance, whereas the fix for relapse is restarting treatment.

The framing that scores. Discontinuation symptoms are a pharmacological withdrawal phenomenon from an abrupt fall in synaptic serotonin availability, not a sign of addiction or drug dependence: there is no craving, no compulsive use and no dose escalation, and the syndrome is self-limiting. The organising fact is that onset, severity and duration all track the **half-life** of the agent, so paroxetine and venlafaxine are the worst offenders and fluoxetine the least (Maudsley 2021; Kaplan 2024). The receptor and cytochrome background sits in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the perinatal analogue is cross-referred to the Perinatal/women's mental health and emergency psychiatry notes.

9.1 The syndrome and the FINISH cluster

The setup. The patient has usually been on the antidepressant for a month or more, and symptoms begin within a few days of stopping, halving the dose, or even missing doses in a poor adherer (Kaplan 2024). The symptoms are typically mild and **self-limiting over one to two weeks**, though for some patients and some agents they last longer.

The cluster. The high-yield handle is **finish** (use "finish"): **F**lu-like symptoms (lethargy, myalgia, sweating), **I**nsomnia (often with vivid dreams), **N**ausea, **I**mbalance (dizziness, lightheadedness, vertigo), **S**ensory disturbances (paraesthesiae and the classic **electric-shock** or "brain-zap"

sensations), and **H**yperarousal (anxiety, irritability, agitation). The sensory "brain zaps", brief intracranial electric-shock feelings often triggered by eye movement, are close to pathognomonic and rarely feature in a depressive relapse (Maudsley 2021; Kaplan 2024).

MNEMONIC

FINISH

Flu-like, Insomnia, Nausea, Imbalance, Sensory disturbances (the electric-shock "brain zaps"), Hyperarousal/anxiety. The six-symptom cluster of antidepressant discontinuation syndrome, coming on within days of stopping and settling over one to two weeks.

RULE **Taper antidepressants slowly, especially the short-half-life agents.** A gradual reduction over weeks, or a switch to fluoxetine to taper, prevents most discontinuation symptoms.

9.2 Risk factors: half-life drives everything

The agent. Onset and severity correlate inversely with half-life. Paroxetine (Pexep) and venlafaxine (Venlor) are the worst because both have short half-lives with no meaningful active metabolite, and paroxetine adds a high serotonin-transporter affinity and anticholinergic rebound; short-half-life agents produce symptoms within a day or two of stopping (Maudsley 2021). Fluoxetine (Fludac) is the least likely to cause a discontinuation syndrome because its parent drug (2 to 3 days) and its active metabolite norfluoxetine (about 2 weeks) mean the drug effectively **self-tapers**; when symptoms do occur they may be delayed by 2 to 6 weeks (Maudsley 2021).

The other two levers. A **longer duration** of treatment and, above all, **abrupt cessation** raise the risk; a higher dose and a rapid taper method compound it (Maudsley 2021). Discontinuation is reported to some degree with every antidepressant class, including SNRIs, TCAs and MAOIs, not just the SSRIs.

AGENT (INDIAN BRAND)	HALF-LIFE	DISCONTINUATION RISK
Paroxetine (Pexep)	Short (~21 h), no active metabolite	**Worst: fast onset, prominent brain-zaps**
Venlafaxine (Venlor)	Short (~5 h; ODV ~11 h)	**Worst: notoriously severe, dizziness prominent**
Most other SSRIs/SNRIs	Intermediate	Moderate, dose- and taper-dependent
Fluoxetine (Fludac)	Long (norfluoxetine ~2 wk)	**Least: self-tapers; onset may be delayed**

Discontinuation risk tracks half-life inversely: shortest-half-life agents (paroxetine, venlafaxine) are the worst, the long-half-life fluoxetine the least (Maudsley 2021; Kaplan 2024).

9.3 Distinguishing discontinuation from relapse, and management

The discriminator. Two features separate **discontinuation** (use "discontinuation") from a depressive relapse. First, **timing**: discontinuation symptoms appear fast, within a few days of

stopping or reducing, and resolve over one to two weeks, whereas a genuine relapse builds gradually over weeks and does not remit on its own. Second, the **somatic and sensory quality**: the flu-like malaise, imbalance and electric-shock paraesthesiae of discontinuation are not part of a depressive syndrome, and a fast, dramatic improvement within hours of a single reinstated dose points firmly to discontinuation rather than relapse (Maudsley 2021; Kaplan 2024).

Management. The core intervention is a slow **taper** (use "taper") over weeks (in practice, weeks to months for a short-half-life agent, with hyperbolic small reductions near the bottom of the dose range), plus reassurance that the symptoms are self-limiting and are not a sign of addiction. If symptoms are already troublesome, reinstate the original antidepressant (or switch to fluoxetine and taper from there, exploiting its long half-life) until stable, then reduce more gradually. Reassurance and forewarning at the outset prevent much of the distress (Kaplan 2024).

TRAP **Mistaking discontinuation symptoms for a depressive relapse.** Restarting or escalating on the wrong call keeps the patient on a drug they were coming off; use timing and the somatic/sensory quality to tell them apart.

9.4 The perinatal analogue: neonatal adaptation syndrome

A related phenomenon follows late-pregnancy antidepressant exposure. The neonate, having been exposed transplacentally, can show a self-limiting **neonatal adaptation syndrome** after delivery, with jitteriness, irritability, feeding and respiratory difficulty and, occasionally, tremor, that mirrors an adult discontinuation picture and settles within days. The examiner's point is that abrupt withdrawal of the antidepressant before delivery is usually the wrong response, because it exposes the mother to relapse and postpartum depression; the fuller perinatal handling belongs to the Perinatal/women's mental health and emergency psychiatry notes.

1 to 2 wk	1 to 2 days	2 to 6 wk
TYPICAL DURATION, SELF-LIMITING	ONSET WITH SHORT-HALF-LIFE AGENTS	DELAYED ONSET WITH FLUOXETINE

HOLD THIS

Discontinuation symptoms come on within days, are captured by FINISH (with the "brain-zap" as the near-pathognomonic clue), are worst with paroxetine and venlafaxine and least with fluoxetine, and are treated by a slower taper and reassurance, not by treating a relapse.

GOOD TO REMEMBER

- **The cluster (FINISH):** Flu-like, Insomnia, Nausea, Imbalance, Sensory (electric-shock "brain zaps"), Hyperarousal, within days of stopping, self-limiting over **1 to 2 weeks**.
- **The discriminator:** fast onset plus somatic/sensory quality (brain-zaps, imbalance) mark discontinuation; a slow-building, purely mood picture marks relapse.
- **Worst agents:** paroxetine (Pexep) and venlafaxine (Venlor), short half-lives; fluoxetine (Fludac) least because it self-tapers.
- **First step:** taper slowly (or switch to fluoxetine to taper) and reassure; reinstate the agent if symptoms are severe. It is not addiction.

10 . Ketamine and esketamine

This is the glutamatergic corner of the antidepressant map, and it is a high-yield one because it breaks two things every resident is taught about depression. The first is the **monoamine model**: ketamine and esketamine do not touch the serotonin, noradrenaline or dopamine pumps as their primary act; they antagonise the glutamate NMDA (nmda) receptor. The second is the **therapeutic lag**: where a monoamine antidepressant is said to take weeks, these **rapid-acting** agents lift depressive symptoms and suicidal ideation within hours (K&S 2024, Maudsley 2021). That combination, a novel target and a rapid onset, is exactly what examiners probe, alongside the safety scaffolding the rapidity forces on you.

Framing. Treat this topic as two agents on one mechanism: racemic ketamine (intravenous, off-label) and esketamine, the S-enantiomer (intranasal, brand Spravato, licensed). For the receptor systems and the wider glutamate story, see the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; for where these agents sit in the treatment-resistant depression ladder and the CANMAT algorithm, see the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; for the acute-suicidality assessment that flanks the licensed indication, see the Somatic-symptom, sexual, impulse-control disorders and suicide notes. Two facts are CRITICAL and verified below: the licensed indication is add-on esketamine for treatment-resistant depression (and for major depression with acute suicidal ideation), and it must be given under observation for dissociation and blood pressure.

10.1 The mechanism: NMDA antagonism, an AMPA burst and synaptogenesis

Block the brake, trigger a glutamate surge, grow synapses. Ketamine is a non-competitive (uncompetitive) antagonist at the NMDA receptor (K&S 2024, Maudsley 2021). The current model is a disinhibition cascade: NMDA blockade falls preferentially on GABAergic inhibitory interneurons, which normally suppress glutamate output; taking that brake off produces an acute cortical **glutamate surge** onto the pyramidal neuron (K&S 2024, Maudsley 2021). That surge activates postsynaptic **AMPA** (ampa) receptors, and the AMPA-throughput step drives brain-derived neurotrophic factor (BDNF) release, TrkB and mTOR activation, and downstream **synaptogenesis** and synaptic potentiation (K&S 2024). Because the antidepressant effect is carried by rapid neuroplasticity rather than by slow receptor down-regulation, it appears within hours, which is the direct **glutamatergic** reframing of depression: a disorder of impaired synaptic plasticity that a glutamate modulator can rapidly reverse.

RULE **NMDA off, AMPA on.** Ketamine works by antagonising NMDA receptors on inhibitory interneurons, which disinhibits a glutamate surge onto AMPA receptors and drives synaptogenesis; that plasticity, not monoamine reuptake block, is why the effect is rapid.

TRAP **Calling it a monoamine drug.** Ketamine has weak serotonergic, dopaminergic and opioid actions, but its rapid antidepressant effect is glutamatergic; framing it as "just another reuptake inhibitor" misses both the mechanism and the therapeutic-lag contrast the examiner wants.

10.2 The two agents: racemic ketamine and the S-enantiomer esketamine

Same target, different enantiomer, different regulatory status. Ketamine is a racemic mixture of two mirror-image enantiomers, (S)-ketamine and (R)-ketamine (arketamine); the S-enantiomer, esketamine, binds the NMDA receptor with roughly four times the affinity of the R-enantiomer (K&S 2024). Racemic ketamine is given **intravenously** and remains an **off-label** treatment for depression, drawing on its long licence as a dissociative anaesthetic (K&S 2024, Maudsley 2021). Esketamine was developed as an **intranasal** spray (brand Spravato) and is the licensed molecule (K&S 2024). A point of contrast worth holding: because esketamine is the more potent NMDA binder, it was the enantiomer taken to licence, yet head-to-head evidence suggests intravenous racemate is possibly at least as effective as intranasal esketamine (Maudsley 2021).

Ketamine (racemic)

50:50 S and R enantiomer mixture; intravenous, off-label for depression, anaesthetic licence.

Esketamine

the S-enantiomer, four-fold higher NMDA affinity; intranasal, brand Spravato, the licensed antidepressant.

Arketamine

the R-enantiomer; lower NMDA affinity, still investigational for depression.

10.3 The licensed indication and the treatment-resistant depression context

Add-on esketamine for treatment-resistant depression, and for major depression with acute suicidal ideation. Intranasal esketamine (Spravato) is licensed as an add-on to an oral antidepressant for **treatment-resistant depression**, defined by failure of at least two adequate antidepressant trials in the current episode, and separately for **major depression with acute suicidal ideation or behaviour** (K&S 2024, Maudsley 2021). It is not a monotherapy: the licence is as an add-on to an SSRI or SNRI. Racemic ketamine itself carries no depression licence and is used off-label (K&S 2024). At guideline level, CANMAT places **add-on intranasal esketamine** as a second-line adjunct for patients failing at least two adequate antidepressant trials, and **add-on intravenous racemic ketamine** as a second-line adjunct for a rapid antidepressant effect including rapid reduction of suicidal ideation, both with blood-pressure and dissociation monitoring (CANMAT 2023). Non-esketamine racemic ketamine by oral, intramuscular or intranasal route is reserved third-line given variable protocols (CANMAT 2023).

The other guidelines. The **Indian Psychiatric Society** depression guideline (Gautam et al.) endorses second-generation antidepressants first-line and reserves novel and specialist strategies for later steps; a specific IPS guidelines agent-level first-line row for esketamine could not be confirmed from the parsed reference library and is therefore not stated. The BAP TRD framework favours augmenting with quetiapine, aripiprazole or lithium first-line for treatment-resistant depression rather than naming esketamine as a first step (BAP). NICE recognises nasal esketamine as a licensed treatment for treatment-resistant major depression but, as of the parsed edition, had not approved it for routine NHS use in the UK, while it is used elsewhere (Maudsley 2021).

2	within hours	2
FAILED ANTIDEPRESSANT TRIALS DEFINING TRD	ONSET OF ANTIDEPRESSANT EFFECT	POST-DOSE OBSERVATION (HOURS)

10.4 The dosing schedule and why the benefit needs maintenance

Induction twice weekly, then step down; the effect is transient and must be scheduled. The intranasal esketamine dose is either **56 mg** or **84 mg** (K&S 2024). In the **induction phase** (weeks 1 to 4) dosing is **twice weekly**, starting at 56 mg after the first administration, titratable up to 84 mg as indicated. In the **maintenance phase** the schedule reduces to **once weekly for 4 weeks**, then continues once weekly or steps down to once every 2 weeks (K&S 2024). Intravenous racemic ketamine in the antidepressant setting is **0.5 mg/kg** infused over **40 minutes**, up to twice weekly, and not exceeding 6 weeks (K&S 2024, Maudsley 2021).

Why a schedule at all. A single ketamine infusion produces a rapid response that peaks around 24 hours but is short-lived: improvement typically lasts about 3 days and symptoms return toward baseline by around 7 days (K&S 2024). That transience is the whole reason for a repeated-dose induction and then a maintenance schedule; the drug is a bridge whose effect decays, not a one-off cure. This is the pharmacological basis of the topic RULE below.

WORKED EXAMPLE

A patient with treatment-resistant depression, already on an adequately dosed SSRI after two prior failed trials, is started on intranasal esketamine 56 mg twice weekly for the 4-week induction, titrated to 84 mg for tolerability, then moved to weekly and later fortnightly dosing while the oral antidepressant continues. Each session is given in the clinic with 2 hours of post-dose observation. The rapid lift in weeks 1 to 2 is real, but the oral antidepressant and the maintenance schedule are what hold it (K&S 2024).

10.5 Adverse effects: dissociation, blood pressure, sedation and abuse potential

The neuropsychiatric signature is dissociation. The hallmark adverse effect of ketamine and esketamine is dissociation and perceptual change: perceptual disturbances, vivid or abnormal sensory experiences, derealisation and depersonalisation, reported by over 70 percent of patients with intravenous ketamine (K&S 2024). These are experienced at the time of administration, are transient, and typically resolve within about 2 hours (K&S 2024). Related short-term effects include sedation, dizziness, confusion, memory disturbance and, particularly in those with a schizophrenia history, **psychotomimetic** (nondissociative psychotic) symptoms. The commonest intranasal esketamine adverse events are dissociation, dizziness, nausea, sedation, vertigo and increased blood pressure (K&S 2024).

The cardiovascular effect is a transient blood-pressure rise. At antidepressant doses both agents cause **transient hypertension and tachycardia** (K&S 2024). Rarely, hypotension, bradycardia, arrhythmias and cardiac decompensation are reported. Both are **contraindicated in uncontrolled significant hypertension**, and esketamine additionally in aneurysmal vascular disease, arteriovenous malformation and intracerebral haemorrhage (K&S 2024). Gastrointestinal nausea and vomiting are common enough to warrant antiemetic readiness.

Abuse potential and other cautions. Ketamine is a Schedule III controlled substance with recognised recreational misuse (the high-dose "K-hole"), and repeated use can produce tolerance and dependence (K&S 2024). Long-term chronic use is associated with a ketamine-induced **cystitis** (dysuria, frequency, haematuria, reduced bladder capacity), which is why longer-term ketamine or esketamine use attracts periodic urinalysis for cystitis (K&S 2024, CANMAT 2023). Esketamine carries a boxed warning for sedation, dissociation, abuse and misuse potential, availability only through the REMS programme, and increased suicidal thoughts in young people. Concomitant benzodiazepines or lamotrigine may attenuate the antidepressant response, and combining ketamine with opioids or other CNS depressants risks profound sedation and respiratory depression (K&S 2024).

TRAP **Giving it to a hypertensive patient unmonitored.** Both agents raise blood pressure transiently and are contraindicated in uncontrolled significant hypertension; administering without a baseline check and post-dose monitoring, or in a psychotic-prone patient without weighing the psychotomimetic risk, is the classic error.

10.6 The monitoring: in-clinic administration and the REMS-style observation

Because it dissociates and raises blood pressure, it is given under observation. The rapidity and the dissociative and cardiovascular effects force a supervised model. In the United States esketamine is dispensed and administered only in a certified, medically supervised setting under a **risk evaluation and mitigation strategy** (REMS), with the patient monitored for at least **2 hours** post-administration (K&S 2024). Practically this means the drug is self-sprayed under direct observation of a healthcare provider, with blood pressure checked before and after, and the patient not driving on the day of dosing or until the following morning (K&S 2024). For intravenous racemic ketamine, the Maudsley advises a pretreatment physical examination with baseline blood pressure and a pretreatment ECG, blood-pressure monitoring before and after the infusion, and observation during and for at least 1 hour after the infusion by a clinician trained in life support (Maudsley 2021). This is the REMS-style monitoring an examiner expects you to name.

PEARL

The monitoring headline maps to the two dangerous effects: observe for **dissociation** (neuropsychiatric) and for the **blood-pressure rise** (cardiovascular). Both are transient and settle within about 2 hours, which is exactly why the observation window is 2 hours for intranasal esketamine (K&S 2024).

RULE **Esketamine works within hours for treatment-resistant depression but must be given under observation for dissociation and blood pressure.** In-clinic administration, blood pressure before and after, and at least 2 hours of post-dose observation.

10.7 India, availability and cost

INDIA

Racemic ketamine is widely available in India as an injectable anaesthetic and is a controlled drug; its use for depression is off-label and confined to specialist and academic settings. Intranasal esketamine (Spravato) is a high-cost, cold-chain, REMS-gated product, and a specific Indian brand or routine Indian availability could not be confirmed from the parsed reference library, so no Indian brand is asserted here and the international brand Spravato is named only as the licensed innovator product. For Indian postgraduate answers, the practical position is that these are rapid-acting glutamatergic agents used in tertiary and research centres rather than routine practice, that the guideline to cite first is the Indian Psychiatric Society depression guideline (Gautam et al.), and that where a rapid response to severe or suicidal depression is needed in Indian teaching hospitals, ECT remains the widely available and heavily used option (see the ECT and neurostimulation notes).

MNEMONIC

"RAPID KETAMINE": Receptor NMDA, AMPA burst, Plasticity, In-clinic, Dissociation and blood pressure, Keeps needing repeats.

Receptor target is NMDA; the effect runs through an AMPA burst driving synaptic Plasticity; it is given In-clinic under observation; watch Dissociation and the blood-pressure rise; and because the benefit is transient it Keeps needing repeats on a maintenance schedule.

HOLD THIS

Esketamine (S-ketamine, intranasal, Spravato) is an NMDA antagonist licensed as an add-on to an oral antidepressant for treatment-resistant depression and for major depression with acute suicidal ideation; it works within hours, dose is 56 or 84 mg twice weekly at induction then stepped down, and it must be given in-clinic with blood-pressure checks and at least 2 hours of post-dose observation for dissociation.

GOOD TO REMEMBER

- **Ketamine, mechanism:** non-competitive NMDA-receptor antagonist producing a glutamate surge onto AMPA receptors and rapid synaptogenesis; a glutamatergic, not monoamine, antidepressant.
- **Ketamine, signature effect and one to hold:** dissociation and a transient blood-pressure rise, with abuse potential and chronic-use cystitis; racemic, intravenous, off-label, 0.5 mg/kg over 40 minutes, up to twice weekly.
- **Esketamine, mechanism:** the S-enantiomer with four-fold higher NMDA affinity, intranasal spray (brand Spravato).
- **Esketamine, indication and one to hold:** licensed add-on to an oral antidepressant for treatment-resistant depression and for major depression with acute suicidal ideation; 56 or 84 mg, twice weekly induction then stepped down, given under REMS-style observation with at least 2 hours of post-dose monitoring for dissociation and blood pressure.
- **The transience rule:** the response is rapid but short-lived (peaks about 24 hours, fades by about 7 days after a single dose), so it is a bridge needing a maintenance schedule and an ongoing oral antidepressant, not a cure.

11 . Choosing an antidepressant

Once the diagnosis of a depressive episode is settled and pharmacotherapy is indicated, the next decision the examiner tests is not *whether* to prescribe but *which* agent, and the reasoning behind it. **Choosing an antidepressant** is a selection topic, and the single organising principle the board rewards is that the first-line antidepressants are broadly equal in antidepressant efficacy, so the choice is driven not by presumed potency but by the adverse-effect profile, the **comorbidity**, past response, drug interactions, safety in overdose and cost (Kaplan & Sadock 2024; Maudsley 2021). This topic teaches **antidepressant selection** in clinical practice as a guideline-anchored algorithm; the pharmacology of each agent lives in its own topic and the deep treatment-resistance ladder is the treatment-resistance topic.

Ground the algorithm in the guidelines. Lead with **CANMAT**: the Canadian Network for Mood and Anxiety Treatments recommends a second-generation antidepressant as the first-line pharmacological treatment for major depression, individualising the choice to patient and medication factors under measurement-based monitoring (CANMAT 2016). Then state the **Indian Psychiatric Society** position, and what NICE and the BAP recommend. Every dose, interval and first-line recommendation below is verified against the CANMAT and IPS guideline rows and the Maudsley (CANMAT 2016; IPS 2017; Maudsley 2021).

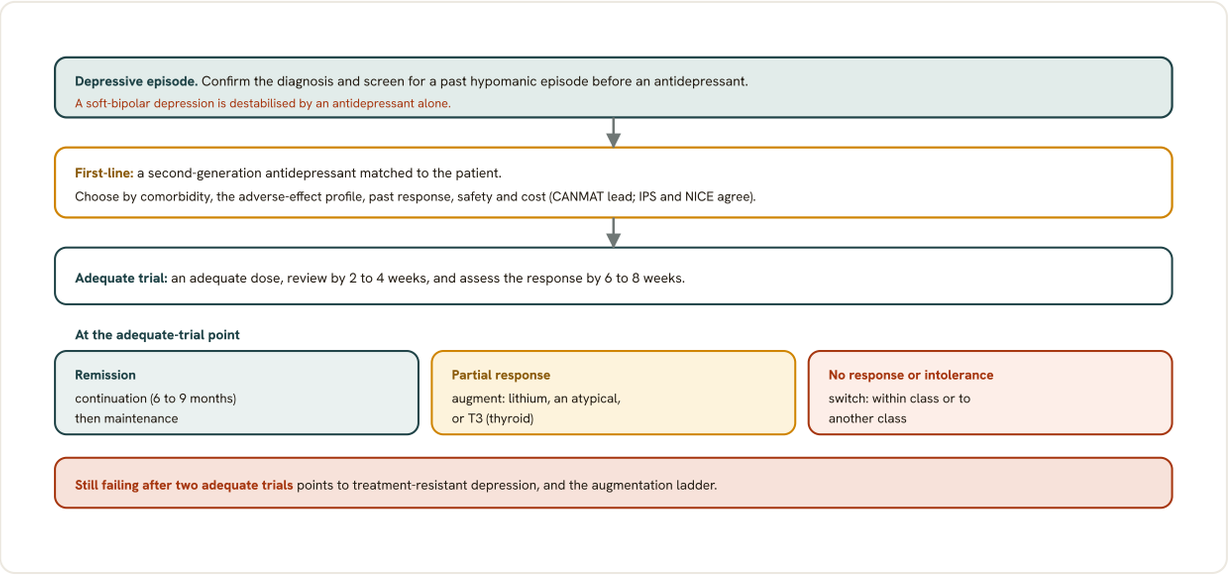

Fig 12.5 Choosing and sequencing an antidepressant. After confirming the diagnosis and screening for past hypomania, choose a second-generation antidepressant matched to the patient (the first-line agents are broadly equal in efficacy, so comorbidity and the adverse-effect profile drive the choice). Run an adequate trial, then act on the response: continue a remission, augment a partial response, switch a non-response. Two failed adequate trials define treatment resistance.

11.1 The governing principle: equal efficacy, so choose by profile

Efficacy is broadly equal. Head-to-head, no first-line antidepressant is convincingly more effective than another for the average patient with major depression, so the whole art of **choosing an antidepressant** is matching the drug to the individual patient rather than ranking drugs by strength (Kaplan & Sadock 2024; Maudsley 2021). A handful of agents (escitalopram, sertraline, venlafaxine, mirtazapine) carry a modest efficacy edge in network meta-analyses and

are worth preferring where maximising response is paramount, but this edge is small and never overrides tolerability.

So the choice is driven by six things. The adverse-effect and tolerability profile; the **comorbidity** (a coexisting condition the drug can help or harm); the patient's past response and any family response; drug interactions with existing medication; safety in overdose; and cost and availability (Kaplan & Sadock 2024; Maudsley 2021). Hold these six as the answer to almost any "which antidepressant and why" viva.

RULE **Choose the antidepressant by the adverse-effect and comorbidity match, not by presumed potency.** First-line agents are broadly equal in efficacy; the fit to the patient is what differs.

11.2 The CANMAT first-line list (lead guideline)

Second-generation antidepressants, first-line. CANMAT names the following as Level-1 first-line agents for major depression, all broadly equal and chosen by profile (CANMAT 2016): the SSRIs, the SNRIs, mirtazapine, bupropion, vortioxetine and agomelatine. The tricyclics and irreversible MAOIs are held back to second and third line because of their adverse-effect burden and danger in overdose.

CANMAT FIRST-LINE AGENT (INDIAN BRAND)	CLASS	DOSE (MG/DAY)	PROFILE NOTE THAT DRIVES SELECTION
Escitalopram (Nexito, S-Citadep)	SSRI	**10 to 20**	Cleanest, fewest interactions; dose-dependent QTc ceiling
Sertraline (Serta, Daxid)	SSRI	50 to 200	Broadest first choice; safe in pregnancy and post-MI
Fluoxetine (Fludac)	SSRI	20 to 60	Long half-life, activating, self-tapering
Paroxetine (Pexep)	SSRI	20 to 50	Anticholinergic, worst discontinuation; avoid in pregnancy
Venlafaxine (Venlor)	SNRI	**75 to 225**	Efficacy edge; monitor blood pressure at higher dose
Duloxetine (Duzela)	SNRI	60	First choice when depression coexists with neuropathic pain
Mirtazapine (Mirtaz)	NaSSA	15 to 45	Sedating, promotes appetite; for insomnia and weight loss
Bupropion (Bupron)	NDRI	150 to 300	No sexual dysfunction, no weight gain, activating; lowers seizure threshold

CANMAT FIRST-LINE AGENT (INDIAN BRAND)	CLASS	DOSE (MG/DAY)	PROFILE NOTE THAT DRIVES SELECTION
Vortioxetine (Vortioxa)	Multimodal	10 to 20	Low sexual dysfunction; possible pro-cognitive benefit
Agomelatine	Melatonergic	25 to 50	For sleep disturbance; monitor liver function tests

The CANMAT 2016 Level-1 first-line antidepressants with verified adult dose ranges and the one profile feature that drives selection; the Indian brand leads the generic. The highlighted cells are the two workhorse first steps.

GOOD TO REMEMBER

- **Escitalopram (Nexito or S-Citadep):** SSRI, cleanest and fewest interactions, dose-dependent QTc; first-line, **10 to 20 mg/day**.
- **Sertraline (Serta or Daxid):** SSRI, broadest first choice, safe post-MI and in pregnancy; first-line, **50 to 200 mg/day**.
- **Venlafaxine (Venlor):** SNRI, efficacy edge, dose-dependent hypertension; first-line, **75 to 225 mg/day**.
- **Duloxetine (Duzela):** SNRI, dual antidepressant and analgesic action; first-line when pain is comorbid, **60 mg/day**.
- **Mirtazapine (Mirtaz):** NaSSA, sedating and appetite-promoting; first-line for insomnia with weight loss, **15 to 45 mg/day**.
- **Bupropion (Bupron):** NDRI, no sexual dysfunction, activating, lowers seizure threshold; first-line, **150 to 300 mg/day**.

11.3 The Indian Psychiatric Society position

SSRIs first. The **indian psychiatric society** Clinical Practice Guidelines for depression (Gautam et al.) make the SSRIs the first-line antidepressant for major depression given their favourable side-effect and safety profile, with the TCAs, mirtazapine, bupropion and venlafaxine as the other preferred options (IPS 2017). For moderate to severe depression the **ips guidelines** name escitalopram 10 to 20 mg, sertraline 50 to 200 mg or fluoxetine 20 to 60 mg as the initial choice, matching the CANMAT list at guideline level.

The IPS reassessment and next-step rule. The IPS advises reviewing pharmacotherapy response at 4 to 6 weeks; if at least a moderate improvement is not seen, reappraise and adjust, by optimising the dose to the maximum tolerated, switching within class (one SSRI to another), or switching across class to an SNRI such as venlafaxine 75 to 225 mg or duloxetine 60 mg (IPS 2017). After acute-phase response the same dose is continued for a total of 6 to 9 months from initiation to prevent relapse. This IPS position is verified against the guideline rows; where a finer IPS specific cannot be confirmed it is flagged under gaps rather than invented.

INDIA

The IPS first-line choice mirrors CANMAT but is calibrated to Indian practice and cost: escitalopram (Nexito or S-Citadep) and sertraline (Serta or Daxid) are the outpatient workhorses because they are cheap generics, well tolerated, and safe in the medically complex and largely out-of-pocket patient. A month of a generic SSRI costs a small fraction of a single private consultation, which matters for adherence. The TCAs remain in wide use in India for comorbid pain and for cost, but their overdose danger keeps them off first line.

11.4 What NICE and the BAP recommend

NICE. When an antidepressant is used, NICE holds that the SSRIs are generally well tolerated, have a good safety profile and should be the first choice for most people; it warns that the TCAs are dangerous in overdose, with lofepramine having the best safety profile of the class (NICE 2022). NICE does not routinely offer an antidepressant first-line for less severe depression, preferring the least intrusive option such as guided self-help, and reviews symptoms and side effects usually within 2 weeks of starting (within 1 week in those aged 18 to 25 or where there is particular suicide concern).

BAP. The British Association for Psychopharmacology likewise directs, in the absence of special factors, to choose antidepressants that are better tolerated and safer in overdose, so the SSRIs and other newer antidepressants are the first-line choices, reserving older TCAs and MAOIs for when first-line treatment has failed (BAP 2015). Where maximising efficacy is paramount in a more severely ill patient, the BAP lists clomipramine, venlafaxine at 150 mg or more, escitalopram 20 mg, sertraline, amitriptyline or mirtazapine in preference to other agents (BAP 2015).

RULE **Every major guideline puts second-generation antidepressants (led by the SSRIs) first.** CANMAT, the IPS, NICE and the BAP all cite tolerability and overdose safety as the reason.

11.5 Practical matching: fit the agent to the comorbidity

The examinable skill is turning "equal efficacy" into a concrete choice by reading the patient. Match a favourable adverse effect or a coexisting condition to the drug that helps it, and avoid the drug that would harm it.

CLINICAL SITUATION	PREFERRED AGENT	WHY (THE PROFILE MATCH)
Comorbid chronic or neuropathic pain	**An SNRI (duloxetine) or a TCA (amitriptyline)**	Dual serotonin-noradrenaline action treats depression and pain with one drug
Insomnia and weight loss	**Mirtazapine**	H1-antihistamine sedation aids sleep; appetite stimulation restores weight
Fatigue or sexual dysfunction	**Bupropion**	Activating dopaminergic agent; no sexual dysfunction, no weight gain

CLINICAL SITUATION	PREFERRED AGENT	WHY (THE PROFILE MATCH)
Cardiac disease or overdose-risk patient	Avoid a TCA; use an SSRI (sertraline)	TCAs are cardiotoxic and lethal in overdose; SSRIs are safe post-MI
The elderly	An SSRI, watch hyponatraemia	Avoid TCA anticholinergic and orthostatic load; SSRIs risk SIADH/hyponatraemia
A woman planning pregnancy	Sertraline	Lowest infant exposure in breastfeeding; avoid paroxetine

The high-yield comorbidity-and-adverse-effect matches for antidepressant selection (Maudsley 2021; CANMAT 2016; IPS 2017). Read the situation, pick the agent whose profile fits, and avoid the agent whose profile harms.

Turn a side effect into an advantage. The sedating, weight-gaining mirtazapine is a liability in an obese sleeper but an asset in the thin, anorexic insomniac; the activating bupropion is wrong for the anxious patient but ideal for the fatigued patient with SSRI-induced sexual dysfunction. This inversion (one drug's adverse effect is another patient's indication) is the crux of the topic.

WORKED EXAMPLE

A 58-year-old man with diabetic peripheral neuropathy presents with a moderate depressive episode, poor sleep and low appetite. Rather than a default SSRI, duloxetine (Duzela) 60 mg is the pragmatic choice: one drug treats both the depression and the neuropathic pain, sparing a second prescription. Had the dominant problem instead been early insomnia with marked weight loss and no pain, mirtazapine (Mirtaz) 15 to 45 mg would be the better fit, using its sedation and appetite stimulation as therapeutic, not merely tolerated, effects.

PEARL

Ask two questions before writing the prescription: "what else does this patient have that a drug could help?" and "what must I not make worse?" The first points you to duloxetine for pain, mirtazapine for insomnia and weight loss, or bupropion for fatigue; the second steers you away from a TCA in cardiac or overdose risk and away from paroxetine in a woman planning pregnancy.

11.6 Safety in overdose and interactions as tie-breakers

Safety in overdose. Because depressed patients are at risk of self-harm, the toxicity of the drug in overdose is a genuine selection factor. The SSRIs and other second-generation agents are far safer in overdose than the tricyclic antidepressants, whose overdose is cardiotoxic (QRS widening, arrhythmia), proconvulsant and frequently fatal; this is a principal reason the guidelines put SSRIs first and hold TCAs back (NICE 2022; BAP 2015). Where a TCA is unavoidable, lofepramine is the least dangerous in overdose (NICE 2022).

Interactions. Existing medication narrows the field. In a polypharmacy or medically complex patient, prefer the clean agents (escitalopram, sertraline) over the potent cytochrome inhibitors (fluoxetine, paroxetine and fluvoxamine); never co-prescribe with an MAOI. The receptor and CYP metabolism that underlie these interactions belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

TRAP **Reaching for a TCA in a patient with cardiac disease or overdose risk.** TCAs are cardiotoxic and lethal in overdose; an SSRI is the safer first-line choice.

11.7 The reassessment rule: review by 2 to 4 weeks

Review early. Having chosen the agent, the guidelines converge on reviewing the patient by 2 to 4 weeks. The BAP directs an initial review every 1 to 2 weeks after starting, noting that a lack of significant improvement by 2 to 4 weeks substantially reduces the chance of eventual sustained response (BAP 2015). CANMAT frames the same window as measurement-based care: for non-improvers at 2 to 4 weeks, increase the dose if tolerated, and switch if tolerability is the problem, with early improvement defined as roughly a 20 to 30 percent reduction on a depression rating scale (CANMAT 2016).

Then step up or switch. If there is no early improvement trajectory, act: optimise the dose to the maximum tolerated, then switch (within or across class, the outcome is similar) after an adequate trial. The BAP assesses response formally at 4 weeks and again at 6 to 8 weeks, switching or moving to a next-step treatment if there is no trajectory by 4 weeks (BAP 2015). The full next-step and augmentation ladder for the patient who fails an adequate trial is the treatment-resistance topic.

TRAP **Switching too early, or persisting past 4 weeks with no trajectory.** Give an adequate trial before declaring failure, but do not sit on a non-responder beyond 4 weeks hoping it will turn.

2 to 4 wk	4 wk	6 to 9 mo
FIRST REVIEW AFTER STARTING	ACT IF NO IMPROVEMENT TRAJECTORY	CONTINUATION AFTER REMISSION

GOOD TO REMEMBER

- **The selection principle:** first-line antidepressants are equal in efficacy, so choose by adverse effects, comorbidity, past response, interactions, overdose safety and cost.
- **CANMAT first-line:** the SSRIs, SNRIs, mirtazapine, bupropion, vortioxetine and agomelatine, individualised to the patient (CANMAT 2016).
- **Comorbidity match:** pain to an SNRI or TCA, insomnia with weight loss to mirtazapine, fatigue or sexual dysfunction to bupropion, cardiac or overdose risk away from a TCA, the elderly to an SSRI watching hyponatraemia, pregnancy planning to sertraline.
- **Reassessment:** review by 2 to 4 weeks; switch or step up if there is no early improvement trajectory by 4 weeks.

MNEMONIC

PICO-SC

What drives the choice when efficacy is equal: **P**ast response, **I**nteractions, **C**omorbidity, **O**verdose safety, **S**ide-effect profile, **C**ost. Run the list and the "which antidepressant and why" answers itself.

HOLD THIS

First-line antidepressants are broadly equal in efficacy, so choose by the adverse-effect and comorbidity match, not by presumed potency: CANMAT leads with the SSRIs, SNRIs, mirtazapine, bupropion, vortioxetine and agomelatine, the IPS and NICE and the BAP agree the SSRIs come first for tolerability and overdose safety, and you review by 2 to 4 weeks and switch or step up if there is no early improvement trajectory by 4 weeks.

12 . Managing an acute depressive episode: the phases

Managing an **acute depressive episode** is not a drug list, it is a sequence: decide **where** to treat, then work through the **phases of treatment** in order, choosing the mode of treatment each phase asks for. This is the mood-block closer, and a high-yield theory question: the examiner rewards the LOCUS to FOCUS to MODUS spine and the exact phase durations, not a recitation of side effects. The deep drug pharmacology, dosing and adverse-effect profiles are owned by the earlier topics in these notes; the augmentation and treatment-resistance ladder is owned by the treatment-resistance topic. This topic carries the phased plan and the durations.

Lead the guideline answer with CANMAT (CANMAT 2016), then give the Indian Psychiatric Society position, now carried by the 2025 IPS depression update (IPS 2025, Tripathi et al., which supersedes the 2017 Gautam guideline), BAP (BAP 2015) and NICE positions. Across all four the single organising principle the exam tests is one instruction, not two: **treat to remission, then continue at the acute dose.** Response is not remission, and remission is not the end point.

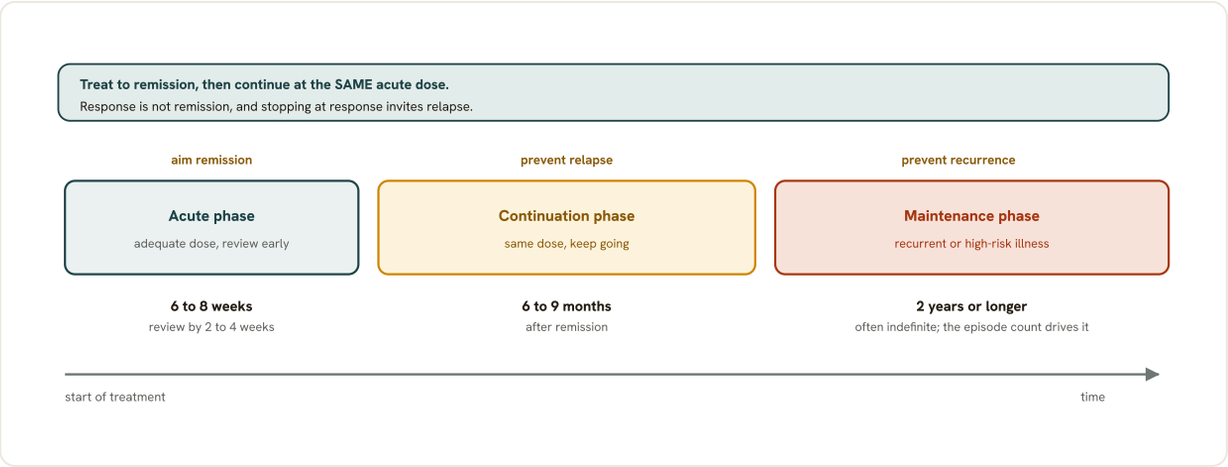

Fig 12.6 The phases and duration of treating an acute depressive episode. The acute phase runs about 6 to 8 weeks to remission, with an early review by 2 to 4 weeks; the continuation phase keeps the same acute dose for 6 to 9 months to prevent relapse; the maintenance phase extends to 2 years or longer, often indefinitely, for recurrent or high-risk depression. The cardinal rule is to treat to remission and continue at the acute dose, never to stop at response.

12.1 LOCUS: where to treat, and when to admit

Outpatient is the default. Most patients with an acute depressive episode are managed in the outpatient or the day care centre setting from the outset. Admission is reserved for a defined set of high-risk situations: **high suicide risk**, depression with **psychotic features**, severe **self-neglect** (not eating or drinking, dehydration), or the need for inpatient-level treatment such as ECT. The full clinical suicide risk assessment and safety planning that set the admission

threshold are owned by the Somatic-symptom, sexual, impulse-control disorders and suicide notes; the ECT technique itself is owned by the ECT and neurostimulation notes. Whatever the locus, care is delivered as **measurement-based care**: CANMAT specifies regular, frequent monitoring of clinical and functional outcomes with a validated scale such as the PHQ-9 or HAM-D, not clinical impression alone (CANMAT 2016; IPS 2017).

RULE **Admit for high suicide risk, psychosis, severe self-neglect, or the need for ECT.** Everything else is outpatient with measurement-based follow-up.

12.2 The ACUTE phase: aim remission, not response

The target of the acute phase is **remission**, the near-complete resolution of symptoms, not merely a partial **response** (conventionally a 50 percent symptom reduction). Stahl frames the whole plan around this: continue treatment until all symptoms are gone, that is remission, because residual symptoms predict relapse (Stahl 2021). Give an **adequate trial at an adequate dose**: a first-line antidepressant titrated to a therapeutic dose and continued for **6 to 8 weeks** before it can be called a failure. Review early: CANMAT and BAP advise reviewing the patient every **1 to 2 weeks** after starting (BAP 2015). Judge response on a trajectory. A lack of significant improvement by **2 to 4 weeks** substantially reduces the chance of eventual sustained response, so for a non-improver at 2 to 4 weeks you increase the dose if tolerated, or switch if tolerability is the problem (CANMAT 2016). BAP frames the same checkpoint as assessing response at 4 weeks and again at **6 to 8 weeks**, switching or stepping up if there is no improvement trajectory by 4 weeks or only minimal improvement by 6 to 8 weeks (BAP 2015). The IPS reappraises at 4 to 6 weeks (IPS 2017).

TRAP **Do not combine two antidepressants at initiation.** CANMAT states this explicitly: start one first-line agent, monitor, then optimise or switch. Combination belongs to the treatment-resistance step, not the start.

12.3 The CONTINUATION phase: protect the remission at the SAME dose

Once remission is achieved, do not stop. The **continuation** phase continues the antidepressant at the **same acute treatment dose** (not a reduced "maintenance" dose) for **6 to 9 months** after symptomatic remission, to prevent early relapse (CANMAT 2016). The IPS is explicit that the dose achieving response is continued and not reduced through the continuation phase, which the 2025 IPS update now sets at **4 to 9 months** (IPS 2025). BAP frames the lower bound as at least 1 year for anyone with an increased relapse risk (BAP 2015); NICE frames it as at least 6 months after symptoms remit (NICE 2022). This is the phase most often failed in practice: the patient feels well at week 8 and stops, and the relapse that follows is a continuation-phase relapse, not a genuinely new episode.

RULE **Continue at the acute dose through continuation; do not drop the dose or stop at response.** Continuation is 6 to 9 months at the same dose after remission (CANMAT 2016; IPS 2017).

12.4 The MAINTENANCE phase: prevent recurrence, and let the episode count set the duration

For recurrent, severe or high-risk depression the plan extends into a **maintenance** phase. CANMAT extends antidepressant treatment to **2 years or more** for patients with risk factors for recurrence (CANMAT 2016). The key examinable principle is that the number of prior episodes drives the **duration**: Stahl states that after a first episode you continue for about 1 year, but for a second and subsequent episodes treatment may need to be indefinite (Stahl 2021). The 2025 IPS update sets the maintenance phase at **6 to 24 months**, extended long-term for recurrent depression, with the probability of recurrence and the frequency and severity of past episodes driving the decision to continue (IPS 2025). BAP names the higher-risk group as, for example, more than five lifetime episodes or two episodes in recent years, and recommends at least 2 years and often long-term (BAP 2015). The maintenance-phase psychological options are CBT or mindfulness-based cognitive therapy (MBCT) to prevent relapse (CANMAT 2016); the technique of these therapies is owned by the Psychotherapies, clinical assessment, MSE and nosology notes.

MNEMONIC

FINISH

When the maintenance phase does end, taper slowly over several weeks to limit antidepressant discontinuation symptoms, which CANMAT summarises as FINISH: **F**lu-like symptoms, **I**nsomnia, **N**ausea, **I**mbalance, **S**ensory disturbances, **H**yperarousal (CANMAT 2016). Taper short half-life drugs (for example paroxetine, venlafaxine) more slowly. The discontinuation syndrome detail is owned by the discontinuation topic in these notes.

12.5 The MODUS: which mode of treatment each phase asks for

At guideline level the mode is an antidepressant, an evidence-based psychotherapy, or both. The **first-line** pharmacological agent is a **second-generation antidepressant**, individualised to the patient with measurement-based monitoring (CANMAT 2016). CANMAT's first-line agents (verified) include the SSRIs escitalopram (Nexito or S-Citadep; 10 to 20 mg/day), sertraline (Serta or Daxid; 50 to 200 mg/day), fluoxetine (Fludac; 20 to 60 mg/day) and the SNRI venlafaxine (Venlor; 75 to 225 mg/day), with bupropion (Bupron), mirtazapine (Mirtaz) and vortioxetine (Vortioxa) also first-line; the full per-agent dosing, mechanism and adverse-effect detail live in the earlier topics of these notes. The IPS names the SSRIs as first-line on grounds of tolerability and overdose safety (IPS 2017), NICE treats SSRIs as the first choice for most people, and BAP prefers newer antidepressants for tolerability and overdose safety (BAP 2015). The first-line psychotherapies for the acute phase are CBT, interpersonal therapy (IPT) and behavioural activation (BA); where feasible, combining a psychotherapy with an antidepressant is superior to either alone (CANMAT 2016; IPS 2017). The receptor-level pharmacology and CYP metabolism that underlie agent selection are cross-referred to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

RULE **First-line = one second-generation antidepressant, individualised, or an evidence-based psychotherapy.** Combination is superior for many, especially the more severe presentations.

12.6 The MODUS: the psychotic-depression rule

Psychotic depression is the one presentation with a fixed combination rule. Treat it with an **antidepressant plus an antipsychotic** from the outset, in preference to either drug alone, or use ECT (BAP 2015; IPS 2017). An antidepressant alone is inadequate here. The mood-with-psychotic-features entity itself is owned by the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes, and the ECT technique by the ECT and neurostimulation notes. One more selection rule sits behind the whole plan: a treatment-emergent switch to mania or hypomania on antidepressant monotherapy reclassifies the diagnosis as bipolar; stop or reduce the antidepressant and add a mood stabiliser (IPS 2017). Giving an antidepressant alone in what is really a bipolar depression is the classic error, and it is owned in full by the bipolar-management topics.

TRAP **Treating psychotic depression with an antidepressant alone.** The rule is antidepressant plus an antipsychotic from the outset, or ECT.

12.7 Putting the phases together: the phase-by-phase plan

The four phases and the locus decision assemble into one table. Learn the highlighted cell in each row: it is the fact the examiner tests.

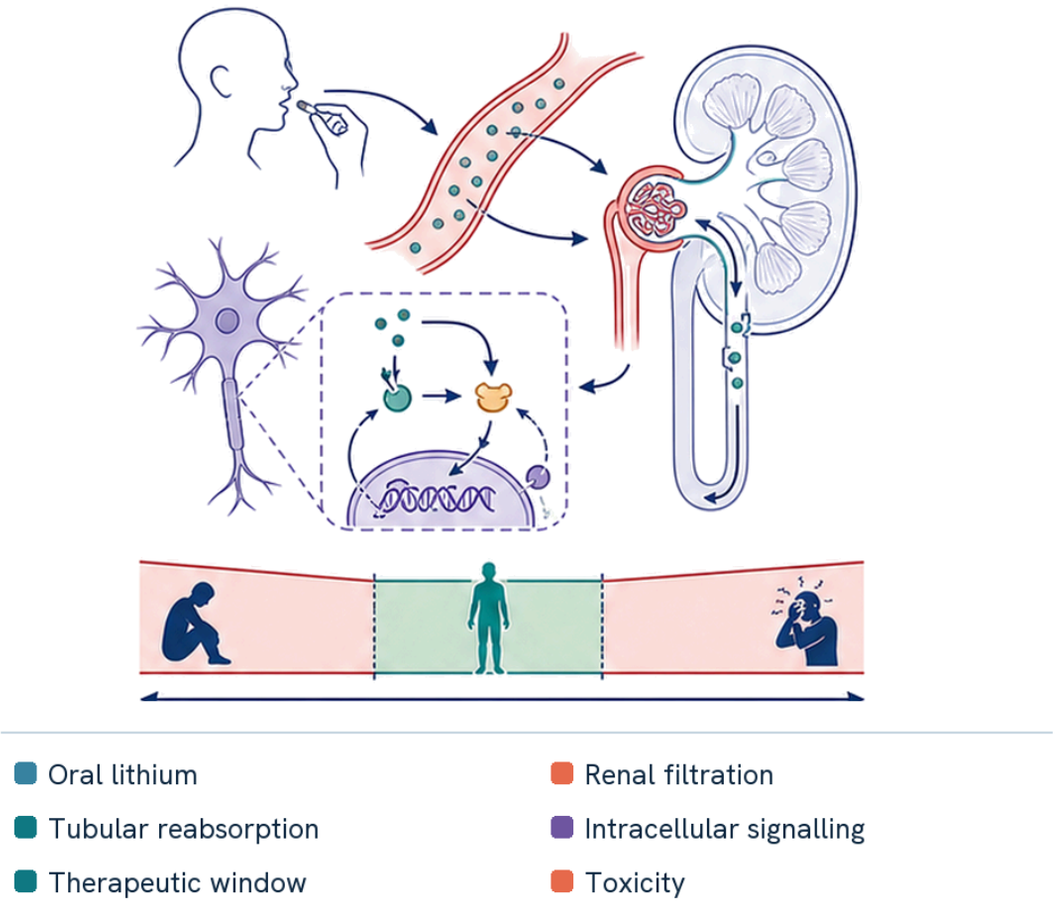

Fig 12.7 Lithium is filtered and substantially reabsorbed by the kidney while acting on intracellular signalling pathways. Its narrow therapeutic window makes changes in renal handling clinically consequential.

6 to 8 wk	2 to 4 wk	6 to 9 mo	2 years+
ADEQUATE ACUTE TRIAL	NON-IMPROVER REVIEW POINT	CONTINUATION AT THE ACUTE DOSE	MAINTENANCE IF RECURRENT

PHASE	TARGET	DURATION / CHECKPOINT	GUIDELINE-FIRST MODE
Locus decision	Choose the safest adequate setting	**Admit for high suicide risk, psychosis, severe self-neglect, or the need for ECT**	Outpatient default; measurement-based care throughout (CANMAT 2016)
Acute	Remission (not just response)	**Adequate dose for 6 to 8 weeks; review every 1 to 2 weeks; judge by 2 to 4 weeks and switch or step up if no trajectory**	One second-generation antidepressant, individualised, and/or CBT, IPT or BA; combination superior for many (CANMAT 2016)

PHASE	TARGET	DURATION / CHECKPOINT	GUIDELINE-FIRST MODE
Continuation	Protect the remission	**Continue at the same acute dose for 6 to 9 months after remission**	Same acute-phase agent at the same dose; do not down-titrate (CANMAT 2016; IPS 2017)
Maintenance	Prevent recurrence	**Extend to 2 years or longer (often indefinite) for recurrent, severe or high-risk depression; the number of prior episodes drives the duration**	Continue antidepressant; CBT or MBCT to prevent relapse; taper slowly (FINISH) at stop (CANMAT 2016)
Psychotic depression	Remission with psychosis control	From the outset	**Antidepressant plus an antipsychotic, or ECT (BAP 2015)**
Inadequate response	Optimise, then augment or switch	Optimise dose first, then reassess	Augmentation or switch; the full ladder is owned by the treatment-resistance topic in these notes

The acute depressive episode managed by the phases of treatment on the LOCUS to FOCUS to MODUS spine; durations verified against CANMAT 2016, IPS 2017 and BAP 2015. Drug detail is cross-referred to the earlier topics in these notes.

INDIA

The Indian Psychiatric Society Clinical Practice Guideline for depression has been updated: the 2025 IPS depression update (IPS 2025, Tripathi et al., Indian J Psychiatry 2026;68:68-93) supersedes the 2017 Gautam guideline and is now the current examinable Indian reference. It sets the treatment phases as acute **8 to 16 weeks** (achieve remission), continuation **4 to 9 months** (consolidate remission, prevent relapse) and maintenance **6 to 24 months** (prevent recurrence, restore functioning), extended long-term for recurrent depression. It selects the initial treatment by severity: for mild low-risk depression, psychotherapy is preferred (pharmacotherapy is acceptable in the Indian setting given limited access to psychologists); for moderate depression, pharmacotherapy or psychotherapy, with pharmacotherapy slightly more efficacious, quicker and more cost-effective; for severe depression without psychosis, combined pharmacotherapy and psychotherapy; for severe depression with psychosis, an antidepressant plus an antipsychotic as first-line; and for life-threatening presentations, ECT with admission. The first-line SSRIs and their doses are unchanged (escitalopram 10 to 20 mg, sertraline 50 to 200 mg, fluoxetine 20 to 60 mg), and the update names vilazodone, vortioxetine and agomelatine among the newer options. All the first-line agents are inexpensive Indian brands: escitalopram (Nexito or S-Citadep), sertraline (Serta or Daxid), fluoxetine (Fludac), venlafaxine (Venlor), duloxetine (Duzela), mirtazapine (Mirtaz), bupropion (Bupron), vortioxetine (Vortioxa). ECT is widely available across Indian teaching hospitals and remains a mainstream option for severe, psychotic, suicidal or treatment-resistant depression rather than a last resort.

GOOD TO REMEMBER

- **LOCUS:** outpatient default; admit for high suicide risk, psychosis, severe self-neglect, or the need for ECT; measurement-based care throughout.
- **Acute phase:** aim **remission**, not response; adequate dose for **6 to 8 weeks**; review every 1 to 2 weeks; switch or step up if no trajectory by 2 to 4 weeks (CANMAT 2016; BAP 2015).
- **Continuation phase:** continue at the **same acute dose** for **6 to 9 months** after remission; do not down-titrate (CANMAT 2016; IPS 2017).
- **Maintenance phase: 2 years or longer** (often indefinite) for recurrent, severe or high-risk depression; the number of prior episodes drives the duration (Stahl 2021; IPS 2017).
- **MODUS:** one second-generation antidepressant, or an evidence-based psychotherapy (CBT, IPT, BA), or both; combination superior for many.
- **Psychotic depression:** antidepressant plus an antipsychotic from the outset, or ECT (BAP 2015).
- **Do-not-combine rule:** two antidepressants are not combined at initiation (CANMAT 2016).

WORKED EXAMPLE

A 38-year-old man with a second moderate-to-severe depressive episode, no psychosis and no active suicidal plan, is managed as an outpatient. He is started on a single first-line SSRI, escitalopram (Nexito or S-Citadep), titrated to a therapeutic dose, and offered CBT alongside because combination is superior to either alone. He is reviewed at 2 weeks and again at 4 weeks: there is a partial improvement trajectory, so the dose is optimised rather than switched, and the adequate trial is allowed to run to 6 to 8 weeks. He reaches remission by month 3. The escitalopram is continued at the same acute dose for 6 to 9 months in the continuation phase, not reduced. Because this is his second episode, the recurrence-risk conversation supports a maintenance phase of at least 1 to 2 years rather than stopping at the end of continuation.

PEARL

"Remission then continuation at the acute dose" is a single instruction. The dose that achieved remission is the dose that maintains it: the continuation phase is the acute-phase drug at the acute-phase dose for 6 to 9 months. Reducing the dose the moment the patient feels well is a common and avoidable cause of relapse.

TRAP **Stopping the antidepressant as soon as the patient feels better.** Response is not remission, and remission is not the end point; early cessation invites relapse.

HOLD THIS

Treat the acute depressive episode to remission on an adequate 6-to-8-week trial, continue at the same acute dose for 6 to 9 months after remission, and extend to 2 years or longer for recurrence, with the number of prior episodes setting the duration.

Mood stabilisers and lithium

13 . Lithium: mechanism and pharmacokinetics

Why this leads the block. Lithium is a monovalent cation with no receptor, no enzyme it was designed for, and no metabolism, yet it remains the gold-standard mood stabiliser and the only agent with a genuine anti-suicide signal (Maudsley 2021). The examiner reward here is mechanistic: two intracellular **mechanism of action** hypotheses that also explain the neuroprotective story, and a **pharmacokinetics** profile so unusual that the drug is effectively a sodium mimic cleared entirely by the kidney. Get the pharmacokinetics right and the interactions, the monitoring schedule and the toxicity all fall out of it; get them wrong and a stable patient tips into toxicity from nothing more than a stomach bug.

This fragment teaches the molecular targets, then the four pharmacokinetic facts a resident must hold, then the bridge that makes lithium's kinetics the source of its danger. The therapeutic ranges, the monitoring intervals and the drug interactions themselves are developed in the sibling topics; the deep monoamine and second-messenger anatomy sits in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

13.1 A drug with no obvious target

The framing problem. Lithium has "practically no acute effects in normal individuals" and is neither sedative nor euphoriant; the mood-stabilising action appears only on prolonged administration (KDT 2019). It does not bind a classical receptor. Instead it acts inside the cell on two enzymes that sit on second-messenger and signalling cascades, and it does so at the low millimolar concentrations reached therapeutically. The two dominant, exam-relevant hypotheses are **inositol** depletion and GSK-3 inhibition. Both converge on dampening an over-active signalling state and on downstream neurotrophic or neuroprotective effects (Stahl 2021).

RULE **Two targets, one theme.** Lithium works intracellularly on inositol monophosphatase and GSK-3 beta, not on a membrane receptor: it turns down an over-active signalling cascade and switches on neuroprotective genes.

13.2 The inositol depletion hypothesis

Inositol monophosphatase and the phosphatidylinositol cycle. Gq-coupled receptors activate phospholipase C, which hydrolyses membrane phosphatidylinositol to the second messengers inositol trisphosphate (IP3) and diacylglycerol. To regenerate the signalling lipid, the cell must recycle inositol, and the enzyme that liberates free **inositol** from inositol monophosphate is inositol monophosphatase (IMPase). Lithium is a powerful inhibitor of IMPase, so the phosphatidylinositol second-messenger cascade runs down as the cell is depleted of inositol (Berridge 1982; New Oxford 2020). Because the brain crosses the blood brain barrier poorly for inositol and is therefore uniquely dependent on recycling, it is selectively sensitive to this depletion (New Oxford 2020).

Uncompetitive inhibition is the elegant part. Lithium inhibits IMPase *uncompetitively*, meaning the block deepens as substrate rises. Lithium therefore acts most where a pathway is hyperfunctional and barely touches pathways ticking over at basal rates, which is exactly the selectivity you want in an anti-manic drug (New Oxford 2020). This "inhibition of inositol monophosphatase dampening the phosphatidylinositol second-messenger cascade" is the phrase to reproduce. Supporting the class relevance, valproate and carbamazepine also deplete brain inositol, though largely by inhibiting a synthetic enzyme rather than IMPase (New Oxford 2020).

MNEMONIC

"I MP-ede the cycle"

IMPase is the enzyme lithium blocks; blocking it *impedes* the phosphatidylinositol cycle by starving it of recycled inositol. Uncompetitive means the busier the pathway, the harder lithium hits.

13.3 GSK-3 beta inhibition and the neurotrophic story

The second target. Glycogen synthase kinase 3 beta (glycogen synthase kinase 3, GSK-3) is a constitutively active kinase that phosphorylates and inactivates a wide set of substrates. Lithium robustly inhibits GSK-3 beta, both directly and indirectly through the beta-arrestin 2 / Akt pathway that dopamine D2 signalling recruits (Companion 2010; Lithium Handbook 2023). Inhibiting GSK-3 releases its downstream substrates from suppression: Wnt / beta-catenin signalling, the cytoskeletal and tau proteins, and the transcription factors CREB and AP-1 (jun) (Companion 2010).

Downstream neurotrophic and neuroprotective effects. The net consequence is upregulation of neurotrophic and cytoprotective programmes, notably brain-derived neurotrophic factor (BDNF) and the anti-apoptotic protein bcl-2 (Kaplan 2024). This is the molecular basis usually invoked for lithium's neuroprotective and putative anti-dementia signal (Lithium Handbook 2023). GSK-3 also phosphorylates core clock proteins, so its inhibition feeds into the **circadian** and signalling pathways that are disordered in bipolar illness, one proposed route by which lithium lengthens and re-entrains the circadian period (Stahl 2021).

TARGET	WHAT LITHIUM DOES	DOWNSTREAM CONSEQUENCE
Inositol monophosphatase (IMPase)	**Uncompetitive inhibition**	Inositol depletion, phosphatidylinositol / IP3 cascade damped, most in hyperactive pathways
GSK-3 beta	**Direct and Akt/beta-arrestin inhibition**	Wnt/beta-catenin, CREB, BDNF, bcl-2 up; neuroprotection; circadian re-entrainment

The two dominant mechanism-of-action hypotheses for lithium and their downstream signalling effects.

PEARL

Both mood-stabiliser mechanisms fit a single idea: lithium quietens an over-active intracellular signal (inositol/PI cycle) while switching on survival and plasticity genes (via GSK-3 inhibition). This "dampen the noise, protect the cell" dual action distinguishes it from receptor-blocking drugs.

13.4 Absorption and distribution

A small ion that behaves like body water plus sodium. Lithium is well absorbed orally with peak plasma levels at **2 to 3 hours** for immediate-release salts, and it is not protein bound (KDT 2019). It first enters the extracellular water, then slowly crosses into cells, giving an apparent **volume of distribution** around **0.8 L/kg**, close to total body water and narrow compared with lipophilic psychotropics (KDT 2019). The slow intracellular equilibration matters clinically: after an acute overdose the plasma level can be alarmingly high while the patient is still asymptomatic, then deteriorate over hours as lithium loads into cells, which is why the serum level and the clinical picture can dissociate early (Kaplan 2024).

2 to 3	0.8	18 to 24
TIME TO PEAK, IR (HOURS)	VOLUME OF DISTRIBUTION (L/KG)	ELIMINATION HALF-LIFE (HOURS)

13.5 Not metabolised: entirely renal excretion

The single most important pharmacokinetic fact. Lithium is not metabolised by the liver and is not protein bound; it undergoes **renal excretion** essentially in its entirety, cleared unchanged by the kidney (KDT 2019; Kaplan 2024). It is filtered at the glomerulus and then handled by the proximal tubule "in much the same way as sodium," where roughly 80% of the filtered load is reabsorbed alongside sodium; its renal clearance is about one fifth of creatinine clearance (KDT 2019). The elimination half-life is of the order of **18 to 24 hours** in a patient with normal renal function, described by Kaplan as "about a day," which is what makes once-daily dosing feasible and why steady state and a valid trough level are reached only after several days at a fixed dose (Kaplan 2024).

WORKED EXAMPLE

A euthymic patient stable for years on a fixed lithium dose develops gastroenteritis, eats little, and becomes volume-deplete over a weekend. Sodium and water avidity rise, the proximal tubule reabsorbs more filtered sodium and therefore more lithium, renal lithium clearance falls, and the serum level climbs even though the dose has not changed. The stable patient is now heading into toxicity with no prescribing error at all.

13.6 The sodium link is the whole game

Why the kinetics drive the toxicity and the interactions. Because lithium is handled like sodium and cleared only by the kidney, anything that lowers total-body sodium or reduces renal clearance raises the level. Sodium depletion, dehydration and a low-salt diet all increase proximal reabsorption of lithium; renal impairment and a falling glomerular filtration rate reduce its excretion (Kaplan 2024; KDT 2019). This is the mechanistic root of the classic interactions developed in the interaction and monitoring topics: thiazide diuretics deplete sodium and raise

levels; NSAIDs and ACE inhibitors or ARBs cut renal perfusion or clearance and raise levels; sodium loading or osmotic diuresis lowers them. There is no hepatic escape route and no protein reservoir to buffer swings, so kinetic changes translate directly into level changes.

RULE **Lithium follows sodium and the kidney.** Lithium is renally cleared and sodium-linked, so anything that lowers sodium or lowers renal clearance raises the level. That single sentence predicts nearly every lithium interaction and every toxicity trigger.

TRAP **The "nothing changed" toxicity.** Forgetting that dehydration, a vomiting or diarrhoeal illness, a heat wave or a new low-salt diet can push a long-stable patient into toxicity with the dose untouched. The level moved because sodium and water moved, not because the prescription did.

13.7 Narrow therapeutic index: why monitoring is mandatory

The margin is thin and individual. Lithium has a **narrow therapeutic index**: therapeutic maintenance levels sit around **0.6 to 1.0 mEq/L** while toxicity appears not far above, with early features from roughly **1.5 mEq/L** and serious toxicity higher still (Meyer and Stahl / Lithium Handbook 2023; CANMAT 2018). Guideline targets are level-defined rather than dose-defined: CANMAT sets maintenance at 0.6 to 1.0 mEq/L and an acute-mania target of 0.8 to 1.2 mEq/L, and the Indian Psychiatric Society (IPS guidelines) similarly anchor maintenance around 0.6 to 1.0 mmol/L with acute targets up to about 1.2 mEq/L (CANMAT 2018; Shah, Grover et al. 2017). Because the same oral dose produces widely different levels between patients (large inter-individual variation in renal clearance) and the same patient's level moves with sodium and hydration, therapeutic drug monitoring of the serum level is not optional, it is the drug (Kaplan 2024; Lithium Handbook 2023). This is the bridge into the initiation, monitoring and toxicity topics.

INDIA

Lithium carbonate is widely available in India as immediate-release and sustained-release tablets, commonly branded Licab and Intalith CR (generic lithium carbonate stays primary in the prose). The narrow-index and sodium-link teaching is especially load-bearing in Indian practice: hot-climate dehydration, gastroenteritis, fasting and low-salt diets are common real-world triggers for a stable patient to drift into toxicity between clinic visits.

HOLD THIS

Lithium is not metabolised and is cleared entirely by the kidney where it is handled like sodium, so with a narrow therapeutic index any fall in sodium, hydration or renal clearance raises the level toward toxicity.

GOOD TO REMEMBER

- **Mechanism (inositol):** inhibits inositol monophosphatase, uncompetitively, depleting inositol and dampening the phosphatidylinositol / IP3 second-messenger cascade, most in hyperactive pathways.
- **Mechanism (GSK-3):** inhibits GSK-3 beta, releasing Wnt/beta-catenin, CREB, BDNF and bcl-2, giving downstream neurotrophic, neuroprotective and circadian effects.
- **Pharmacokinetics:** not protein bound, not metabolised, renal excretion entirely; handled like sodium (proximal reabsorption ~80%); Vd ~0.8 L/kg; half-life ~18 to 24 hours; peak at 2 to 3 hours (IR).
- **The clinical rule:** narrow therapeutic index (maintenance ~0.6 to 1.0 mEq/L) makes serum monitoring mandatory; sodium depletion, dehydration and renal impairment raise the level.

14 . Lithium: indications, initiation, dosing and range

Lithium is the oldest and still the single most important mood stabiliser, and the examiner treats it as a set-piece: the indications, the baseline work-up before the first tablet, the starting dose, and above all the **serum lithium** therapeutic range that differs between acute mania and maintenance. It is the gold-standard prophylactic agent in bipolar disorder and carries the strongest anti-suicidal evidence of any psychotropic (Maudsley 2021; CANMAT 2018), so a resident is expected to prescribe it correctly and to know its numbers cold. A wrong serum level or a skipped renal or thyroid baseline is the classic marked error.

Organise the topic around one idea: **aim high for acute mania, aim lower for maintenance**, and never start without a baseline renal, thyroid and calcium screen. The ranges below are verified against the Maudsley and the CANMAT and Indian Psychiatric Society guideline rows (Maudsley 2021; CANMAT 2018; IPS 2017); the neurobiology of mood and the wider guideline-anchored management PLAN belong to the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes, and the deep antimanic-antipsychotic detail to the Schizophrenia: management, antipsychotics and adverse effects notes.

14.1 Mechanism: a monovalent cation with intracellular targets

The molecular target. Lithium is a monovalent cation with no single agreed mechanism; the best-supported candidates are inhibition of glycogen synthase kinase 3 (GSK3-beta) and interference with the phosphatidylinositol second-messenger cycle through inhibition of inositol monophosphatase, together with effects on CREB and on neuronal sodium and calcium handling (Maudsley 2021; Stahl 2021). It also promotes hippocampal neurogenesis and has putative neuroprotective effects.

Why the narrow window matters. Lithium is not metabolised; the ion is handled entirely by the kidney and excreted with a half-life of about 24 hours, so anything that alters sodium handling or renal function moves the serum level directly (Kaplan and Sadock 2024). That renal-only clearance, and the fact that the therapeutic and toxic ranges nearly abut, is why serum monitoring is non-negotiable.

14.2 Lithium indications: mania, maintenance and augmentation

The core indications. The set of **lithium indications** a resident must recite: **acute mania** (a first-line antimanic agent), bipolar maintenance and **prophylaxis** (the gold-standard mood stabiliser for preventing both manic and depressive recurrence), augmentation of an antidepressant in treatment-resistant unipolar depression, and prophylaxis of recurrent unipolar depression (Maudsley 2021; CANMAT 2018).

Acute mania

First-line, alone or combined with an antipsychotic; a faster antimanic onset is gained by adding a dopamine antagonist (Maudsley 2021; CANMAT 2018).

Bipolar maintenance / prophylaxis

The best-performing single agent for long-term relapse prevention; in 2024 it remains the gold-standard maintenance treatment (Maudsley 2021).

Unipolar antidepressant augmentation

A first-choice augmenting agent in treatment-resistant depression, most effective at a serum level of 0.6 to 1.0 mmol/L (Maudsley 2021).

Recurrent unipolar depression

Prophylaxis is indicated after two depressive episodes in five years, or after one severe episode with strong suicide risk (Maudsley 2021).

The anti-suicidal signal. Lithium is the one psychotropic with dedicated anti-suicide evidence: a meta-analysis of clinical trials concluded it reduced attempted and completed suicide by roughly 80 percent in bipolar illness, and this protection extends to unipolar depression (Maudsley 2021; IPS 2017). About 15 percent of people with bipolar disorder die by suicide, which frames why this matters. The full clinical suicide risk assessment and safety planning belong to the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

RULE **Lithium is the anti-suicidal mood stabiliser.** In a bipolar patient with suicidality it is the preferred long-term agent for its specific, class-unique anti-suicide evidence.

14.3 Initiation: the baseline work-up before the first tablet

The pre-lithium screen. Because clearance is renal and the drug is a putative teratogen with thyroid, parathyroid and cardiac effects, a baseline work-up is mandatory before **initiation** (Maudsley 2021; IPS 2017). As a minimum, check: renal function (estimated GFR with urea and electrolytes), thyroid function (TSH), serum calcium, a baseline weight, and a pregnancy test with contraceptive counselling in women of child-bearing potential. An ECG is recommended in those with cardiovascular risk factors or established cardiac disease.

BASELINE TEST	WHY
Renal function (eGFR, U and Es)	Lithium is cleared only by the kidney; sets the safety floor and the interaction baseline
Thyroid function (TSH)	Lithium causes hypothyroidism (up to ~20 percent in middle-aged women over time)
Serum calcium	Hyperparathyroidism with hypercalcaemia occurs in about 4 percent
ECG (if cardiovascular risk)	Recommended where cardiac risk factors or disease exist
Weight / BMI	Weight gain is a common, adherence-limiting adverse effect
Pregnancy test / contraception	Putative teratogen (Ebstein anomaly with first-trimester exposure)

The pre-lithium baseline work-up (Maudsley 2021; IPS 2017). Renal, thyroid and calcium are the non-negotiable trio; ECG is conditional on cardiac risk. The perinatal detail is cross-referred.

TRAP **Starting lithium without baseline renal and thyroid function.** You lose the safety baseline, miss pre-existing renal impairment or hypothyroidism, and cannot later attribute change to the drug.

14.4 Dosing: starting dose and titration to the target level

Starting and titrating. The standard **dosing** approach: start lithium carbonate at **400 mg at night** in an adult, or **200 mg at night** in the elderly, then titrate against the serum level, not against a fixed milligram target (Maudsley 2021). Check the first plasma level after 7 days, and again 7 days after every dose change, until the desired level is reached; once stable it is checked every 6 months (Maudsley 2021; IPS 2017).

Timing the sample. The blood sample must be taken 12 hours after the last dose (the standardised 12-hour trough), because a sample drawn too early reads falsely high (Maudsley 2021). The usual maintenance dose lands around 600 to 1200 mg daily, but the number that matters is the serum level, not the dose.

RULE **Titrate to the level, and take the sample at 12 hours.** A lithium level drawn before the 12-hour trough overreads and can trigger a wrongful dose cut.

WORKED EXAMPLE

A 34-year-old man in acute mania is started on lithium carbonate 400 mg nocte after a normal baseline eGFR, TSH and calcium. A level after one week, drawn 12 hours post-dose, reads 0.6 mmol/L. Because the target for acute mania is higher, the dose is increased and a repeat level 7 days later reaches 0.9 mmol/L, within the 0.8 to 1.0 mmol/L acute band, with good tolerability. Had the day-7 sample been taken at 3 hours post-dose it would have read spuriously high and prompted an inappropriate dose reduction.

14.5 The therapeutic range: aim high for mania, lower for maintenance

The two targets. This is the single highest-yield fact of the topic. The **therapeutic range** is phase-dependent. For **acute mania** aim for a serum lithium of **0.8 to 1.0 mmol/L**, extending up to 1.2 mmol/L in difficult-to-treat mania (Maudsley 2021; CANMAT 2018; IPS 2017). For maintenance and prophylaxis aim lower, at **0.6 to 0.8 mmol/L**, with the option to go up to 1.0 mmol/L for insufficient response and good tolerance, or down to 0.4 to 0.6 mmol/L for good response but poor tolerance (Maudsley 2021; CANMAT 2018).

The elderly and the augmentation targets. In older adults a lower maintenance target of about **0.4 to 0.6 mmol/L** is often used, starting low (for example 150 to 200 mg at night) because renal clearance falls with age (Maudsley 2021; CANMAT 2018). For unipolar antidepressant augmentation the effective serum level is 0.6 to 1.0 mmol/L. The minimum effective prophylactic level is probably about 0.4 mmol/L, but the practical prophylaxis target remains 0.6 to 0.8 mmol/L (Maudsley 2021).

INDICATION / PHASE	SERUM LITHIUM TARGET (MMOL/L)	SOURCE
Acute mania	**0.8 to 1.0 (up to 1.2 in difficult mania)**	Maudsley 2021; CANMAT 2018; IPS 2017
Maintenance / prophylaxis (bipolar)	**0.6 to 0.8 (up to 1.0)**	Maudsley 2021; CANMAT 2018
Maintenance in the elderly	0.4 to 0.6	Maudsley 2021; CANMAT 2018
Unipolar antidepressant augmentation	0.6 to 1.0	Maudsley 2021
Toxicity threshold	above 1.5 (seizures usually above 2.0)	Maudsley 2021

Verified serum lithium targets by phase (mmol/L; for lithium, 1 mmol/L equals 1 mEq/L). The two highlighted rows are the must-hold numbers: higher for acute mania, lower for maintenance. Toxicity begins reliably above 1.5 mmol/L.

0.8 to 1.0	0.6 to 0.8	above 1.5
ACUTE MANIA TARGET (MMOL/L)	MAINTENANCE TARGET (MMOL/L)	TOXICITY THRESHOLD (MMOL/L)

TRAP **Using the maintenance range to treat acute mania.** A 0.6 to 0.8 mmol/L level undertreats an acute manic episode; the acute target is higher, 0.8 to 1.0 (up to 1.2) mmol/L.

14.6 The Indian brands and continued front-line use

What is prescribed here. In Indian practice lithium is prescribed as lithium carbonate, and remains a genuine first-line mood stabiliser rather than a legacy drug, endorsed as first-line for acute mania and as the primary maintenance agent in the Indian Psychiatric Society guidelines (the IPS guidelines; IPS 2017). Its low cost and the strength of the maintenance and anti-suicide evidence keep it front-line in a largely out-of-pocket health system.

INDIA

Lithium carbonate is marketed in India as Licab and as Intalith (both lithium carbonate), available as standard and sustained-release tablets. It stays a genuine front-line agent: the Indian Psychiatric Society guidelines place lithium first-line for acute mania (target 0.8 to 1.2 mmol/L) and as the primary maintenance mood stabiliser for preventing both manic and depressive recurrence, at a maintenance level of 0.6 to 1.0 mmol/L, with its specific anti-suicide evidence explicitly noted (IPS 2017). Serum-level access is widely available in district and teaching hospitals, and the drug is inexpensive, both of which support its continued heavy use in Indian outpatient departments.

GOOD TO REMEMBER

- **Lithium (Licab or Intalith):** monovalent cation, GSK3-beta and inositol-cycle effects; renal clearance only; first-line for acute mania and the gold-standard maintenance agent with unique anti-suicide evidence.
- **Acute mania target:** serum lithium **0.8 to 1.0 mmol/L** (up to 1.2 in difficult mania).
- **Maintenance / prophylaxis target:** serum lithium **0.6 to 0.8 mmol/L** (up to 1.0; 0.4 to 0.6 in the elderly).
- **Initiation:** baseline renal (eGFR, U and Es), thyroid (TSH), calcium, weight, ECG if cardiac risk, pregnancy test; start **400 mg nocte** (200 mg elderly).
- **Monitoring:** level at 7 days and 7 days after each change, sampled 12 hours post-dose, then 6-monthly with eGFR and TFTs.

HOLD THIS

Lithium is first-line for acute mania and the gold-standard maintenance mood stabiliser with the strongest anti-suicidal evidence: aim for a serum level of 0.8 to 1.0 mmol/L in acute mania and 0.6 to 0.8 mmol/L in maintenance, always after a baseline renal, thyroid and calcium screen, sampling the level 12 hours post-dose.

15 . Lithium monitoring

lithium monitoring is examined more precisely than almost any other prescribing topic, because lithium has the narrowest therapeutic index in psychiatry: the gap between an effective and a toxic level is small, so the drug is unusable without a disciplined monitoring routine. The two things the board rewards are the **sampling rule** (how and when to draw the level) and the **investigation schedule** (what to check at baseline and how often afterwards). Get the timing of the blood sample wrong and the number is meaningless; let the renal or thyroid checks lapse and you miss the two organ toxicities that end lithium therapy.

The whole topic hangs on one physiological fact: lithium is renally cleared with a long distribution phase, so the plasma level is only interpretable at a standardised time after the dose. That time is twelve hours. Everything below, the target ranges, the check after a dose change, the six-monthly organ panel, is verified against the Maudsley Prescribing Guidelines, Stahl's Prescriber's Guide, the CANMAT guideline and the Indian Psychiatric Society clinical practice guideline (Maudsley 2021; Stahl 2021; Yatham 2018; Shah 2017). The lithium initiation and toxicity detail sits alongside this in the mood-block pharmacotherapy notes; the guideline-

anchored management PLAN that puts lithium first-line is set out in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

Fig 12.8 The lithium therapeutic window and the monitoring rule. The window is narrow: aim about 0.8 to 1.0 (up to 1.2) mmol/L for acute mania and 0.6 to 0.8 (up to 1.0) for maintenance, with a lower 0.4 to 0.6 target in the elderly; toxicity is expected above 1.5, though any level with toxic features counts as toxic. Sample as a 12-hour trough, recheck 5 to 7 days after any dose change, and monitor renal and thyroid function with the baseline work-up shown.

15.1 The sampling rule: the twelve-hour trough

Sample at the trough, twelve hours post-dose. The single most examined fact in **lithium monitoring** is when to draw the blood. Because lithium has a long distribution phase, an early sample catches the drug still redistributing and reads falsely high. The standard is the **twelve-hour trough**: the blood is taken as the **12-hour** post-dose sample, ideally 10 to 14 hours after the last dose, with 12 hours the target, in a patient on a once-daily bedtime regimen (Maudsley 2021). This is the **serum level** that every published target range refers to. In practice, for a patient who takes lithium at night, the sample is drawn the next morning before the day's dose.

Standardise the timing. Because the level changes across the dosing interval, the timing must be held constant from one sample to the next, so that a change in the number reflects a change in the patient and not a change in when you took the blood. A CANMAT and the Indian Psychiatric Society both anchor drug-level sampling to this trough point (Yatham 2018; Shah 2017).

RULE **Draw the lithium level as a twelve-hour trough.** The 12-hour post-dose sample, timed the same way each time, is the only interpretable serum level.

TRAP **Taking a random, non-trough level and acting on it.** A sample drawn a few hours after the dose reads spuriously high and invites a wrong dose cut, or a spuriously reassuring number if drawn late; always standardise to 12 hours.

15.2 The target ranges the level is read against

What number you are aiming for. The trough **serum level** is only useful against a target. For maintenance and prophylaxis in bipolar disorder the accepted range is **0.6 to 1.0 mmol/L**

(CANMAT keeps maintenance at 0.6 to 1.0 mEq/L; the Maudsley narrows the prophylactic optimum to 0.6 to 0.8 mmol/L) (Yatham 2018; Maudsley 2021). In acute mania a slightly higher level of **0.8 to 1.2 mmol/L** is targeted, and for lithium augmentation of an antidepressant in unipolar depression the target is **0.6 to 1.0 mmol/L**, the same as maintenance (Maudsley 2021). Toxic effects reliably appear above **1.5 mmol/L**, which is why the trough discipline matters so much.

0.6 to 1.0	0.8 to 1.2	1.5
MAINTENANCE LITHIUM (MMOL/L)	ACUTE MANIA TARGET (MMOL/L)	TOXICITY THRESHOLD (MMOL/L)

15.2b Checking the level after a dose change

Recheck 5 to 7 days after every dose change. Lithium reaches a new steady state roughly five half-lives after any change in dose, which is about 5 to 7 days in an adult with normal renal function. So after starting lithium or altering the dose you draw the next twelve-hour trough about 5 to 7 days later, and you repeat this after each successive change until the level is stable in the target range (Maudsley 2021; Shah 2017). The Maudsley states the interval as a level after 7 days and then 7 days after every dose change; the Indian Psychiatric Society states it as 5 to 7 days after a dose change, and CANMAT applies the same 5 to 7 day rule after any dose or interacting-drug change in older adults (Maudsley 2021; Shah 2017; Yatham 2018). Practically, hold 5 to 7 days.

RULE **After any dose change, recheck the trough level in 5 to 7 days.** Steady state is about five half-lives; repeat after each change until stable.

15.3 The frequency of level monitoring once stable

Frequent during titration, then every 3 months. During titration the level is checked every few days to a week as the dose is adjusted (each check 5 to 7 days after the preceding change). Once the patient is established on a stable dose with the level in range, routine **serum level** monitoring settles to **every 3 months** in the Indian Psychiatric Society schedule, while some guidelines including the Maudsley move to **6-monthly** lithium levels once the patient is stable (Shah 2017; Maudsley 2021). CANMAT sits between these, repeating levels every 3 to 6 months after two consecutive therapeutic acute-phase readings (Yatham 2018).

Check more often in the vulnerable. The interval shortens in the **elderly**, in anyone starting or stopping an interacting drug (see 15.6), in renal impairment or other relevant physical illness, and whenever toxicity is suspected clinically (Maudsley 2021). In these groups a routine 6-monthly level is not enough.

15.4 Baseline investigations before starting lithium

The pre-lithium work-up. The **baseline investigations** exist to establish the two organ functions lithium threatens and to flag cardiac risk. Before prescribing, check **renal function** (estimated glomerular filtration rate, that is eGFR, with urea and electrolytes and serum creatinine) and **thyroid function** (thyroid-stimulating hormone, that is TSH), together with a baseline serum calcium, a baseline weight or body mass index, and an ECG where the patient has

risk factors for or established cardiovascular disease (Maudsley 2021; Yatham 2018). Because lithium is a putative human teratogen, a woman of child-bearing potential should be counselled on reliable contraception and a pregnancy test considered at baseline (Maudsley 2021).

Renal function
eGFR, serum creatinine, urea and electrolytes; the organ that clears lithium and the one at long-term risk.

Thyroid function
TSH (with free T4 if abnormal); lithium causes hypothyroidism, up to about 20% in middle-aged women over time.

Calcium
baseline serum calcium; lithium can cause hyperparathyroidism and hypercalcaemia.

ECG
at baseline where cardiovascular risk factors or disease exist.

Weight / BMI
baseline, because lithium causes weight gain.

15.5 The follow-up panel: renal and thyroid roughly 6-monthly

Repeat renal and thyroid at 6 months. The on-treatment organ panel mirrors the baseline one. **Renal function** (eGFR and creatinine) and **thyroid function** (TSH) are rechecked roughly 6-monthly, along with serum calcium and weight, and at least annually thereafter or as clinically indicated; the Maudsley checks plasma lithium, eGFR, U&Es, TFTs and calcium every 6 months, CANMAT assesses thyroid and renal function and plasma calcium at 6 months and at least annually, and the Indian Psychiatric Society specifies baseline and 6-monthly TSH, creatinine, eGFR, calcium and weight (Maudsley 2021; Yatham 2018; Shah 2017). Thyroid function is often checked more frequently in the first year, when hypothyroidism most commonly emerges (Maudsley 2021).

Note that the follow-up level (15.3) and the follow-up organ panel run on slightly different clocks: the trough level is checked 3-monthly (some guidelines 6-monthly once stable), while the renal and thyroid panel is checked roughly 6-monthly. Both intervals shorten in the elderly and with interacting drugs.

INVESTIGATION	BASELINE	TITRATION	ONCE STABLE (INTERVAL)	NOTE
Serum lithium (12-hour trough)	not applicable	**5 to 7 days after each dose change**	**every 3 months (some guidelines 6-monthly)**	Draw 12 h post-dose; standardise timing
Renal function (eGFR, creatinine)	yes	if concern	**roughly 6-monthly**	More often in the elderly / interacting drugs / CKD
Thyroid function (TSH)	yes	if concern	**roughly 6-monthly**	Consider more often in first year

INVESTIGATION	BASELINE	TITRATION	ONCE STABLE (INTERVAL)	NOTE
Serum calcium	yes	if concern	roughly 6-monthly	Hyperparathyroidism / hypercalcaemia
Weight / BMI	yes	monitor	roughly 6-monthly	Lithium causes weight gain
ECG	where CV risk	not routine	as clinically indicated	Baseline if cardiovascular risk factors or disease

Lithium monitoring schedule: the twelve-hour trough serum level after each dose change and then 3-monthly (some guidelines 6-monthly), with renal and thyroid function roughly 6-monthly, plus calcium, weight and ECG where indicated (Maudsley 2021; Yatham 2018; Shah 2017). Highlighted cells are the board-critical intervals.

TRAP **Letting renal or thyroid monitoring lapse.** A patient stable for years still needs the roughly 6-monthly renal and thyroid panel; silent hypothyroidism or a creeping fall in eGFR is missed when the panel is dropped.

15.6 Interacting drugs that force closer monitoring

Anything that raises the lithium level tightens the schedule. Lithium sits on the renal sodium-handling system, so drugs that alter that system change its level and mandate more frequent checks. The classic culprits are thiazide diuretics, ACE inhibitors and angiotensin-receptor blockers, and NSAIDs, each of which raises the lithium level and can precipitate toxicity (Maudsley 2021). Whenever one of these is started, stopped or dose-adjusted, recheck the twelve-hour trough 5 to 7 days later and monitor renal function more closely; in the elderly, ACE inhibitors raise the risk of lithium-toxicity hospitalisation several-fold (Maudsley 2021).

COMMON TRAP

A stable lithium patient develops hypertension and is started on a thiazide or an ACE inhibitor by another clinician. Without a repeat trough level 5 to 7 days later, the rising lithium level goes unnoticed until the patient presents with tremor, ataxia and confusion. Any new interacting drug is a trigger to recheck the level, not to wait for the next routine appointment.

INDIA

Lithium is cheap, freely available and heavily prescribed in Indian practice; the generic is lithium carbonate, marketed as Licab and as the controlled-release Intalith CR. The serum level assay is inexpensive and widely available, but the twelve-hour trough discipline is easily lost in a busy outpatient department, so counsel the patient to attend fasting in the morning before the day's dose and to note the time of the last tablet. The Indian Psychiatric Society schedule (serum level 5 to 7 days after a dose change, then 3-monthly when stable, with baseline and 6-monthly TSH, creatinine, eGFR, calcium and weight) is the practical standard to memorise for Indian exams (Shah 2017).

MNEMONIC

TRoTTeR

What lithium monitoring turns on: **T**welve-hour trough (the sample timing), **R**echeck at 5 to 7 days after a dose change, **o**ngoing level every 3 months once stable, **T**hyroid (TSH) roughly 6-monthly, **T**ests of renal function (eGFR/creatinine) roughly 6-monthly, and **R**emember calcium, weight and ECG where indicated.

GOOD TO REMEMBER

- **Serum level timing:** twelve-hour trough, the 12-hour post-dose sample (ideally 10 to 14 hours), standardised each time.
- **After a dose change:** recheck the trough level in 5 to 7 days (about five half-lives to steady state), repeat until stable.
- **Routine level once stable:** every 3 months (some guidelines 6-monthly), more often in the elderly or with interacting drugs.
- **Renal function (eGFR/creatinine):** at baseline then roughly 6-monthly; the organ that clears lithium and the long-term risk.
- **Thyroid function (TSH):** at baseline then roughly 6-monthly (often more in the first year); lithium causes hypothyroidism.
- **Also:** baseline and 6-monthly calcium and weight; baseline ECG where cardiovascular risk exists.
- **Target ranges the level is read against:** maintenance **0.6 to 1.0 mmol/L**, acute mania **0.8 to 1.2 mmol/L**, toxicity above **1.5 mmol/L**.

HOLD THIS

Sample lithium as a standardised twelve-hour trough, recheck 5 to 7 days after every dose change until stable, then run the level 3-monthly (some guidelines 6-monthly) and the renal and thyroid panel roughly 6-monthly, checking more often in the elderly or on interacting drugs.

16 . Lithium toxicity

lithium toxicity is the one lithium emergency the board expects you to recognise on sight, grade, and manage in the right order. Lithium has the narrowest therapeutic index in psychiatry, so a patient sitting comfortably in the maintenance range of **0.6 to 1.0 mmol/L** can be pushed into toxicity by an ordinary intercurrent event: a bout of gastroenteritis, a hot spell with poor fluid intake, a new diuretic, or an NSAID bought over the counter. The examinable core is the **graded picture keyed to the serum level** and the **stepwise management**, because both are scored precisely and both save lives.

Everything below is keyed to the twelve-hour trough **serum level** and verified against the Maudsley Prescribing Guidelines, with the guideline-level counselling and threshold cross-checked against CANMAT and the Indian Psychiatric Society clinical practice guideline (Maudsley 2021; Yatham 2018; Shah 2017). The Maudsley states that toxic effects reliably occur at levels above **1.5 mmol/L**, that disorientation and seizures usually appear above 2 mmol/L progressing to coma and death, and that dialysis is often used above 3 mmol/L (Maudsley 2021). The sampling rule, target ranges and organ monitoring sit alongside this in the lithium initiation

and monitoring notes; the wider emergency frame for acute management and the perinatal picture is set out in the Perinatal/women's mental health and emergency psychiatry notes.

Fig 12.9 Lithium toxicity graded by serum level. Mild toxicity from 1.5 to 2.0 mmol/L gives coarse tremor, GI upset and lethargy; moderate toxicity (2.0 to 2.5) adds confusion, ataxia and dysarthria; severe toxicity above 2.5 brings seizures, coma and renal failure and needs haemodialysis. Any level with toxic features counts as toxicity, and dehydration or an interacting drug is the usual precipitant.

16.1 Why toxicity happens: the precipitants

Anything that raises the lithium level or the brain's exposure to it. Lithium is handled by the kidney exactly like sodium, so most precipitants act by changing sodium balance or renal clearance. The examinable list is: **dehydration** (vomiting, diarrhoea, fever, hot climate, reduced intake), **sodium loss** or a low-salt diet, **renal impairment** (which lowers clearance), **drug interactions**, and **overdose** (deliberate or accidental) (Maudsley 2021). The Maudsley notes that most risk factors involve a fall in sodium or a change in how the body handles sodium, for example low-salt diets, dehydration, drug interactions and uncommon illnesses such as Addison's disease (Maudsley 2021).

The interacting drugs to hold. Three classes raise the level and precipitate toxicity: thiazide diuretics, ACE inhibitors and angiotensin-receptor blockers, and NSAIDs (Maudsley 2021). Each reduces renal lithium clearance, so a stable patient started on any of them needs a repeat level and can tip into toxicity within days.

RULE **Any coarse tremor, ataxia or confusion in a patient on lithium is toxicity until the level proves otherwise.** Check the level before you look for another cause.

TRAP **Continuing lithium through an intercurrent illness with vomiting or dehydration.** Fluid loss concentrates the drug; the level climbs even though the dose has not changed. Withhold lithium and rehydrate.

16.2 The graded picture: mild, moderate, severe

Read the features against the level. Toxicity follows a **mild moderate severe** gradient that tracks the rising **serum level**, and the board rewards you for stating the **grading** with the

matching level band. The Maudsley anchors the two hard thresholds: toxic effects reliably occur above **1.5 mmol/L** (gastrointestinal upset plus early CNS signs), and above 2 mmol/L disorientation and seizures usually occur, progressing to coma and death (Maudsley 2021). The widely taught three-band scheme places mild toxicity from 1.5 to 2.0 mmol/L, moderate from 2.0 to 2.5 mmol/L, and severe above 2.5 mmol/L, consistent with the Maudsley anchors above (serious neurotoxicity and seizures usually appear above 2, and dialysis is often needed above 3).

Mild (1.5 to 2.0 mmol/L)

coarse **tremor** (the fine physiological tremor becomes coarse), gastrointestinal upset (anorexia, nausea, diarrhoea), lethargy and mild drowsiness.

Moderate (2.0 to 2.5 mmol/L)

confusion, **ataxia**, dysarthria, myoclonus and muscle twitching, worsening coarse tremor, marked drowsiness.

Severe (above 2.5 mmol/L)

seizure, coma, cardiovascular collapse, and renal failure; ultimately death.

The level is only a guide. The Maudsley cautions that these plasma levels are a guide only and individuals vary in susceptibility, and that neurotoxicity has been described even at normal plasma levels because brain lithium may not be reflected in the plasma concentration (Maudsley 2021). Treat the patient in front of you, not the number alone.

1.5 to 2.0	2.0 to 2.5	above 2.5
MILD TOXICITY (MMOL/L)	MODERATE TOXICITY (MMOL/L)	SEVERE TOXICITY (MMOL/L)

16.3 The graded table of level, features and management

The one table to hold for the viva. Grade, features and the corresponding management step line up as follows (Maudsley 2021).

GRADE	SERUM LEVEL (MMOL/L)	CLINICAL FEATURES	MANAGEMENT
Mild	**1.5 to 2.0**	coarse tremor, GI upset (anorexia, nausea, diarrhoea), lethargy	Stop lithium; check level, renal function and electrolytes; rehydrate; recheck level
Moderate	**2.0 to 2.5**	confusion, ataxia, dysarthria, myoclonus, coarse tremor	Stop lithium; admit; intravenous normal saline to restore volume and sodium; serial levels and renal function; supportive care
Severe	**above 2.5**	seizure, coma, cardiovascular collapse, renal failure	Stop lithium; medical/ICU care; correct volume; **haemodialysis** for severe features or renal failure, usually at levels above 2.5 to 3.0 mmol/L

Lithium toxicity grading: features and management keyed to the twelve-hour trough serum level, mild 1.5 to 2.0, moderate 2.0 to 2.5, severe above 2.5 mmol/L; haemodialysis is reserved for severe toxicity (Maudsley 2021). Highlighted cells are the board-critical level bands.

16.4 Management: stop, assess, rehydrate, dialyse if severe

Four steps in order. The management of **lithium toxicity** is a fixed sequence. First, **stop lithium** immediately. Second, **check the level and renal function and electrolytes** (serum lithium, creatinine and eGFR, urea and electrolytes) and repeat serially, because the level can keep rising as the drug redistributes. Third, **rehydrate with saline**: intravenous normal (0.9%) saline restores intravascular volume and sodium and promotes renal excretion of lithium. Fourth, use **haemodialysis** for severe toxicity, that is high levels, renal failure, or severe clinical features such as seizures, coma or haemodynamic collapse (Maudsley 2021). The Maudsley states that above 3 mmol/L peritoneal or haemodialysis is often used, and that in more severe symptomatic cases osmotic or forced alkaline diuresis has historically been used in a medical facility (Maudsley 2021).

Why dialysis, and why it may need repeating. Lithium is a small, non-protein-bound ion that dialyses readily, so haemodialysis rapidly clears it from plasma. But lithium leaves the intracellular and brain compartments slowly, so the plasma level can rebound after a session ends, and dialysis may need to be repeated until the post-dialysis rebound level stays below the toxic threshold. This is why serial levels continue after the first run.

RULE **Stop lithium, give saline, and dialyse the severe.** Haemodialysis is indicated for very high levels, renal failure, or severe neurological or cardiovascular features, regardless of the exact number.

16.5 The silent sequel: delayed and irreversible neurotoxicity

Recovery is not always complete. A minority of patients who survive significant neurotoxicity are left with persistent, sometimes permanent, cerebellar and other neurological deficits: the **silent** picture, described as the syndrome of irreversible lithium-effectuated neurotoxicity (SILENT). The hallmark is a persisting cerebellar syndrome, most often ataxia and dysarthria, that outlasts the acute episode and the fall in serum level. The teaching point is that lithium neurotoxicity is not always a fully reversible event, which is a further reason to act quickly and not to let a moderate picture drift toward the severe. Delayed neurotoxic sequelae can persist after the plasma level has normalised, consistent with the Maudsley observation that brain lithium is not reflected in the plasma (Maudsley 2021).

INDIA

Lithium is cheap, freely available and heavily prescribed in Indian practice, marketed as lithium carbonate (Licab, and the controlled-release Intalith CR). The commonest real-world precipitants here are summer dehydration, gastroenteritis with vomiting and diarrhoea, and over-the-counter NSAIDs bought without a prescription, so counsel every patient at initiation to withhold lithium and increase fluids during any vomiting, diarrhoea or febrile illness and to attend for a level. Serum lithium, creatinine and electrolyte assays are inexpensive and widely available; the practical management chain to hold is stop lithium, send a stat level with renal function and electrolytes, start intravenous normal saline, and refer for **haemodialysis** if the level is high, renal function is failing, or the patient has seizures or coma (Maudsley 2021; Shah 2017). Where dialysis is not immediately available, transfer the severely toxic patient to a centre that has it rather than waiting.

PEARL

The discriminator between a therapeutic tremor and toxicity is its character: lithium normally causes a fine physiological tremor, but a **tremor** that has become coarse, especially with any GI upset, ataxia or confusion, signals toxicity and demands a level. Do not attribute new ataxia or confusion in a lithium patient to age, alcohol or a virus until the level is back.

MNEMONIC

SALT loss climbs the level; STOP-SALINE-DIALYSE brings it down

Precipitants act through **SALT** and water: dehydration, sodium loss, NSAIDs and diuretics, renal impairment, overdose. Management is **STOP** lithium, check the level and renal function and electrolytes, **SALINE** (rehydrate with normal saline), and **DIALYSE** if severe (high level, renal failure or severe features).

GOOD TO REMEMBER

- **Mild toxicity (around 1.5 mmol/L):** coarse tremor, GI upset and lethargy; the earliest and commonest feature.
- **Moderate toxicity (around 1.5 to 2.5 mmol/L):** ataxia, dysarthria, confusion and myoclonus; the patient is now clearly encephalopathic.
- **Severe toxicity (above 2.5 mmol/L):** seizures, coma and cardiovascular collapse; a medical emergency.
- **Precipitants:** dehydration and NSAIDs are the classic ones; also sodium loss, diuretics, ACE inhibitors/ARBs, renal impairment and overdose.
- **First management step:** stop lithium, check level plus renal function and electrolytes, rehydrate with saline; dialyse if severe.
- **Discriminator (silent sequel):** haemodialysis for severe toxicity; a persisting cerebellar syndrome (silent, irreversible neurotoxicity) can outlast the normalised level.

HOLD THIS

Coarse tremor and GI upset at ~1.5, ataxia/dysarthria/confusion at 1.5 to 2.5, seizures/coma above 2.5 mmol/L: stop lithium, check level with renal function and electrolytes, rehydrate with saline, and haemodialyse the severe (Maudsley 2021).

17 . Lithium and the kidney

The kidney is where lithium is cleared and where lithium does its most talked-about harm, so **lithium and the kidney** is a favourite examiner theme. Two effects sit at opposite ends of the time axis: an **early, common, largely reversible** concentrating defect that the patient feels as thirst and frequent urination, and a **slow, long-term** decline in filtration that only a monitoring trend will reveal. The board rewards you for separating the two, for naming the drug that treats the first, and for knowing that the second is managed by watching the eGFR trend and taking a measured nephrology-guided decision rather than stopping lithium on a single reading.

The whole topic follows from one physiological fact set out in the Mood disorders: pharmacotherapy renal-handling detail: lithium enters collecting-duct principal cells through the epithelial sodium channel (ENaC), competing with sodium, and its intracellular accumulation inhibits the renal response to antidiuretic hormone and, over years, drives interstitial fibrosis (Meyer and Stahl 2023; Maudsley 2021). Everything below, the polyuria, the amiloride, the eGFR trend, the CKD risk-benefit, derives from that. The initiation, dosing and toxicity detail sits in the mood-block pharmacotherapy notes; the twelve-hour trough and the full baseline and follow-up panel are in the lithium monitoring topic; the guideline-anchored PLAN that keeps lithium first-line is in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes. The receptor and channel background is in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

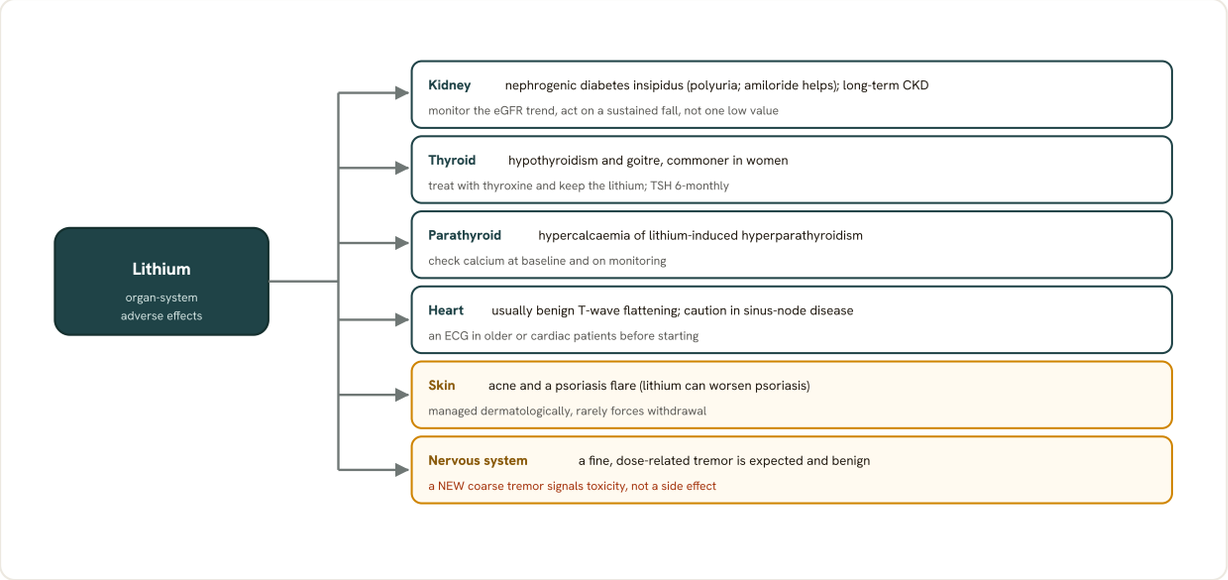

Fig 12.10 The organ-system adverse effects of lithium and their monitoring. The kidney (nephrogenic diabetes insipidus, long-term chronic kidney disease) and thyroid (hypothyroidism, goitre) are the load-bearing ones, caught by routine renal and thyroid monitoring; hypercalcaemia, benign cardiac T-wave changes, acne and psoriasis, and a fine dose-related tremor complete the picture. A new coarse tremor is the exception: it signals toxicity rather than a tolerable side effect.

17.1 Nephrogenic diabetes insipidus: the mechanism

Lithium blocks the renal response to ADH. The earliest and commonest renal effect is nephrogenic diabetes insipidus. Lithium entering the collecting-duct principal cell via ENaC accumulates intracellularly and, in roughly 20% of patients, produces insensitivity to antidiuretic

hormone (ADH, vasopressin) with downregulation of the water-absorbing aquaporin-2 channels on the apical surface (Meyer and Stahl 2023). The kidney can no longer concentrate the urine in response to ADH, so dilute urine is passed in large volume. The result is **polyuria** and, secondarily, **polydipsia** as the patient drinks to keep up. It is nephrogenic (the defect is at the kidney, the ADH itself is normal or high), which is why it is called nephrogenic diabetes insipidus rather than a central one.

Common, and usually reversible early. A reduction in urinary concentrating capacity is common on lithium and, in the short to medium term, is usually reversible on stopping or dose reduction; renal effects may become irreversible only after long-term treatment (Grierson and companion authors, Companion to Psychiatric Studies; Meyer and Stahl 2023). Polyuria is defined as a 24-hour urine output above **3 litres** (Meyer and Stahl 2023). It is the effect patients notice first and complain about most, and it is the single commonest cited reason for wanting to stop lithium, so recognising and treating it early forestalls unnecessary discontinuation.

RULE **Lithium polyuria is nephrogenic diabetes insipidus until proven otherwise.** ADH is normal, the kidney cannot respond, and the defect is usually reversible if caught early.

17.2 Assessing the polyuria

Ask at every visit, then quantify. Assessment of **polyuria** starts with routine inquiry at each office visit about excessive thirst and urination, because some patients underreport the functional impact (Meyer and Stahl 2023). Two office tools then quantify it. The 24-hour fluid intake record (FIR) is a simple screen the patient can keep: an intake below 2000 mL over 24 hours makes polyuria very unlikely, while an intake climbing towards 3000 to 3500 mL makes it likely. The early morning urine osmolality (EMUO) estimates concentrating ability directly and tracks response to treatment.

Polyuria (definition)
24-hour urine output above 3 litres; the standard threshold.

24-hour fluid intake record (FIR)
patient-kept screen; below 2000 mL/24 h makes polyuria unlikely, above 3500 mL/24 h makes it likely.

Early morning urine osmolality (EMUO)
direct measure of concentrating ability; normal exceeds about 850 mOsm/kg.

Full nephrogenic diabetes insipidus
EMUO below 300 mOsm/kg; treat regardless of how loudly the patient complains.

A normal EMUO is above about **850 mOsm/kg** after overnight water deprivation; a value below **300 mOsm/kg** represents full nephrogenic diabetes insipidus and warrants treatment whatever the patient reports, because it signals clear lithium accumulation in the principal cells (Meyer and Stahl 2023).

17.3 Managing nephrogenic diabetes insipidus: dose review, once-daily dosing, amiloride

First tighten the regimen, then add amiloride. Management of lithium-related **nephrogenic diabetes insipidus** proceeds in a logical order. First, review the dose and the serum level: keep the maintenance twelve-hour trough modest, and prefer once-daily dosing, because polyuria occurs more frequently with twice-daily than once-daily regimens and modern once-daily dosing lowers renal risk (Maudsley 2021; Meyer and Stahl 2023). Second, where polyuria persists, add amiloride.

Amiloride blocks lithium entry into the collecting duct. Amiloride is a potassium-sparing diuretic that specifically blocks ENaC, the very channel lithium uses to enter principal cells, so it reduces lithium's intracellular accumulation and improves urine concentrating ability (Meyer and Stahl 2023; Kortenoeven et al. 2009). It is the primary, best-evidenced treatment for lithium-related nephrogenic diabetes insipidus and should be started as soon as a concentrating problem is detected; the claim that the only option is to switch off lithium is simply untrue (Meyer and Stahl 2023). Importantly, amiloride is one of the diuretics whose effect on lithium clearance is clinically insignificant, so it does not itself push the lithium level up the way a thiazide does, though at least one repeat lithium level after starting it is prudent (Meyer and Stahl 2023).

TRAP **Reaching for a thiazide to treat lithium polyuria.** A thiazide reduces polyuria but raises the lithium level and risks toxicity; amiloride, an ENaC blocker, treats the concentrating defect at its mechanism without that hazard.

WORKED EXAMPLE

A patient stable on lithium complains of drinking constantly and passing urine through the night. You confirm a 24-hour fluid intake record above 3500 mL and an early morning urine osmolality of 250 mOsm/kg, which is full nephrogenic diabetes insipidus. You do not stop the lithium. You move the patient to once-daily bedtime dosing, keep the twelve-hour trough modest, and start amiloride, then track the early morning urine osmolality as it recovers. The patient stays on the drug that protects them from relapse.

17.4 The long-term risk: chronic kidney disease

A slow decline in eGFR over years. The second, separate concern is chronic kidney disease. Years of lithium exposure can be associated with a slow decline in the estimated glomerular filtration rate (eGFR), the histological substrate being a chronic interstitial nephropathy, that is proximal tubular atrophy and interstitial fibrosis driven by intracellular lithium inhibiting GSK-3-beta in principal cells (Meyer and Stahl 2023). Lithium can lead to a reduction in glomerular filtration rate, though the magnitude of the risk is uncertain; it is driven mainly by cumulative exposure, repeated episodes of toxicity, older multiple-daily dosing and comorbidity (hypertension, diabetes) rather than by any single therapeutic level (Companion to Psychiatric Studies; Meyer and Stahl 2023).

Lithium is not the whole story. The modern reframing matters for the exam. Much of the renal risk historically pinned on lithium alone actually reflects two things: old prescribing practices (multiple daily dosing, allowing trough levels to exceed 1.2 mEq/L) and the chronic kidney

disease risk factors, hypertension, metabolic syndrome, diabetes and smoking, that are disproportionately common in bipolar patients (Meyer and Stahl 2023). Having a bipolar diagnosis itself carries a roughly 3-fold increased CKD risk independent of drug treatment. With once-daily dosing and modest outpatient trough levels below about 1.0 mEq/L, progression to end-stage renal disease attributable to lithium has become very rare (Meyer and Stahl 2023). So chronic kidney disease is a real long-term risk that mandates monitoring, but not the near-inevitability it was once feared to be.

HOLD THIS

Lithium harms the kidney in two separable ways: an early, common, usually reversible nephrogenic diabetes insipidus (polyuria, treated with amiloride) and a slow, long-term chronic kidney disease seen as a declining eGFR trend, watched over time and never acted on from one low value.

17.5 Monitoring the eGFR trend, not a single value

Watch the trend. Because the long-term change is a gradual slope, the practical rule is to monitor the **eGFR trend** rather than react to any one reading. Renal function (eGFR and creatinine) is checked at baseline and then roughly 6-monthly on stable lithium, more often when eGFR is already reduced or an interacting drug is in play (Maudsley 2021; Meyer and Stahl 2023). What triggers action is not a value but a verified downward slope. The Lithium Handbook operationalises this: increase lab frequency to every 3 months when the eGFR is below **60 ml/min**, or when there is an initial decline of more than **2 ml/min over 6 months** or more than **4 ml/min over 12 months** confirmed on a repeat specimen (Meyer and Stahl 2023).

When to bring in nephrology. A nephrology review is warranted when the eGFR falls in a sustained way, not on a single blip: a second confirmed decline exceeding those thresholds, an eGFR below **45 ml/min** verified on repeat, progression of albuminuria to stage A3, or nephrogenic diabetes insipidus unresponsive to maximal amiloride plus adjunctive acetazolamide (Meyer and Stahl 2023). The point of the nephrology referral is a joint, measured decision, weighing the renal trajectory against lithium's mood-stabilising and anti-suicide benefit, rather than a reflex switch.

RULE **Monitor the eGFR trend on long-term lithium and act on a sustained fall, not a single value.** A confirmed decline (for example more than 4 ml/min over 12 months on repeat) triggers closer monitoring and nephrology review; one isolated low reading does not.

RENAL PARAMETER	BASELINE	STABLE FOLLOW-UP	ESCALATE FREQUENCY WHEN	REFER TO NEPHROLOGY WHEN
eGFR (with creatinine)	yes	**roughly 6-monthly**	**below 60 ml/min, or decline over 2 ml/min in 6 months / over 4 ml/min in 12 months (repeat-verified)**	**second confirmed decline, or eGFR below 45 ml/min on repeat**

RENAL PARAMETER	BASELINE	STABLE FOLLOW-UP	ESCALATE FREQUENCY WHEN	REFER TO NEPHROLOGY WHEN
Early morning urine osmolality (EMUO)	consider if over 50 years	if polyuria / on amiloride	new or increased polyuria, or EMUO below 300 mOsm/kg	full NDI unresponsive to maximal amiloride plus acetazolamide
Albumin-to-creatinine ratio (ACR)	as indicated	for CKD risk factors	progression from stage A1 to A2 (repeat-verified)	stage A3
24-hour fluid intake record (FIR)	not routine	periodic office screen	polyuria complaints	not a referral trigger by itself

Practical renal monitoring on long-term lithium: the eGFR trend is the spine, with EMUO and the fluid intake record tracking the concentrating defect and the ACR tracking glomerular injury from comorbid CKD risk factors (Meyer and Stahl 2023; Maudsley 2021). Highlighted cells are the trend-based triggers a resident must hold.

17.6 Do not stop abruptly: the rebound-mania trap

A low eGFR is not a reason to stop lithium overnight. The most dangerous reflex on this topic is to see one reduced eGFR and abruptly discontinue lithium. Abrupt cessation carries a much greater than expected incidence of manic relapse in the first few months, even in patients who have been symptom-free for years (Maudsley 2021). If a decision to withdraw lithium is genuinely reached, the dose should be reduced gradually over at least a month, preferably three, avoiding stepwise plasma-level reductions greater than 0.2 mmol/L, which lowers the relapse risk (Maudsley 2021). Where the concern is renal, the correct path is the eGFR trend and a nephrology-guided risk-benefit decision, continuing lithium unless the likelihood of progression to end-stage disease clearly outweighs its benefit (Meyer and Stahl 2023).

TRAP **Stopping lithium abruptly on one low eGFR.** That risks rebound mania; the measured move is to confirm the trend, involve nephrology, and if withdrawing at all, taper over at least a month.

3	60	45
POLYURIA THRESHOLD (LITRES/24 H)	ESCALATE LABS BELOW (EGFR ML/MIN)	NEPHROLOGY REVIEW BELOW (EGFR ML/MIN)

INDIA

Lithium carbonate (marketed as Licab and as the controlled-release Intalith CR) is cheap, freely available and heavily prescribed in Indian practice, so its renal monitoring falls to the psychiatrist. Serum creatinine and eGFR are inexpensive and widely available; amiloride is available and affordable. The Indian Psychiatric Society schedule builds the renal check into routine care: baseline and 6-monthly creatinine and eGFR alongside TSH, calcium and weight, with counselling on dehydration risk (Shah et al., Indian Psychiatric Society bipolar guideline). The practical Indian-exam point is that a falling eGFR trend, not a single value, drives escalation, and that amiloride, not switching off lithium, is the first answer to lithium polyuria.

MNEMONIC

PEAR-T

Lithium and the kidney: **P**olyuria and polydipsia are the early, common, usually reversible sign, **E**NaC entry drives it (so amiloride, an ENaC blocker, treats it), **A**miloride plus once-daily dosing and a dose review is the management, **R**enal trend (the eGFR slope) is what you watch long term for chronic kidney disease, and **T**aper never abruptly stop (rebound mania).

GOOD TO REMEMBER

- **Nephrogenic diabetes insipidus:** lithium blocks the renal response to ADH at the collecting duct (via ENaC entry, aquaporin-2 downregulation), causing polyuria and polydipsia; common (about 20%), usually reversible early.
- **Amiloride:** a potassium-sparing ENaC blocker that stops lithium entering the collecting duct; the first-line, best-evidenced treatment for lithium polyuria, alongside dose review and once-daily dosing, does not raise the lithium level.
- **Polyuria assessment:** ask at every visit; quantify with the 24-hour fluid intake record and early morning urine osmolality; polyuria is over 3 litres/24 h, full NDI is EMUO below 300 mOsm/kg.
- **Chronic kidney disease:** a slow, long-term eGFR decline (chronic interstitial nephropathy); real but modest with modern once-daily dosing and troughs below about 1.0 mEq/L, and partly driven by comorbid hypertension and diabetes.
- **Monitoring:** watch the eGFR trend, not a single value; escalate labs below eGFR 60 ml/min or a confirmed decline (over 4 ml/min in 12 months); nephrology review for a sustained fall or eGFR below 45 ml/min on repeat.
- **Do not stop abruptly:** one low eGFR is not grounds to stop; abrupt cessation risks rebound mania, so confirm the trend, involve nephrology, and if withdrawing, taper over at least a month.

18 . Lithium and the thyroid and parathyroid

Why it matters. lithium is the most effective long-term agent in bipolar disorder, yet clinician fear of its endocrine effects drives underuse (Meyer and Stahl 2020). The examinable point is that the two glandular effects, on the **thyroid** and the **parathyroid**, are common, detectable on routine bloods, and treatable without ever stopping the lithium. This is the topic where a resident must resist the reflex to withdraw an effective drug for a monitorable, correctable side effect.

Frame the whole topic around three verified truths: lithium accumulates in the thyroid and inhibits thyroid hormone release, producing **hypothyroidism** (often with a **goitre**) that is picked up by the routine TSH and corrected with levothyroxine; it also shifts the parathyroid calcium set point, producing hypercalcaemia of lithium-induced hyperparathyroidism, picked up by the routine serum calcium; and neither event, on its own, is a reason to discontinue lithium.

18.1 Mechanism at the thyroid follicle

Iodide trapping and hormone release. Lithium is a substrate for the sodium-iodide symporter (NIS) and concentrates in the thyroid gland at levels **3 to 4 times** those in plasma (Meyer and Stahl 2020). Its dominant action is **inhibition of T4 and T3 release** from the gland; it additionally alters thyroglobulin conformation so that coupling of iodinated tyrosine residues to form T4 and T3 is impaired. The net effect is a fall in circulating thyroid hormone, a

compensatory rise in TSH, and, over time, clinical hypothyroidism. Importantly, lithium is **not** associated with Hashimoto thyroiditis, Graves disease, an excess of antithyroid antibodies, or thyroid tumours (Meyer and Stahl 2020, Companion 2010).

RULE **Concentrate then throttle.** Lithium is trapped by the NIS and chiefly blocks thyroid hormone release, so TSH rises and hypothyroidism, not autoimmunity, is the signature.

18.2 Hypothyroidism: the common, treatable thyroid effect

Frequency and who is at risk. Slight falls in T4 with compensatory rises in TSH appear within a few months and usually stabilise within 12 months (Companion 2010). The annual incidence of new-onset **hypothyroidism** on lithium is about **1.5 percent**, and overt hypothyroidism occurs in roughly **8 to 19 percent** across long-term studies (Meyer and Stahl 2020). It is distinctly **commoner in women**, with female rates about three times those of men. The classic at-risk profile is a woman over 45 with circulating antithyroid antibodies and a slight but sustained TSH elevation (Companion 2010).

Detection and management. It is detected by the **routine TSH monitoring** already built into lithium follow-up: a sustained TSH elevation, even with a normal T4, is sufficient indication to supplement. It is managed with levothyroxine (L-thyroxine, Indian brand Thyronorm), titrated to the TSH, **without stopping lithium** (Meyer and Stahl 2020). A prior history of hypothyroidism is not a reason to withhold lithium, and new-onset hypothyroidism is not a reason to discontinue it.

HOLD THIS

Lithium hypothyroidism is a TSH diagnosis with a levothyroxine solution: supplement and keep the lithium, never stop the lithium to treat the thyroid.

18.3 The goitre, and the rarer hyperthyroidism

Goitre. Lithium-induced **goitre** is under-recognised on palpation but, on ultrasonography, is common, affecting over 50 percent of long-term users (Companion 2010). Most goitres are not palpable, and enlargement alone does not signify hypofunction. The mechanism reflects impaired iodine incorporation into thyroid hormone. Asymptomatic goitre, like biochemical or clinical hypothyroidism, is **not a contraindication** to continued lithium; only the rare multinodular goitre needing surgery is an exception, and long-term lithium does not increase thyroid carcinoma risk (Companion 2010).

Hyperthyroidism. Less commonly, patients may show hyperthyroidism, but on the best data this is rare and is likely **incidental** to lithium rather than caused by it (Meyer and Stahl 2020). In one large database analysis, lithium exposure was not significantly associated with hyperthyroidism after adjustment. The practical rule is unchanged: if TSH is low, continue lithium, confirm with T4 and T3, and work up Graves or Hashimoto disease on their own merits.

TRAP **Stopping the wrong drug.** Discontinuing an effective lithium to treat a hypothyroidism that levothyroxine would fully correct sacrifices the mood benefit for a problem that needed a second tablet, not withdrawal.

18.4 Hyperparathyroidism and hypercalcaemia: check calcium

Mechanism and picture. Lithium enters the parathyroid chief cell and, via GSK3-beta inhibition, disrupts the **calcium-sensing receptor** pathway, shifting the PTH set point to the right: a higher serum calcium is now required to suppress PTH. The earliest measurable change is therefore a rise in serum calcium, which is why routine monitoring includes **calcium** (Meyer and Stahl 2020). Chronic therapy in a subset unmasks a parathyroid adenoma or drives multiglandular hyperplasia; the clinical picture then is identical to primary **hyperparathyroidism**, is commoner in women, and may not reverse when lithium is stopped. A meta-analysis found total calcium raised by 0.09 mmol/L and PTH by 7.32 pg/mL on lithium (Meyer and Stahl 2020).

Detection and management. Sporadic elevated calcium is repeated in 3 to 6 months; persistent elevation is confirmed with an ionized calcium, then a PTH level, then endocrine referral. Because stopping lithium may not reverse established adenoma or hyperplasia, discontinuation is not the first move: symptomatic or criteria-meeting disease goes to parathyroid surgery, and calcimimetics such as cinacalcet allosterically activate the calcium-sensing receptor and offer a non-surgical option that lets lithium continue (Meyer and Stahl 2020).

GLAND	EFFECT	SCREENING TEST	MANAGEMENT (KEEP LITHIUM)
Thyroid	Hypothyroidism, goitre (commoner in women)	routine TSH	levothyroxine to TSH target
Thyroid	Hyperthyroidism (rare, usually incidental)	routine TSH (low)	confirm T4/T3, treat cause on merits
Parathyroid	Hyperparathyroidism with hypercalcaemia	routine serum calcium	surgery if criteria met, else cinacalcet

The two glandular effects of lithium, each caught by a routine test already in the monitoring panel, each treatable without withdrawing lithium.

18.5 Why this rarely forces lithium withdrawal, and where it sits in monitoring

The unifying principle. Thyroid and parathyroid dysfunction on lithium is **common, monitorable and treatable**, so it rarely forces lithium withdrawal. Hypothyroidism is not among the ten leading causes of lithium discontinuation and, in surveillance, accounts for only about a 2 percent discontinuation rate (Meyer and Stahl 2020). The guideline-anchored monitoring that catches both is standard: baseline TSH and calcium before starting, then thyroid and renal function plus plasma calcium checked at around 6 months and at least annually thereafter (CANMAT 2018). The Indian Psychiatric Society advises baseline and 6-monthly TSH, creatinine, eGFR and calcium, with TSH checked once or twice in the first 6 months then 6-monthly to yearly (IPS 2017); this could not be re-confirmed to the exact interval against the

primary IPS text here and is taken from the guideline digest. For the wider emergency frame around lithium and the perinatal frame, see the Perinatal/women's mental health and emergency psychiatry notes; for the initiation and toxicity detail, this note sits within the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes management thread.

8 to 19	1.5	6 to 12
OVERT HYPOTHYROIDISM ON LITHIUM (PERCENT)	ANNUAL INCIDENCE NEW HYPOTHYROIDISM (PERCENT)	TSH PLUS CALCIUM REVIEW INTERVAL (MONTHS)

GOOD TO REMEMBER

- **Lithium (thyroid):** concentrated by the NIS to 3 to 4 times plasma and inhibits T4/T3 release; signature effect is hypothyroidism with goitre, commoner in women; the one thing to hold is that a sustained TSH rise triggers supplementation, not withdrawal.
- **Hypothyroidism:** detected by routine TSH, managed with levothyroxine (Thyronorm) titrated to TSH; keep the lithium.
- **Goitre:** common on ultrasound (over 50 percent), usually impalpable and euthyroid; not a contraindication and no increase in thyroid carcinoma.
- **Hyperparathyroidism:** lithium shifts the parathyroid PTH set point rightward via the calcium-sensing receptor; discriminator on bloods is a rising serum calcium; confirm with ionized calcium then PTH, treat with surgery or cinacalcet, keep the lithium where possible.

INDIA

Lead with the Indian brand where you name one: lithium carbonate is Licab (Intas) or Intalith CR (Samarth); levothyroxine for the hypothyroidism is Thyronorm (Abbott) or Eltroxin. Generic names stay primary in prescribing; the brand is the parenthetical the patient will recognise on the strip.

PEARL

Both glandular effects are caught by tests you are already drawing: the TSH catches the thyroid, the serum calcium catches the parathyroid. Add calcium to the lithium panel and neither surprise you.

19 . Lithium: dermatological and cardiac effects

Two organ-system effects of **lithium** (Licab or Intalith; lithium carbonate) are examined less as reasons to stop the drug and more as things you must recognise, counsel about, and manage without reflex withdrawal. The **dermatological** effects are cosmetic and usually treatable topically, but they drive real-world non-adherence if missed; the **cardiac** effects are mostly benign ECG changes, with one genuine caution in sinus-node disease. The exam framing is: name the skin problems and the ECG changes, state that both are usually manageable, and know the single situation where the heart forces your hand (Maudsley 2021; Meyer and Stahl 2021).

Everything below is verified against the Meyer and Stahl Lithium Handbook for the detailed derm and cardiac profile, cross-checked against the Maudsley Prescribing Guidelines and Kaplan and Sadock for the class-level statements (Maudsley 2021; Meyer and Stahl 2021; Kaplan 2024).

The renal, thyroid, toxicity and monitoring picture sits alongside this in the lithium initiation and monitoring notes; the baseline pre-lithium ECG rule is set out there too.

19.1 Dermatological effects: acne, psoriasis, and hair thinning

Skin and hair problems are new-onset or an exacerbation of what was already there. The **dermatological** set that the board expects is: acne (an acneiform eruption, new or worsened), a **psoriasiform rash**, the **exacerbation of psoriasis** (lithium can worsen or unmask psoriasis), and diffuse hair thinning (alopecia). Folliculitis and a maculopapular rash also occur (Meyer and Stahl 2021). The Maudsley states plainly that some skin conditions such as psoriasis and acne can be aggravated by lithium therapy (Maudsley 2021). The true incidence is uncertain because the literature is mostly case reports, and controlled data have not clearly separated lithium from placebo, but the association is real enough that you counsel about it and ask at every visit (Meyer and Stahl 2021).

Managed dermatologically, rarely forcing withdrawal. The governing principle is that lithium discontinuation is not always necessary for these problems. Acne responds to topical benzoyl peroxide (2 to 10 percent) and, if needed, topical retinoids or a dermatology referral; a psoriasis flare is discussed honestly and co-managed with a dermatologist, and modern biologic therapy may let some patients stay on lithium; hair thinning is treated as any pattern hair loss, with topical minoxidil (5 percent), remembering that regrowth is slow, so early detection by routine inquiry is the real intervention (Meyer and Stahl 2021). Only a problem with no obvious option other than stopping, such as a persistent maculopapular rash, prompts a slow taper with dermatology input if you wish to rechallenge (Meyer and Stahl 2021).

RULE **Ask about skin eruptions and hair loss at every visit and manage them dermatologically, not by stopping lithium.** Most respond to topical treatment; discontinuation is the exception, not the rule.

TRAP **Stopping lithium reflexively for acne or a psoriasis flare in a patient it has stabilised.** You trade a treatable, cosmetic problem for a real relapse risk; treat the skin and keep the mood stabiliser.

19.2 Cardiac effects: benign T-wave changes, and the sinus-node caution

The common ECG changes are benign. The usual **cardiac** finding on the ECG is a benign, reversible **T-wave** flattening or inversion, reflecting an effect on ventricular repolarisation; long-term treatment can also produce benign PR-interval prolongation and U-waves that resemble those of hypokalaemia (Meyer and Stahl 2021; Kaplan 2024). These reflect the chronicity of lithium exposure and do not carry sudden-death risk, so a novel benign ECG finding is not a reason to stop the drug; any real impact on cardiac conduction is unlikely at therapeutic serum levels and becomes prominent mainly in toxicity (Meyer and Stahl 2021). Lithium, unlike antipsychotics, tricyclics, citalopram, escitalopram and lamotrigine, carries no routine QT-monitoring warning outside overdose (Meyer and Stahl 2021).

The one genuine caution: sinus-node dysfunction. Lithium can worsen or unmask sick sinus syndrome, so it is associated with bradycardia, **sinus node** dysfunction, sinus block and sinus arrest (Meyer and Stahl 2021; Kaplan 2024). The mechanism is not that lithium creates the pathology but that it hastens the appearance of an underlying, often age-related, degenerative sinus-node disease; the rare patient who develops symptomatic bradycardia at therapeutic levels represents unmasked sick sinus syndrome and may need lithium interrupted until a pacemaker is placed (Meyer and Stahl 2021). This is why a baseline ECG is advised in the older or cardiac patient, that is roughly above age 40 or with cardiovascular risk factors, syncope or a family history of sudden cardiac death, before starting lithium (Meyer and Stahl 2021).

toxic or chronic	**above 40**
EXPOSURE DRIVING ANY CONDUCTION EFFECT	BASELINE ECG ADVISED FROM THIS AGE (YEARS)

RULE **Lithium ECG changes are usually benign, but avoid lithium in sinus-node dysfunction.** Benign T-wave changes are no reason to stop; symptomatic sick sinus syndrome is.

TRAP **Starting lithium in significant conduction disease without a cardiology view.** In an older or cardiac patient, get a baseline ECG first; unmasked sinus-node disease can present with symptomatic bradycardia and near-syncope.

HOLD THIS

Lithium's skin effects (acne, psoriasis flare, hair thinning) are treated dermatologically and rarely force withdrawal; its ECG changes (T-wave flattening or inversion) are usually benign, and the one real caution is sinus-node disease, where lithium can unmask sick sinus syndrome, so get a baseline ECG in the older or cardiac patient.

GOOD TO REMEMBER

- **Dermatological (lithium):** acne, a psoriasiform rash and exacerbation of psoriasis, plus hair thinning; managed dermatologically (topical benzoyl peroxide, minoxidil, dermatology co-management), rarely forcing withdrawal (Meyer and Stahl 2021; Maudsley 2021).
- **Cardiac (lithium):** usually benign T-wave flattening or inversion on the ECG (a benign t-wave change on the ecg, plus benign PR prolongation and U-waves); not a reason to stop (Meyer and Stahl 2021; Kaplan 2024).
- **The discriminator to hold:** benign ECG change means continue; symptomatic bradycardia at therapeutic level means unmasked sick sinus syndrome, so interrupt lithium and involve cardiology.
- **The one caution:** caution with sinus node dysfunction; lithium can worsen sick sinus syndrome, so an ECG in the older or cardiac patient before starting (Meyer and Stahl 2021).

20 · Lithium drug interactions

Lithium is renally cleared, has a narrow therapeutic index and is handled by the kidney exactly like sodium. That single fact drives almost every clinically important interaction: any drug or state that makes the proximal tubule reabsorb more sodium, or that drops the glomerular filtration rate, drags lithium up with it and can tip a stable patient into toxicity. Because the safe window is so tight (**0.6 to 1.0 mmol/L** maintenance, toxicity from about **1.5 mmol/L**), a change

that would be trivial for most drugs is dangerous here. Examiners test this as a keyed direction question: does the drug **raise** or **lower** the level, and what do you do about it.

This note teaches the **lithium drug interactions** as a two-column split (drugs that raise versus drugs and states that lower the level), then the pharmacodynamic combinations that are dangerous even at a normal level, then the one practical monitoring rule that ties it together. Verify the direction of every interaction; a swapped direction is a critical error. For the wider prescribing frame, initiation and the toxicity syndrome, see the mood-block pharmacotherapy notes; for the renal and thyroid monitoring schedule and teratogenicity, cross to those; the receptor and CYP background sits in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

20.1 Why lithium interacts: the renal mechanism

Sodium mimicry. About 70 percent of filtered lithium is reabsorbed in the proximal tubule through the sodium/hydrogen exchanger (NHE3), where lithium competes with sodium for uptake (The Lithium Handbook 2023). When the body senses sodium or volume depletion it up-regulates proximal reabsorption, and lithium is reabsorbed alongside the sodium, so the serum level climbs. Anything that cuts the glomerular filtration rate does the same by reducing clearance. Lithium is not metabolised and not protein-bound, so there are essentially no cytochrome interactions: the interactions are pharmacokinetic-renal (level-changing) or pharmacodynamic (toxicity-adding at any level).

RULE **Sodium and lithium move together.** Volume depletion, a low-salt state, or any fall in GFR raises the lithium level, because the kidney reabsorbs lithium wherever it reabsorbs sodium.

20.2 Drugs that RAISE the level (the dangerous ones)

Reduced renal clearance. Three classes are the classic level-raisers a resident must hold, plus metronidazole. NSAIDs inhibit renal prostaglandins, constrict the afferent arteriole and cut renal blood flow, raising the level (Maudsley 2021); the effect is class-wide but aspirin and sulindac raise it less (The Lithium Handbook 2023). Thiazide diuretics deplete sodium, driving compensatory proximal reabsorption of lithium and a substantial rise. ACE inhibitors and ARBs limit angiotensin II mediated efferent arteriolar tone and cause volume depletion, both dropping GFR and raising the level. Metronidazole raises the level by reducing renal clearance.

CLASS / DRUG	DIRECTION	MECHANISM	PRACTICAL NOTE
NSAIDs (ibuprofen, diclofenac, indomethacin, naproxen, celecoxib)	**RAISE**	Inhibit renal prostaglandins, afferent vasoconstriction, reduced clearance	Includes over-the-counter ibuprofen; aspirin and sulindac raise it less
Thiazide diuretics (hydrochlorothiazide, chlorthalidone)	**RAISE**	Sodium depletion drives proximal lithium reabsorption	The strongest, most predictable diuretic riser
ACE inhibitors (enalapril, ramipril, lisinopril)	**RAISE**	Reduced efferent tone and volume depletion, lower GFR	Elderly especially vulnerable
ARBs (losartan, telmisartan, valsartan)	**RAISE**	Same efferent / volume mechanism as ACE inhibitors	Treat as equivalent to ACE inhibitors
Metronidazole	**RAISE**	Reduces renal lithium clearance	Recheck if a course is started

The four level-raisers to hold: NSAIDs, thiazides, ACE inhibitors and ARBs, plus metronidazole; each reduces clearance or depletes sodium.

TRAP **The over-the-counter NSAID.** A stable patient buys ibuprofen for backache, no prescriber is told, the level climbs over days and toxicity is precipitated. NSAID access is the commonest hidden riser.

20.3 A note on loop diuretics and potassium-sparing agents

Not all diuretics behave alike. Thiazides are the reliable, dangerous risers. Loop diuretics (furosemide) also reduce clearance and can raise the level, but the effect is more variable and less pronounced than with a thiazide. The safest rule for the exam and the clinic is to treat any diuretic start or stop as a level-changing event and recheck, rather than trusting one class to be neutral.

20.4 Drugs and states that LOWER the level

Increased clearance. The mirror image: anything that increases renal lithium clearance drops the level and risks loss of prophylaxis. Osmotic diuretics (mannitol) and, classically, the carbonic-anhydrase and osmotic agents increase lithium excretion. Theophylline and aminophylline increase renal clearance and lower the level. Caffeine, in the same way, modestly increases clearance, so a big swing in caffeine intake shifts the level. A high sodium intake competes lithium out of the proximal tubule and lowers the level, which is the flip side of the salt-restriction rule: a patient who suddenly increases dietary salt may lose efficacy, and one who crash-diets on salt may become toxic.

AGENT / STATE	DIRECTION	MECHANISM
Osmotic diuretics (mannitol)	**LOWER**	Increase lithium excretion
Theophylline / aminophylline	**LOWER**	Increase renal lithium clearance
Caffeine (sustained high intake)	**LOWER**	Increases clearance; abrupt cessation can raise the level
High sodium intake	**LOWER**	Sodium competes lithium out of proximal reabsorption
Low sodium intake / dehydration	RAISE	Volume/sodium depletion drives proximal lithium reabsorption

The level-lowering agents and the salt paradox: high salt lowers the level, low salt or dehydration raises it.

20.5 Pharmacodynamic interactions: toxicity added at a normal level

Danger without a level change. Some combinations are hazardous even when the serum level reads normal, because the toxicity is additive at the target rather than through clearance. First, the neurotoxicity risk with a high-dose antipsychotic: reports of lithium plus a high-dose antipsychotic (historically haloperidol) producing an encephalopathic, delirious, sometimes irreversible neurotoxic picture relate largely to the excessive antipsychotic doses used in earlier decades, and many such cases were actually neuroleptic malignant syndrome (The Lithium Handbook 2023). The practical message is caution and dose restraint, not absolute avoidance. Second, the serotonin-syndrome risk with serotonergic drugs: lithium is pro-serotonergic, so combining it with an SSRI, an SNRI (venlafaxine) or other serotonergic agents raises the risk of serotonin syndrome, and lithium augmentation of an antidepressant should be started low and titrated slowly (Shorter Oxford 2018). Third, the additive tremor: lithium tremor stacks with the tremor of an SSRI, valproate or a beta-agonist, worsening a benign but distressing side effect.

WORKED EXAMPLE

A woman stable at **0.7 mmol/L** on lithium and sertraline is prescribed hydrochlorothiazide for hypertension by her GP. Over the next week she develops a coarse tremor, nausea and unsteadiness. The thiazide has raised the lithium level; the additive serotonergic and tremor load with sertraline makes her more symptomatic. Withhold lithium, check the level and renal function, and rethink the antihypertensive.

20.6 The practical monitoring rule

Recheck around any interacting drug. The one rule that operationalises all of the above: whenever an interacting drug, especially an NSAID, a thiazide or an ACE inhibitor, is **started or stopped**, recheck the lithium level. Stopping a riser is as important as starting one, because a level that was in range only because of the interaction will fall. The verified interval is a trough (12 hours post-dose) level about **5 to 7 days** after any dose change or interacting-drug change (CANMAT 2018; Maudsley 2021). Counsel every patient not to buy over-the-counter NSAIDs, and to flag any new blood-pressure or water tablet, before it is dispensed.

Fig 12.11 Perinatal mood-stabiliser planning balances maternal relapse risk against fetal and neonatal exposure through shared specialist decisions, medication review, monitoring and an explicit postpartum and lactation plan.

0.6 to 1.0	1.5	5 to 7
MAINTENANCE LITHIUM (MMOL/L)	TOXICITY THRESHOLD (MMOL/L)	RECHECK AFTER INTERACTING-DRUG CHANGE (DAYS)

RULE **An NSAID, a thiazide or an ACE inhibitor raises the lithium level, so recheck it.** Recheck a trough level 5 to 7 days after any interacting drug is started or stopped.

HOLD THIS

NSAIDs, thiazides and ACE inhibitors / ARBs all RAISE the lithium level by cutting renal clearance; theophylline, caffeine and high sodium LOWER it; recheck a trough level 5 to 7 days after any interacting drug starts or stops.

MNEMONIC

NTA raises, CATS lowers

NSAID, **T**hiazide, **A**CE inhibitor (and ARB) RAISE the level. **C**affeine, **A**minophylline/theophylline, **T**oo much **S**alt LOWER it.

INDIA

Lithium carbonate is marketed in India as Licab (Torrent) and Intalith, among others; the generic stays primary in prescribing. The interaction trap is amplified here by easy over-the-counter access to NSAIDs (ibuprofen, diclofenac) and to combination analgesic and cold preparations, so explicit counselling to avoid self-medicated painkillers is essential.

PEARL

Caffeine cuts both ways: a heavy coffee drinker may run a lower level, and abruptly stopping caffeine (for example on admission) can nudge the level up. Ask about caffeine and salt habits when a level drifts without an obvious drug cause.

GOOD TO REMEMBER

- **NSAIDs:** inhibit renal prostaglandins and reduce clearance, so they RAISE the level; aspirin and sulindac raise it less; over-the-counter ibuprofen is the classic hidden precipitant.
- **Thiazide diuretics:** deplete sodium, drive proximal lithium reabsorption, RAISE the level; the strongest, most predictable diuretic riser.
- **ACE inhibitors / ARBs:** lower GFR via efferent tone and volume depletion, RAISE the level; the elderly are most vulnerable.
- **Metronidazole:** reduces renal clearance, RAISES the level; recheck if a course is started.
- **Theophylline / caffeine:** increase renal clearance, LOWER the level; a big change in caffeine intake shifts the level.
- **High sodium intake:** competes lithium out of the proximal tubule, LOWERS the level; low salt or dehydration does the opposite and RAISES it.
- **High-dose antipsychotic:** caution for a neurotoxic encephalopathy at a normal level; restrain the dose rather than avoid absolutely.
- **Serotonergic drugs (SSRI, venlafaxine):** additive serotonin-syndrome risk; start lithium augmentation low and titrate slowly.
- **The one rule:** recheck a trough lithium level 5 to 7 days after any interacting drug, especially an NSAID, thiazide or ACE inhibitor, is started or stopped.

21 . Lithium in pregnancy and lactation

Reproductive-age women make up a large share of the bipolar caseload, and **lithium in pregnancy** is the single most examined perinatal prescribing decision in psychiatry. The board wants three things from you: the specific **teratogenicity** signal (the first-trimester link with Ebstein anomaly), the way lithium pharmacokinetics shift across pregnancy and swing sharply at delivery, and the guideline-anchored logic of a planned risk-benefit discussion rather than a reflex stop. The whole topic is a study in numbers that are **small but raised**: the absolute risk to

the fetus is low, yet it is high enough that continuation demands fetal echocardiography and closer level monitoring.

Everything below is verified against the Maudsley Prescribing Guidelines and the Meyer and Stahl Lithium Handbook for the pharmacology and monitoring, with the class detail cross-checked against Kaplan and Sadock and the Companion to Psychiatric Studies (Maudsley 2021; Meyer 2023; Sadock 2024; Johnstone 2010). The wider perinatal frame, including relapse-prevention planning and postpartum psychosis, sits in the Perinatal/women's mental health and emergency psychiatry notes; the toxicity grading it references is in the lithium toxicity notes. Lithium is dispensed in Indian practice as lithium carbonate (Licab, and the controlled-release Intalith CR).

21.1 Teratogenicity: the Ebstein anomaly signal

The classic association is with a right-sided cardiac malformation. First-trimester **lithium in pregnancy** carries a well-known association with Ebstein anomaly, a malformation in which the tricuspid valve is displaced downward into the right ventricle (a right-sided cardiac lesion causing tricuspid regurgitation and a small, functionally impaired right ventricle) (Maudsley 2021; Sadock 2024). The historical Register of Lithium Babies vastly overstated this because uneventful pregnancies went unreported; corrected estimates put the risk of Ebstein anomaly with first-trimester exposure at roughly **0.05 to 0.1%**, a roughly 10- to 20-fold rise over the very low population baseline, but still an absolute risk well under 1% (Johnstone 2010).

Small but raised is the phrase to hold. The Maudsley notes that more recent data suggest the magnitude of the effect is much smaller than previously estimated, and that a surveillance study of 5.6 million births found Ebstein anomaly linked to maternal mental illness generally rather than specifically to lithium; the Lithium Handbook gives a number needed to harm of 37 for any major malformation from first-trimester exposure (Maudsley 2021; Meyer 2023). The overall risk of major malformation, and of atrial and ventricular septal defects, is raised but low. The period of maximum fetal risk is **2 to 6 weeks after conception**, before many women know they are pregnant (Maudsley 2021). Because the risk is real but small, the decision is a risk-benefit one, and if lithium is continued the woman is offered fetal echocardiography and high-resolution ultrasound in liaison with fetal-medicine obstetric services.

RULE **If lithium is continued in pregnancy, monitor the level closely and offer fetal echocardiography.** The first-trimester Ebstein signal is screened for with high-resolution ultrasound and fetal echocardiography in liaison with fetal medicine.

TRAP **Stopping lithium abruptly on discovering the pregnancy.** Abrupt discontinuation carries a very high relapse risk (postpartum relapse up to 70% in women who stop before conception); the correct move is a planned risk-benefit discussion, not a reflex stop (Maudsley 2021).

0.05 to 0.1	10 to 20	2 to 6
EBSTEIN RISK, FIRST-TRIMESTER LITHIUM (%)	FOLD RISE OVER BASELINE	WEEKS POST-CONCEPTION: PEAK FETAL RISK

21.2 Pharmacokinetic shifts across pregnancy

The level falls as pregnancy advances, then rebounds at delivery. Renal plasma flow and glomerular filtration rise across pregnancy and total body water expands, so lithium clearance increases and the serum level falls; an increasing dose is needed to hold the level in the therapeutic range, and the level must be monitored more often (Maudsley 2021; Sadock 2024). This is why the sample cannot be taken at pre-pregnancy intervals. NICE recommends checking the plasma lithium level **every 4 weeks**, then **weekly from week 36**, adjusting the dose to keep the level in the woman's therapeutic range while maintaining adequate fluid balance (Maudsley 2021).

At delivery the requirement snaps back to pre-pregnancy levels. The raised clearance reverses abruptly the moment the baby is delivered, so a dose that was correct in the third trimester becomes an overdose within a day, and the large intercompartmental electrolyte and fluid shifts around labour make sudden maternal toxicity possible (Maudsley 2021; Johnstone 2010). The dose is therefore adjusted around the birth: the woman delivers in hospital where fluid balance can be monitored, lithium is stopped during labour, and the plasma level is checked **12 hours after the last dose**; the pre-pregnancy dose is resumed post-delivery with a level check (Maudsley 2021).

RULE **Monitor levels more often in pregnancy and adjust the dose around delivery.** The level falls as renal clearance rises antenatally, then rebounds sharply postpartum; deliver in hospital, hold lithium in labour, and check the level 12 hours after the last dose.

21.3 The peripartum neonate: floppy baby and toxicity

Lithium equilibrates fully across the placenta, so the neonate is exposed. Lithium completely crosses the placenta, and peripartum exposure produces the **floppy baby** picture: neonatal hypotonia and lethargy, poor feeding and low Apgar scores, together with reported neonatal goitre, cardiac arrhythmia and respiratory symptoms (Maudsley 2021). Neonatal lithium toxicity is a real peripartum risk because the newborn's immature renal function clears lithium slowly; the Lithium Handbook notes that newborn reactivity is better when the maternal level at birth is below about **0.64 mEq/L**, which is one rationale for a modest dose reduction in the week before delivery (Meyer 2023).

Balance the neonatal risk against the maternal relapse risk. The counterweight is that lithium is the drug most likely to keep the mother well, and abrupt discontinuation drives a very high peripartum and postpartum relapse rate; lithium probably does not affect neonatal brain development (Maudsley 2021). The floppy, poorly feeding neonate is managed supportively with a neonatal lithium level and fluid attention, and typically resolves as the infant's renal function matures.

21.4 Lactation: passes into milk, generally cautioned

Lithium enters breast milk and is a relative contraindication in many guidelines. Lithium passes into breast milk and is renally cleared by an infant whose kidneys are still maturing, so **lactation** on lithium is generally cautioned; the Maudsley advises that lithium should be

continued in the mother but that breastfeeding should not be permitted, treating it as the exception among the mood stabilisers (Maudsley 2021). The Companion likewise states that because lithium passes into breast milk, breastfeeding should be avoided (Johnstone 2010).

The position is individualised, not absolute. Newer data soften the older blanket prohibition: a systematic review and the Lithium Handbook report that infant lithium levels fall significantly after the second week of life as renal function matures, and that breastfeeding while taking lithium does not pose a risk to the majority of infants under close monitoring, so lithium-treated women need not be automatically discouraged from breastfeeding provided infant growth and lithium-related bloods are tracked, especially in the early weeks (Meyer 2023). The exam-safe line is that lactation on lithium is a relative contraindication decided case by case; the wider perinatal decision frame is set out in the Perinatal/women's mental health and emergency psychiatry notes.

TRAP **Treating breastfeeding on lithium as absolutely forbidden or as freely permitted.** The Maudsley cautions against breastfeeding while newer monitored-cohort data are reassuring; the answer is an individualised, monitored decision, not a blanket rule either way.

21.5 The management algorithm: a planned risk-benefit decision

Guideline-level logic, not a reflex. The framework is consistent across sources (Maudsley 2021; NICE 2014; Yatham 2018). No mood stabiliser is clearly safe, and the decision turns on how well and how quickly the woman relapses off treatment.

SCENARIO	GUIDELINE-LEVEL ACTION
Planning pregnancy, long remission, low relapse risk	**Consider slow discontinuation before conception, or switch to a mood-stabilising antipsychotic; taper over about 4 weeks, never abruptly**
Becomes pregnant, well, lower risk	Consider stopping lithium gradually over 4 weeks; explain the postnatal relapse risk
Severe illness or rapid relapse off treatment	**Continue lithium after a documented risk-benefit discussion; offer fetal echocardiography and high-resolution ultrasound**
If lithium continued	Level every 4 weeks, then weekly from week 36; deliver in hospital; hold lithium in labour; check level 12 hours after last dose
Breastfeeding	Generally cautioned (relative contraindication); individualise with infant monitoring

Guideline-anchored algorithm for lithium in pregnancy and lactation: the decision keys to relapse risk, and continuation triggers fetal echocardiography plus intensified level monitoring (Maudsley 2021; NICE 2014). Highlighted cells are the board-critical branch points.

Where the guidelines converge. NICE advises considering a gradual stop over 4 weeks if the woman is well, switching to an antipsychotic or restarting in the second trimester if she is at higher risk, and continuing lithium where relapse risk is high and an antipsychotic is unlikely to work (Maudsley 2021; NICE 2014). CANMAT frames the perinatal period as one of very high bipolar relapse risk and prioritises maintaining prophylaxis in women who relapse quickly, with

lithium among the first-line maintenance options (Yatham 2018). The Indian Psychiatric Society bipolar clinical practice guideline (Shah et al.) similarly counsels a planned pre-conception risk-benefit discussion rather than abrupt cessation; the precise IPS wording on breastfeeding could not be confirmed from the parsed sources and is flagged under gaps.

WORKED EXAMPLE

A 29-year-old woman with bipolar I disorder, well on lithium for four years with two severe manic relapses whenever she has stopped it, presents at 7 weeks pregnant, having just found out. The wrong move is to stop lithium today. The right move is a documented risk-benefit discussion: her rapid, severe relapse pattern favours continuation; she is counselled on the small but raised Ebstein risk, referred for fetal echocardiography and high-resolution ultrasound, her level is checked every 4 weeks and weekly from week 36, she is booked to deliver in hospital with lithium held in labour and a level 12 hours after her last dose, and breastfeeding is discussed as a cautioned, individualised decision (Maudsley 2021).

INDIA

Lithium carbonate (Licab, Intalith CR) is cheap and widely used in Indian bipolar practice, and reproductive-age women are a large part of the caseload, so this decision is common. The practical points that matter here: many pregnancies are unplanned and present after the 2 to 6 week window of peak risk has already passed, so counsel women of childbearing potential about the plan at initiation, not at conception. Serum lithium, creatinine and TSH assays are inexpensive and available; fetal echocardiography and high-resolution anomaly scanning are available in most tertiary and many secondary obstetric units and should be arranged in liaison with the obstetric team if lithium is continued. Deliver in hospital, hold lithium in labour, and check a level after delivery because the dose requirement drops back to pre-pregnancy levels at once (Maudsley 2021; Shah 2017).

PEARL

The two numbers that decide the antenatal plan pull in opposite directions: the Ebstein absolute risk is tiny (well under 1%), while the postpartum relapse risk after abrupt discontinuation is huge (up to 70%). Stated side by side they explain why guidelines lean toward a planned continuation-with-monitoring in women who relapse quickly, rather than a reflex stop.

MNEMONIC

ECHO: Ebstein, Clearance rises, Hold in labour, Off breastfeeding (cautioned)

Ebstein anomaly is the first-trimester teratogenic signal (small but raised); **C**learance rises antenatally so the level falls and is checked more often, then rebounds at delivery; **H**old lithium in labour, deliver in hospital, check the level 12 hours after the last dose; breastfeeding is generally **O**ff / cautioned (relative contraindication, individualised). ECHO also cues the fetal echocardiography offered on continuation.

GOOD TO REMEMBER

- **Teratogenicity:** first-trimester lithium associates with Ebstein anomaly (a right-sided cardiac malformation); absolute risk about 0.05 to 0.1%, small but raised (10- to 20-fold over baseline).
- **If continued:** monitor the level closely and offer fetal echocardiography plus high-resolution ultrasound; peak fetal risk is 2 to 6 weeks post-conception.
- **Pharmacokinetics:** the level falls as renal clearance rises in pregnancy (check every 4 weeks, then weekly from week 36), then rebounds sharply at delivery; adjust the dose around the birth.
- **Peripartum neonate:** floppy baby (hypotonia, lethargy, poor feeding) and neonatal toxicity risk; deliver in hospital, hold lithium in labour, check the level 12 hours after the last dose.
- **Lactation:** lithium passes into breast milk and is generally cautioned (a relative contraindication in many guidelines, individualised with infant monitoring).
- **The trap:** do not stop lithium abruptly on discovering pregnancy (relapse up to 70%); make it a planned risk-benefit decision.

HOLD THIS

First-trimester lithium raises the risk of Ebstein anomaly (small but raised, about 0.05 to 0.1%): if continued, monitor levels closely and offer fetal echocardiography; the level falls as clearance rises antenatally and rebounds at delivery, so adjust the dose around the birth; breastfeeding is generally cautioned; never stop abruptly (Maudsley 2021).

22 . Valproate

Valproate is the second workhorse mood stabiliser after lithium, and the examiner treats it as a paired set-piece: a genuinely effective antimanic and maintenance agent that carries the single worst reproductive-safety profile of any mood stabiliser. The whole topic hangs on two axes, the drug pharmacology (mechanism, forms, dose, the serum range, the adverse-effect set and monitoring) and the **teratogenicity**, which is a marked-error magnet: neural-tube defects, a dose-related fall in IQ, and an autism signal (Maudsley 2021). A resident is expected to prescribe it competently in a man or a woman past childbearing, and to know that in a woman who could become pregnant it is effectively contraindicated unless a formal pregnancy-prevention programme is running.

Organise the topic around one idea: **valproate is anti-manic and a maintenance agent, not a bipolar-depression monotherapy, and it is the drug you do not give to a woman who could conceive without counselling and a pregnancy-prevention programme.** Every dose, serum level and teratogenicity fact below is verified against the Maudsley, the CANMAT and Indian Psychiatric Society rows and Stahl (Maudsley 2021; CANMAT 2018; IPS 2017; Stahl 2021). The neurobiology of mood and the wider guideline-anchored management PLAN belong to the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; the perinatal frame and acute emergency management belong to the Perinatal/women's mental health and emergency psychiatry notes.

22.1 Mechanism: GABA potentiation, sodium-channel block and more

The molecular target. Valproate is a simple branched-chain fatty acid whose mechanism is multiple and incompletely understood (Maudsley 2021; Stahl 2021). The best-taught actions are

potentiation of GABA: it inhibits the catabolism of gamma-aminobutyric acid (by inhibiting GABA-transaminase) and probably increases GABA synthesis, raising inhibitory tone; and a phenytoin-like, use-dependent blockade of voltage-gated sodium channels that dampens high-frequency neuronal firing (Maudsley 2021; Stahl 2021).

The downstream and neuroplastic actions. Beyond GABA and sodium channels, valproate weakly attenuates calcium T-currents, reduces the turnover of arachidonic acid, depletes inositol, activates the ERK pathway and promotes brain-derived neurotrophic factor expression while reducing protein kinase C, and it acts as a histone deacetylase inhibitor altering gene transcription (Maudsley 2021; Stahl 2021). These signalling and epigenetic effects are the presumed substrate of its mood-stabilising and neuroplastic actions.

22.2 The forms: sodium valproate, valproic acid and divalproex

Three interchangeable forms of one active moiety. Valproate is dispensed in three forms, all metabolised to **valproic acid**, which is the pharmacologically active species (Maudsley 2021). Distinguish them by name because the examiner will: **sodium valproate** and valproic acid (classically licensed for epilepsy), and **divalproex** (semi-sodium valproate, the 1:1 coordination compound of valproic acid and sodium valproate, classically licensed for acute mania) (Maudsley 2021). There are no important efficacy differences between the forms; divalproex may have marginally better gastric tolerability.

Sodium valproate

The sodium salt; the controlled-release form can be given once daily, other forms at least twice daily (Maudsley 2021).

Valproic acid

The free acid and the active moiety to which all forms are metabolised (Maudsley 2021).

Divalproex (semi-sodium valproate)

A 1:1 compound of valproic acid and sodium valproate; the form used in most mania trials, slower-absorbed, possibly better tolerated (Maudsley 2021).

INDIA

Lead with the Indian brand, then the generic. Sodium valproate is marketed in India as **Valprol-CR**, **Encorate** or Valparin Chrono (sodium valproate); divalproex as **Valance** or Divaa (divalproex) (KDT 2019). All three chemical forms convert to valproic acid, so brand choice is driven by formulation (once-daily controlled-release versus twice-daily) and tolerability, not by a difference in the active drug.

22.3 Indications: acute mania and maintenance, not bipolar depression alone

Where it works. The core **indications**: **acute mania** (a first-line antimanic agent, response rate around 50 percent, number needed to treat 2 to 4) and **bipolar maintenance** or prophylaxis, best supported when it was the agent that worked in the acute manic episode (Maudsley 2021; CANMAT 2018; IPS 2017). CANMAT lists divalproex as a first-line monotherapy for acute mania and among first-line maintenance monotherapies for bipolar I disorder (CANMAT 2018). The Indian Psychiatric Society names valproate as a first-line monotherapy for acute mania and,

with lithium, as a best-evidenced maintenance agent, and the IPS guidelines quote an acute-mania serum target of 50 to 125 mcg/mL (IPS 2017).

Where it is not first choice. Valproate is **not for bipolar depression as monotherapy**: the evidence in bipolar depression is at best a small-to-medium effect and it is not a first-line agent for the depressive pole (Maudsley 2021; CANMAT 2018). It has limited utility in rapid-cycling illness. A hard practice point: NICE recommends against starting valproate for bipolar disorder in primary care, and both NICE and the Indian Psychiatric Society bar its use to treat bipolar illness in women of childbearing age (NICE 2014; IPS 2017).

RULE **Valproate is an anti-manic and maintenance agent, not a bipolar-depression monotherapy.** Reach for it in mania and for relapse prevention, not to lift the depressive pole on its own.

22.4 Initiation, dosing and the serum range

Starting and titrating. Titrate the dose upward against response and adverse effects; loading-dose regimens are generally well tolerated and give a faster antimanic response (Maudsley 2021). A common adult approach starts around 500 mg twice daily (or a weight-based load of roughly 20 to 30 mg/kg/day) and increases every few days. Controlled-release sodium valproate can be given once daily; other formulations require at least twice-daily dosing (Maudsley 2021).

The serum level, held more loosely than lithium. Plasma level monitoring is of more limited use than with lithium, but there is a linear relationship in acute mania: levels below **55 mg/L** are no more effective than placebo, and levels above **94 mg/L** give the most robust response (Maudsley 2021). The practical acute-mania target is a serum valproate of about **50 to 100 mg/L** (CANMAT: 350 to 700 micromol/L; IPS quotes 50 to 125 mcg/mL), taken as a trough immediately before the next dose (CANMAT 2018; IPS 2017; Maudsley 2021). Adverse effects and toxicity rise sharply once the level exceeds 100 mg/L.

PARAMETER	VALUE	SOURCE
Acute-mania serum target	**50 to 100 (levels below 55 no better than placebo; above 94 most robust)**	Maudsley 2021
CANMAT acute-mania target	**350 to 700 micromol/L (50 to 100 microg/mL)**	CANMAT 2018
IPS acute-mania target	50 to 125 mcg/mL	IPS 2017
Sample timing	trough, immediately before the next dose	Maudsley 2021
Adverse effects escalate above	100	Maudsley 2021

Valproate serum monitoring, in mg/L (equivalently microg/mL or mcg/mL) unless stated. Used more loosely than the lithium level; the number that matters most is the acute-mania trough (Maudsley 2021; CANMAT 2018; IPS 2017).

50 to 100
ACUTE-MANIA SERUM VALPROATE (MG/L)

below 55
SERUM NO BETTER THAN PLACEBO (MG/L)

above 100
ADVERSE EFFECTS ESCALATE (MG/L)

22.5 Adverse effects: the common set and the dangerous ones

The everyday set. The common, adherence-limiting adverse effects: **weight gain** (can be marked, worse when combined with clozapine or olanzapine), a dose-related **tremor** (intention or postural, in up to a quarter of patients), **hair loss** with curly regrowth, **sedation** and lethargy (especially at starting doses above 750 mg/day), gastric irritation and nausea (Maudsley 2021). Peripheral oedema also occurs.

The haematological and metabolic dangers. Valproate can cause **thrombocytopenia** (also leucopenia and red-cell hypoplasia), and **hyperammonaemia**, which can produce nausea and, when marked, an encephalopathy even with normal liver enzymes (Maudsley 2021). Two organ-threatening reactions dominate the safety picture: **hepatotoxicity**, ranging from the common early asymptomatic transaminase rise to rare fulminant hepatic failure (young children on multiple anticonvulsants are at greatest risk), and **pancreatitis** (Maudsley 2021; KDT 2019). Any patient with rising liver enzymes should be evaluated clinically, with albumin and clotting checked.

ADVERSE EFFECT	NOTE
Weight gain	Can be significant; worse with clozapine or olanzapine (Maudsley 2021)
Tremor	Dose-related, in up to a quarter; intention or postural (Maudsley 2021)
Hair loss	With characteristic curly regrowth (Maudsley 2021)
Sedation / lethargy	Especially at starting doses above 750 mg/day (Maudsley 2021)
Thrombocytopenia	Also leucopenia, red-cell hypoplasia; drives the FBC monitoring (Maudsley 2021)
Hyperammonaemia	Nausea, and an encephalopathy that can occur with normal LFTs (Maudsley 2021)
Hepatotoxicity	Common early transaminase rise; rare fulminant hepatic failure, highest in young children on polytherapy (Maudsley 2021)
Pancreatitis	Rare but serious; drives the low threshold to investigate abdominal pain (Maudsley 2021)

The valproate adverse-effect set. The four highlighted rows are the ones that drive baseline and periodic FBC and LFTs (Maudsley 2021).

MNEMONIC

VALPROATE

Weight gain, Ammonia (hyperammonaemia), Liver toxicity (hepatotoxicity), Pancreatitis, Reduced platelets (thrombocytopenia), Oedema, Alopecia (curly regrowth), Tremor, teratogen: a memory hook for the adverse-effect and reproductive-risk set to hold cold.

22.6 Monitoring: baseline and periodic LFTs and FBC

The pre-treatment work-up. Because the organ dangers are hepatic and haematological, the baseline screen is a **full blood count** and **liver function tests**, with a baseline weight or BMI (Maudsley 2021; NICE 2014). Take a menstrual history and a pregnancy test with contraceptive counselling in any woman of childbearing potential before the first tablet.

On-treatment monitoring. NICE recommends repeating the **FBC and LFTs** at 6 months and monitoring BMI; the product characteristics advise more frequent LFTs in the first 6 months, with albumin and clotting if enzymes are abnormal (Maudsley 2021; NICE 2014). CANMAT frames it as menstrual history, haematology and liver function at 3-to-6-month intervals in the first year on maintenance divalproex, then yearly, alongside serum valproate levels (CANMAT 2018).

TRAP **Starting valproate without baseline FBC and LFTs.** You lose the safety baseline for the two organ-threatening reactions, hepatotoxicity and thrombocytopenia, and cannot later attribute a change to the drug.

22.7 Teratogenicity: the highest-risk mood stabiliser

The malformation risk. Valproate is an established major human teratogen and the single worst mood stabiliser in pregnancy. It has a clear causal link with **neural tube** defects including spina bifida, and the overall major-malformation rate is around **10 percent**, higher than carbamazepine (Maudsley 2021). It is also linked to atrial septal defects, cleft palate, hypospadias, polydactyly, craniosynostosis and reduced neonatal head circumference (Maudsley 2021). Folate does not reliably prevent anticonvulsant-induced neural-tube defects once pregnancy is established because the tube closes within about twenty-eight days, in the fourth week, so folate must be given before conception.

The neurodevelopmental risk, and its dose-dependence. Beyond structural malformation there is a clear causal association with **neurodevelopmental** harm: a European Medicines Agency review found that up to **40 percent** of pre-school children exposed in utero had some developmental delay (delayed walking and talking, memory, speech and language problems, lower intellectual ability), with lower IQ and an increased rate of autism-spectrum diagnosis, and the processing, working-memory and learning deficits are dose-related (Maudsley 2021). This IQ and autism signal, dose-related and lasting, is the fact the examiner most wants verified.

~10%	up to 40%	5 mg/day
MAJOR MALFORMATION RATE (MAUDSLEY)	PRE-SCHOOL DEVELOPMENTAL DELAY AFTER IN-UTERO EXPOSURE	HIGH-DOSE PRE-CONCEPTION FOLIC ACID

The prescribing rule that follows. Because of this, valproate is contraindicated in women of childbearing potential unless a formal pregnancy-prevention programme is in place (Maudsley 2021; NICE 2014; IPS 2017). If a woman planning pregnancy is already on it, withdraw it gradually (over at least 4 weeks, or 2 to 4 weeks per the perinatal guidance) while she uses effective contraception, adding high-dose folic acid **5 mg/day** continued through the first trimester (Maudsley 2021; CANMAT 2018; BAP 2016). If she becomes pregnant on valproate it

should generally be stopped. In the UK it may not be initiated in patients under 55 or continued in a woman of childbearing potential unless two specialists agree no other treatment is effective or tolerated (Maudsley 2021).

RULE **Do not use valproate in a woman who could become pregnant without a pregnancy-prevention programme.** The neural-tube and dose-related IQ and autism risk makes it the mood stabiliser to avoid in childbearing-potential women.

TRAP **Prescribing valproate to a young woman for bipolar disorder without counselling the teratogenicity.** It is the classic marked error: no discussion of neural-tube defects, the IQ and autism risk, contraception or pre-conception folate.

INDIA

The childbearing-potential rule applies squarely in Indian practice: valproate (Valprol-CR, Encorate; divalproex Valance) is common and cheap, but in a woman who could conceive it should not be started for bipolar disorder without a documented pregnancy-prevention plan and explicit counselling on neural-tube and neurodevelopmental risk (IPS 2017; NICE 2014). The Indian Psychiatric Society explicitly advises avoiding valproate in pregnancy for its high teratogenicity, neural-tube defects and neurodevelopmental harm (IPS 2017).

22.8 PCOS, menstrual disturbance and other reproductive effects

The endocrine effect in women. Separate from teratogenicity, valproate causes hyperandrogenism in women and is linked to **pcos** (polycystic ovary syndrome) with menstrual disturbance, weight gain and metabolic features, though the strength of the association is debated (Maudsley 2021). This is a further reason to take and monitor a menstrual history in women on valproate, and to prefer an alternative in a young woman where reproductive and metabolic concerns weigh heavily (CANMAT 2018).

PEARL

Two distinct reproductive harms travel together for valproate: the in-utero **teratogenicity** (neural-tube and neurodevelopmental), which threatens a future fetus, and **pcos** with menstrual disturbance, which affects the woman herself. Both push toward avoiding valproate in young women of childbearing potential.

22.9 Interactions: protein binding, enzyme inhibition and glucuronidation

The key interactions. Valproate is highly protein-bound and can be displaced by other protein-bound drugs such as aspirin, raising free levels toward toxicity; aspirin also inhibits its metabolism (Maudsley 2021). Conversely valproate can displace warfarin, raising the free anticoagulant level. As an enzyme inhibitor of glucuronidation it raises the levels of several drugs, most importantly lamotrigine (valproate roughly doubles lamotrigine exposure, hence the halved lamotrigine titration and the raised rash risk), and also tricyclics such as clomipramine, quetiapine and phenobarbital (Maudsley 2021). Drugs that inhibit CYP enzymes (erythromycin, fluoxetine, cimetidine) can raise valproate levels in turn.

INTERACTING DRUG	EFFECT
Lamotrigine	Valproate inhibits its glucuronidation, roughly doubling levels; halve the lamotrigine dose and titrate slowly (raised rash risk) (Maudsley 2021)
Aspirin	Displaces protein-bound valproate and inhibits its metabolism, raising free valproate toward toxicity (Maudsley 2021)
Warfarin	Displaced by valproate, raising free anticoagulant level (Maudsley 2021)
Erythromycin, fluoxetine, cimetidine	CYP inhibition raises valproate levels (Maudsley 2021)
Carbapenems	Sharply lower valproate levels (a well-known interaction to avoid) (KDT 2019)

The high-yield valproate interactions. The lamotrigine interaction is the one most often examined, because it dictates the halved lamotrigine titration (Maudsley 2021).

HOLD THIS

Valproate is an effective anti-manic and maintenance mood stabiliser, but with the worst reproductive profile of the class: a roughly 10 percent major-malformation rate with neural-tube defects and a dose-related fall in IQ with an autism signal, so it is contraindicated in women of childbearing potential without a pregnancy-prevention programme.

GOOD TO REMEMBER

- **Mechanism:** GABA potentiation (inhibits GABA-transaminase) plus use-dependent sodium-channel blockade, with histone-deacetylase and neuroplastic effects (Maudsley 2021; Stahl 2021).
- **Indications:** anti-manic and maintenance mood stabiliser (first-line acute mania, first-line maintenance), NOT bipolar depression as monotherapy (CANMAT 2018; IPS 2017).
- **Forms and Indian brands:** sodium valproate (Valprol-CR, Encorate), valproic acid, divalproex/semi-sodium valproate (Valance); all become valproic acid (KDT 2019; Maudsley 2021).
- **Serum target:** acute-mania trough around 50 to 100 mg/L (CANMAT 350 to 700 micromol/L; IPS 50 to 125 mcg/mL), held more loosely than the lithium level (Maudsley 2021; CANMAT 2018; IPS 2017).
- **Signature adverse effects:** weight gain, tremor, hair loss, sedation, thrombocytopenia, hyperammonaemia, and the organ-threatening hepatotoxicity and pancreatitis (Maudsley 2021).
- **Monitoring:** baseline and periodic FBC and LFTs, plus weight or BMI (Maudsley 2021; NICE 2014).
- **Teratogenicity:** the highest-risk mood stabiliser, around 10 percent major malformations with neural-tube defects and up to 40 percent developmental delay, dose-related IQ loss and autism risk; contraindicated in women of childbearing potential without a pregnancy-prevention programme, with pre-conception folic acid 5 mg/day (Maudsley 2021; NICE 2014; IPS 2017).
- **PCOS:** hyperandrogenism, polycystic ovary syndrome and menstrual disturbance in women (Maudsley 2021).
- **Key interaction:** inhibits glucuronidation of lamotrigine, roughly doubling its level, so halve and slow the lamotrigine titration (Maudsley 2021).

23 · Carbamazepine and oxcarbazepine

Carbamazepine is the interaction-heavy mood stabiliser: an anticonvulsant that works but is a second-line anti-manic and a third-line prophylactic agent, chosen after lithium and valproate have failed or are unsuitable. Examiners rarely ask you to reach for it; they ask you to survive it. The whole topic is really three keyed facts: it blocks sodium channels (the mechanism it shares with phenytoin and lamotrigine), it is a potent CYP3A4 inducer that **induces its own metabolism** so the level falls over the first few weeks, and it carries a distinctive safety set of hyponatraemia, blood dyscrasias and the HLA-B*1502 Stevens-Johnson association. Get those three right and the question is yours.

This note teaches **carbamazepine** and its better-tolerated analogue **oxcarbazepine** as mood stabilisers: the mechanism, the dose and plasma level, the pharmacokinetic headache of enzyme induction, the adverse-effect set with its monitoring, and where each sits in the guideline algorithm. Verify every level and interaction; a swapped direction or a forgotten contraceptive failure is a critical error. For where mood stabilisers sit in the acute-mania and maintenance algorithm see the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; the CYP background sits in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

23.1 What it is and where it sits

A second-line stabiliser. Carbamazepine (Tegretol or Mazetol) is an iminostilbene anticonvulsant, structurally related to the tricyclics, licensed for bipolar illness in patients who do not respond to lithium (Maudsley 2021). Two placebo-controlled trials of the extended-release formulation confirm efficacy in acute mania, with roughly double the placebo response, but it is not well tolerated and NICE does not recommend it first-line for mania (Maudsley 2021, NICE 2014). CANMAT places carbamazepine as a second-line monotherapy for acute mania and as a recommended (not first-line) maintenance agent (CANMAT 2018). It is thus the agent you reach for when lithium and valproate have failed, not the agent you start with.

RULE **Second line, not first.** Carbamazepine is a second-line anti-manic and a later-line maintenance stabiliser, used after lithium and valproate, not instead of them.

23.2 Mechanism: sodium-channel blockade

Use-dependent sodium-channel blockade. The core action is blockade of voltage-dependent (voltage-gated) sodium channels, stabilising the inactivated state and dampening high-frequency repetitive firing (Stahl 2021). This is the same molecular target as phenytoin and lamotrigine, and it is thought to underlie both the anticonvulsant and the mood-stabilising effect. Oxcarbazepine (Oxetol), a structural derivative of carbamazepine, blocks the same voltage-dependent sodium channels but in addition increases potassium conductance and modulates high-voltage-activated calcium channels (Maudsley 2021). Its active moiety is the monohydroxy metabolite (licarbazepine), which is why oxcarbazepine avoids the epoxide metabolite responsible for much of carbamazepine's toxicity and much of its enzyme induction.

23.3 Dose and plasma level

Titrate low and slow, monitor the trough. Start at **100 to 200 mg** twice daily and titrate against response and tolerability towards **400 mg** twice daily, higher in some patients; controlled clinical trials of efficacy in bipolar disorder use **800 to 1200 mg/day** (Maudsley 2021). The modified-release preparation (Tegretol Retard) gives smoother levels and is better tolerated. The therapeutic plasma range used as an anticonvulsant is **4 to 12 mg/L** (evidence in affective illness is weaker; a level of at least 7 mg/L may be needed), sampled as a trough immediately before the first dose of the day (Maudsley 2021). Levels above 12 mg/L carry a higher side-effect burden. Carbamazepine cannot be loaded, and rapid titration provokes sedation and ataxia (Goodman and Gilman 2018).

PARAMETER	CARBAMAZEPINE	NOTE
Starting dose (mg twice daily)	**100 to 200**	Titrate slowly; cannot be loaded
Usual target (mg twice daily)	400	Trial doses often 800 to 1200 mg/day total
Therapeutic plasma level (mg/L)	**4 to 12**	Trough, before the morning dose; anticonvulsant range
When to recheck the level	**2 to 4 weeks after a dose change**	Because autoinduction moves the level

Carbamazepine dosing and plasma monitoring: start low, target a trough of 4 to 12 mg/L, and recheck after autoinduction settles.

23.4 The pharmacokinetic headache: enzyme induction and autoinduction

A potent CYP3A4 inducer that induces its own metabolism. This is the single most examined fact. Carbamazepine is a hepatic **enzyme induction** agent, a potent inducer of CYP3A4 (and P-glycoprotein), and it induces the very enzymes that metabolise itself. An initial plasma half-life of around **30 hours** falls to around **12 hours** on chronic dosing, so the level a resident measures in week one drifts downward over the first few weeks even on a fixed dose (Maudsley 2021, K&S 2024). This is why the level must be re-checked **2 to 4 weeks** after any dose increase: the target may no longer be met once autoinduction is complete. Because CYP3A4 handles a large fraction of drugs, carbamazepine lowers the plasma level of many co-prescribed agents, making it one of the most interaction-heavy drugs in psychiatry.

RULE **Carbamazepine induces CYP3A4, including its own metabolism and the pill.** The level falls over the first weeks, and the level of many co-drugs (oral contraceptives, other psychotropics) falls with it; watch the level and the interactions.

23.5 The interactions that matter: the oral contraceptive and the psychotropics

Induction lowers other drug levels. As a CYP3A4 inducer, carbamazepine accelerates the metabolism of oral contraceptives, reducing their plasma concentration and causing contraceptive failure and unplanned pregnancy; adequate non-hormonal or higher-oestrogen contraception must be ensured, and prophylactic folate given, if it cannot be avoided in a woman of childbearing potential (Maudsley 2021). It similarly lowers the levels of many psychotropics

metabolised by CYP3A4, including some antipsychotics and other anticonvulsants (for example it lowers plasma lamotrigine and, by inducing UGT and CYP, valproate). Pharmacodynamically, its anticonvulsant effect is opposed by seizure-threshold-lowering drugs, its marrow-suppressing potential is amplified by clozapine, and its hyponatraemic tendency is worsened by sodium-depleting diuretics; rare neurotoxicity is reported when combined with lithium (Maudsley 2021).

CO-DRUG	EFFECT OF CARBAMAZEPINE	CONSEQUENCE
Oral contraceptive	**Level LOWERED (CYP3A4 induction)**	Contraceptive failure, unplanned pregnancy
Lamotrigine	Level LOWERED	Loss of stabiliser cover; lamotrigine dose may need raising
Some antipsychotics (CYP3A4 substrates)	Level LOWERED	Reduced efficacy; monitor clinically
Clozapine	**Additive marrow suppression**	Avoid combination; agranulocytosis risk
Diuretics	Additive sodium depletion	Worse hyponatraemia
Lithium	Pharmacodynamic	Rare neurotoxicity reported

Carbamazepine as an enzyme inducer: it lowers the level of the pill and CYP3A4-handled psychotropics, and stacks marrow-suppression and hyponatraemia risks.

TRAP **Forgetting that carbamazepine makes the oral contraceptive fail.** A woman started on carbamazepine, still on the combined pill, is now unprotected; the classic missed interaction is contraceptive failure and pregnancy on a teratogenic drug.

23.6 Hyponatraemia (SIADH)

A common, sometimes dangerous, electrolyte effect. Carbamazepine has vasopressin-like (antidiuretic) effects, promoting water resorption and producing dilutional hyponatraemia, an SIADH-like picture (K&S 2024). Older adults, women and higher doses are the vulnerability factors, and co-prescribed sodium-depleting diuretics worsen it. Severe hyponatraemia can present as confusion or delirium. Baseline and on-treatment urea and electrolytes are checked, at least annually and whenever clinically suspected (CANMAT 2018, NICE 2014). This is the one area where oxcarbazepine is worse: it causes hyponatraemia more often, in roughly **3 to 5 percent** of patients (K&S 2024).

23.7 Blood dyscrasias and FBC monitoring

Benign leucopenia is common; aplastic anaemia and agranulocytosis are rare but fatal. Carbamazepine commonly causes a chronic, usually clinically insignificant fall in the white cell count (benign leucopenia), through inhibition of colony-stimulating factor, and lithium can reverse it (K&S 2024). The dangerous events are idiosyncratic: aplastic anaemia, agranulocytosis and pancytopenia occur in roughly **1 in 25,000 to 100,000** patients (K&S 2024; the Maudsley cites about 1 in 20,000 for agranulocytosis and/or aplastic anaemia). Because routine full blood count (FBC) monitoring poorly predicts these rare events, the practical rule is a baseline FBC plus firm counselling that fever, sore throat, rash, bruising or bleeding demand an immediate FBC and

medical review (Maudsley 2021, K&S 2024). Baseline and periodic FBC and liver function tests are standard; a raised GGT or a GGT two to three times normal is rarely a concern.

WORKED EXAMPLE

A man three weeks into carbamazepine for treatment-resistant mania develops fever, mouth ulcers and a sore throat. This is not a viral illness to be observed; it is a potential agranulocytosis until proven otherwise. Stop the drug, take an urgent FBC, and manage the neutropenia. The counselling given at the outset (report fever or sore throat at once) is what makes this catch possible.

23.8 Rash and the HLA-B*1502 Stevens-Johnson association

Screen at-risk ancestry before prescribing. About 3 percent of patients develop a benign erythematous rash, but carbamazepine can rarely progress to Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The vulnerability is genetically determined: the HLA-B*1502 allele is strongly associated with carbamazepine-induced SJS/TEN, and it is prevalent in Han Chinese, Thai and some other Southeast Asian populations (Maudsley 2021, K&S 2024, Goodman and Gilman 2018). Genetic testing of people of Han Chinese or Thai origin is recommended before carbamazepine is started, and the drug is avoided if the patient is HLA-B*1502 positive. Because any carbamazepine rash may be the early phase of a serious reaction, most clinicians stop the drug even on a benign-looking rash; oxcarbazepine, which cross-reacts less, is a common switch (roughly two-thirds do not re-rash) (K&S 2024).

TRAP **Skipping the HLA-B*1502 screen in an at-risk patient.** In a Han Chinese or Thai patient, prescribing carbamazepine without genotyping risks a preventable Stevens-Johnson syndrome; the allele must be checked first.

23.9 Teratogenicity and the monitoring headline

An established human teratogen. Carbamazepine is a known human teratogen, associated with neural tube defects (spina bifida, of the order of 1 percent) and craniofacial abnormalities; folate pretreatment is advised and the combination with valproate is especially avoided (K&S 2024, CANMAT 2018). CANMAT and NICE advise avoiding it in pregnancy where possible; if used in a woman of childbearing potential the contraceptive interaction makes reliable non-hormonal contraception essential. The maintenance monitoring headline that CANMAT specifies: before and during carbamazepine, genotype at-risk Asian ancestry for HLA-B*1502, educate about rash and SJS, and check serum sodium at least annually, alongside baseline and periodic FBC and LFTs (CANMAT 2018).

4 to 12	30 to 12	2 to 4
THERAPEUTIC LEVEL (MG/L, TROUGH)	HALF-LIFE FALL ON AUTOINDUCTION (HOURS)	RECHECK LEVEL AFTER DOSE CHANGE (WEEKS)

23.10 Oxcarbazepine: the better-tolerated analogue

Less induction, more hyponatraemia, weaker evidence. Oxcarbazepine (Oxetol) shares the sodium-channel mechanism but is metabolised to licarbazepine without the toxic epoxide, so the

toxic effects due to the epoxide metabolite are avoided; separately it is a much weaker enzyme inducer and better tolerated: less rash, no routine benign WBC suppression, and no elevated serious blood-dyscrasia rate (K&S 2024). The two trade-offs are that it causes hyponatraemia more often (about 3 to 5 percent) and that the trial evidence in bipolar disorder is thin: a Cochrane review found insufficient adequate-quality trials to judge its efficacy or acceptability in acute bipolar episodes, and only small studies support adjunctive prophylactic use (Maudsley 2021). It is therefore a tolerability-driven alternative rather than a stronger drug. Typical tablet strengths in India are 150, 300 and 600 mg (KDT 2019).

FEATURE	CARBAMAZEPINE	OXCARBAZEPINE
Mechanism	Na-channel blockade	Na-channel blockade plus K conductance / Ca modulation
Enzyme induction	**Potent CYP3A4 inducer, autoinducing**	Much weaker inducer
Hyponatraemia	Common	**More common (about 3 to 5 percent)**
Blood dyscrasias	**Benign leucopenia; rare aplastic anaemia / agranulocytosis**	No routine WBC suppression; serious dyscrasia not elevated
Rash / SJS	HLA-B*1502 associated SJS/TEN	Lower rash frequency; many carbamazepine-rash patients tolerate it
Bipolar evidence	Second-line, RCT-supported for mania	**Insufficient adequate-quality trials (Cochrane)**

Carbamazepine versus oxcarbazepine: oxcarbazepine trades away potent induction and most of the blood and skin risk, at the cost of more hyponatraemia and weaker bipolar evidence.

HOLD THIS

Carbamazepine is a second-line stabiliser that blocks sodium channels, is a potent autoinducing CYP3A4 inducer (its own level and the pill both fall), and carries hyponatraemia, benign leucopenia with rare aplastic anaemia / agranulocytosis, and HLA-B*1502-linked Stevens-Johnson syndrome; oxcarbazepine is the better-tolerated analogue with less induction but more hyponatraemia.

INDIA

Carbamazepine is marketed in India as Tegretol (Novartis) and Mazetol, and oxcarbazepine as Oxetol; the generic stays primary in prescribing. The HLA-B*1502 point is not only a Han Chinese or Thai concern: the allele is present across parts of South and Southeast Asia, so ancestry-informed caution and a low threshold to stop on any rash are practical rules in Indian practice.

MNEMONIC

CBZ: Cuts Blood, Zaps sodium and the pill

Cuts **B**lood counts (leucopenia, rare aplastic anaemia and agranulocytosis), **Z**aps sodium (hyponatraemia) and the pill (CYP3A4 induction, contraceptive failure); plus HLA-B*1502 Stevens-Johnson syndrome. Autoinducing, so the level falls.

GOOD TO REMEMBER

- **Carbamazepine:** voltage-dependent sodium-channel blocker; potent autoinducing CYP3A4 inducer whose signature harm is the enzyme induction that fails the oral contraceptive; second-line for mania, trough level 4 to 12 mg/L.
- **Enzyme induction:** half-life falls from about 30 to 12 hours over the first weeks, so recheck the level 2 to 4 weeks after any dose change; it lowers oral contraceptive and many psychotropic levels.
- **Hyponatraemia (SIADH):** common, SIADH-like, worse with diuretics and in older women; check serum sodium at least annually.
- **Blood dyscrasias:** benign leucopenia is common; aplastic anaemia and agranulocytosis are rare (about 1 in 25,000 to 100,000) but fatal, so do a baseline FBC and counsel to report fever, sore throat or bruising at once.
- **HLA-B*1502:** allele linked to Stevens-Johnson syndrome and toxic epidermal necrolysis; screen at-risk Han Chinese, Thai and some Asian ancestry before prescribing and avoid if positive.
- **Teratogenicity:** established human teratogen (neural tube defects, craniofacial); avoid in pregnancy where possible, give folate, and never rely on a hormonal contraceptive it induces.
- **Oxcarbazepine (Oxetol):** same sodium-channel mechanism, much weaker inducer, better tolerated with no routine WBC suppression; the one drug where hyponatraemia (about 3 to 5 percent) is more frequent, and bipolar evidence is thin.

24 . Lamotrigine

lamotrigine (Lamitor, Lametec) is the mood stabiliser the board most wants tied to one clinical fact: it is the agent with the best evidence for **bipolar depression** and for maintenance, especially the prevention of depressive relapse, yet it is weak against acute mania. That split personality, strong on the depressive pole and prophylaxis but not a drug you reach for to break a manic episode, is the whole examinable point and the reason it is never used as monotherapy for acute mania (Stahl 2021). Every other high-yield fact about the drug flows from a single pharmacokinetic vulnerability: it must be introduced by **slow titration** to avoid a serious rash, and that titration is halved by valproate and roughly doubled by an enzyme inducer.

This is a pharmacology topic, so the marks are in the mechanism, the titration schedule, the interaction with valproate, and the **rash** stop-rule. The doses, the halving with valproate, the enzyme-inducer doubling and the benign-versus-serious rash distinction below are verified against Stahl's Prescriber's Guide, the Maudsley Prescribing Guidelines, the CANMAT guideline, the Indian Psychiatric Society clinical practice guideline (Stahl 2021; Maudsley 2021; Yatham 2018; Shah 2017). The guideline-anchored place of lamotrigine within the full bipolar management PLAN is set out in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; the CYP and metabolism background sits in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

Week	Standard mg/day	With valproate mg/day, halved	With an enzyme inducer mg/day (e.g. carbamazepine)
Weeks 1 to 2	25 once daily	25 on alternate days	50 once daily
Weeks 3 to 4	50 once daily	25 once daily	100 (in divided doses)
Week 5	100 once daily	50 once daily	increase by 100 each week
Week 6	200 once daily	100 once daily	up toward 400 (divided)
Usual target	100 to 200	100	400

Stevens-Johnson stop-rule
STOP at any confluent, purpuric or tender rash, any mucosal involvement (eyes, lips, mouth), or a rash with fever or malaise. The slow titration, and halving it with valproate, are what keep the serious-rash risk low.

Fig 12.12 Lamotrigine titration and the Stevens-Johnson risk. Lamotrigine must be titrated slowly over about six weeks; the schedule is halved when combined with valproate (which raises the lamotrigine level) and roughly doubled with an enzyme inducer such as carbamazepine. The rash risk is highest with fast titration and with valproate co-therapy, so a confluent, purpuric, tender or mucosal rash, or a rash with fever, is a stop signal.

24.1 The place: best for bipolar depression and maintenance, weak for mania

Strong on the depressive pole, weak on mania. Lamotrigine has FDA and guideline standing for the **maintenance** of bipolar I disorder, where its particular strength is preventing the depressive relapse rather than the manic one (Stahl 2021; Yatham 2018). It is a first-line option (monotherapy or adjunctive) for acute **bipolar depression**, and both CANMAT and the Indian Psychiatric Society name lithium or lamotrigine among the first-line agents for that indication, particularly where antipsychotic burden is undesirable (Yatham 2018; Shah 2017). What it does **not** do is treat acute mania: onset is far too slow for a manic emergency and the evidence is weak, so it is at best adjunctive and second-line there and never a mania monotherapy (Stahl 2021).

Guideline anchoring. CANMAT lists lamotrigine (monotherapy or adjunctive) for acute bipolar I depression, targeting a minimum of 200 mg/day with slow titration from 25 mg, and lists it among first-line maintenance monotherapies for bipolar I disorder; the Indian Psychiatric Society places lamotrigine as a first-line alternative for acute bipolar depression and as a maintenance agent that is better for depressive-recurrence prevention (Yatham 2018; Shah 2017). The mirror-image caution belongs here: an antidepressant given alone in a bipolar depression risks a switch, whereas lamotrigine treats the depressive pole without that manic-switch liability.

RULE **Reach for lamotrigine for the depressive pole and for maintenance, not for acute mania.** Best evidence is in bipolar depression and depressive-relapse prevention; it is weak and slow against mania.

TRAP **Starting lamotrigine to control an acute manic episode.** It is too slow and too weak for mania; use an antimanic (lithium, valproate, or an antipsychotic) and reserve lamotrigine for the depressive pole and maintenance.

24.2 Mechanism: sodium-channel blockade and glutamate modulation

A use-dependent sodium-channel blocker that damps glutamate. In the Neuroscience-based Nomenclature lamotrigine is a glutamate voltage-gated sodium channel blocker (Glu-CB) (Stahl 2021). It acts as a **use-dependent blocker of voltage-sensitive sodium channels**, binding the open-channel conformation at the alpha pore-forming subunit; by stabilising the inactivated state of the channel it reduces the presynaptic release of the excitatory neurotransmitters glutamate and aspartate (Stahl 2021). This glutamate-modulating action is the proposed basis of its mood-stabilising, and specifically its antidepressant-in-bipolar, effect, and distinguishes its profile from the antimanic anticonvulsants.

> **PEARL**
>
> The mechanism explains the clinical split. Sodium-channel blockade with downstream reduction of glutamate release maps onto relapse prevention and the depressive pole rather than onto the rapid dopaminergic damping needed to abort mania, which is why lamotrigine prevents and treats bipolar depression but is a poor antimanic.

24.3 The slow titration: why it takes weeks

Titrate over weeks, not days. Lamotrigine must be introduced by **slow titration** over several weeks: the incidence of serious rash rises steeply with a fast start and with high initial doses, so the standard monotherapy schedule creeps up from 25 mg/day to a target of 200 mg/day over about six weeks (Stahl 2021; Maudsley 2021). The dose should never be escalated faster than recommended, because the excess risk is not of a trivial side effect but of Stevens-Johnson syndrome. If the patient stops the drug for 5 days or more, the titration is restarted from the beginning, as rashes have been reported on re-exposure (Stahl 2021).

Two modifiers rewrite the schedule. Valproate roughly doubles the lamotrigine level, so the schedule is **halved** when the two are combined; an enzyme inducer such as carbamazepine lowers the level, so the schedule is roughly **doubled** (higher steps, higher target) (Stahl 2021). The monotherapy, with-valproate and with-inducer schedules are set out in the table below.

PHASE	MONOTHERAPY (MG/DAY)	WITH VALPROATE, HALVED (MG/DAY)	WITH ENZYME INDUCER, DOUBLED (MG/DAY)
Weeks 1 to 2	25 daily	**25 on alternate days**	50 daily
Weeks 3 to 4	50 daily	**25 daily**	100 daily (divided)
Week 5	100 daily	50 daily	increase by 100 each week
Week 6	200 daily	100 daily	up towards 400 (divided)
Usual target	**100 to 200**	**100**	**400**

Lamotrigine bipolar titration: the monotherapy schedule creeps 25 to 200 over about 6 weeks; valproate halves every step and the target (start at 25 on alternate days, target 100); an enzyme inducer such as carbamazepine roughly doubles the schedule (start 50, target 400) (Stahl 2021; Maudsley 2021). Highlighted cells are the board-critical numbers.

25	100 to 200	6
MONOTHERAPY STARTING DOSE (MG/DAY)	MONOTHERAPY BIPOLAR TARGET (MG/DAY)	TITRATION LENGTH (WEEKS)

RULE **Titrate lamotrigine slowly and halve the schedule with valproate.** Creep 25 to 200 over about six weeks; with valproate start at 25 on alternate days and target 100.

24.4 The valproate interaction: halve the dose

Valproate can double the lamotrigine level. This is the single most examined interaction of the drug. Valproate inhibits the glucuronidation that clears lamotrigine, so it roughly **doubles** the lamotrigine plasma level; the titration rate and the ultimate dose must therefore be **reduced by 50%** to hold down the rash risk (Stahl 2021). Concretely, in the presence of valproate the start is 25 mg on alternate days (not 25 mg daily), the steps are half-sized, and the usual target falls to about 100 mg/day (Stahl 2021; Maudsley 2021). The mirror rule matters too: if valproate is later stopped once lamotrigine is stabilised, the lamotrigine dose is cautiously doubled over at least two weeks to keep it therapeutic (Stahl 2021).

The enzyme-inducer direction. Carbamazepine and the other enzyme-inducing antiepileptics (phenytoin, phenobarbital, primidone) do the opposite, lowering the lamotrigine level, so the schedule and target are roughly doubled (start 50 mg/day, target up to 400 mg/day in divided doses) (Stahl 2021). Oral contraceptives and pregnancy also lower lamotrigine levels, so the maintenance dose needs review around starting or stopping the pill and around delivery (Stahl 2021).

WORKED EXAMPLE

A woman on maintenance divalproex for bipolar I has a breakthrough depression and lamotrigine is added. Because valproate doubles the lamotrigine level, you do not use the standard 25 mg daily start: you begin lamotrigine at 25 mg on alternate days, increase in half-sized steps, and aim for about 100 mg/day rather than 200 mg/day, watching closely for rash. Using the monotherapy schedule here would roughly double the true lamotrigine exposure and sharply raise the Stevens-Johnson risk.

24.5 Stevens-Johnson syndrome and the serious rash: the stop-rule

The dangerous adverse effect is the rash. Lamotrigine can cause a **rash** in roughly 10% of patients, and the great majority of these are benign; the fear is the small minority that are a serious cutaneous reaction, namely stevens-johnson syndrome or toxic epidermal necrolysis, sometimes with multi-organ hypersensitivity (Stahl 2021). The risk of a serious rash is highest with a fast titration, with high starting doses, in children, and with valproate co-therapy, which is precisely why the schedule is slow and is halved with valproate (Stahl 2021). Most serious rashes appear early, within the first 8 weeks or so of treatment, which is the window the slow titration is designed to cover.

Tell the benign rash from the serious one. A **benign** rash peaks within days, settles in about 10 to 14 days, is spotty, non-confluent, non-tender, has no systemic features and normal bloods; here

you may reduce the dose or hold the increase, warn the patient, and monitor. A **serious** rash is confluent and widespread, or purpuric or tender, involves the neck or upper trunk, or involves the eyes, lips or mouth (mucosal involvement), or carries fever, malaise, pharyngitis, anorexia or lymphadenopathy, or abnormal blood counts or liver function (Stahl 2021). The stop-rule follows: at any sign of a serious or mucosal rash, **stop lamotrigine at once** (and stop concomitant valproate), investigate for organ involvement and admit if needed (Stahl 2021).

COMMON TRAP

A patient a fortnight into lamotrigine develops a rash with sores at the lips and mouth and a low-grade fever. Treating this as the common benign rash and merely holding the dose is the error: mucosal involvement plus systemic features is a serious rash, and the correct action is to stop lamotrigine (and valproate) immediately and investigate, not to wait and watch.

TRAP **Titrating lamotrigine too fast, or ignoring the valproate interaction, and precipitating Stevens-Johnson syndrome.** A fast start or a full monotherapy schedule on top of valproate drives the serious-rash risk; go slow and halve with valproate.

FEATURE	BENIGN RASH	SERIOUS RASH (STOP THE DRUG)
Time course	peaks in days, settles 10 to 14 days	confluent, widespread, progressive
Appearance	spotty, non-confluent, non-tender	**confluent, purpuric or tender**
Site	trunk and limbs, no mucosa	**neck / upper trunk; eyes, lips, mouth (mucosal)**
Systemic features	none	**fever, malaise, pharyngitis, anorexia, lymphadenopathy**
Bloods	normal	abnormal FBC, LFTs, urea/creatinine
Action	reduce dose / hold increase, monitor	**stop lamotrigine (and valproate); investigate; admit if needed**

Benign-versus-serious rash on lamotrigine: any mucosal involvement, systemic features or abnormal bloods marks a serious rash and mandates immediate cessation (Stahl 2021). The wider acute management of a serious drug reaction is in the Perinatal/women's mental health and emergency psychiatry notes.

INDIA

Lamotrigine is widely available in India as the generic and under brands such as Lamitor and Lametec; the tablet strengths (25, 50, 100, 200 mg) suit the six-week creep, and a 25 mg tablet on alternate days is the practical with-valproate start. The same two examinable points hold for Indian practice: lamotrigine is particularly effective for bipolar depression, and the skin-rash risk is higher with faster dose escalation and with valproate co-prescription, so titrate very gradually as per the summary of product characteristics. Note that carbamazepine-linked Stevens-Johnson syndrome is separately tied to the HLA-B*1502 allele common in Asian ancestry; the lamotrigine rash is not gene-tested that way, but the slow-titration discipline is the safeguard.

MNEMONIC

SLOW

What lamotrigine turns on: **S**tevens-Johnson risk is the danger (go slow to avoid it), **L**ow and slow titration (25 to 200 over about six weeks), **O**ne interaction to halve for (valproate doubles the level, so halve the schedule), **W**eak against mania but best for the depressive pole and maintenance.

GOOD TO REMEMBER

- **Lamotrigine (Lamitor, Lametec):** use-dependent voltage-gated sodium-channel blocker that reduces glutamate release; best evidence in bipolar depression and maintenance (depressive-relapse prevention), weak for acute mania.
- **Slow titration:** monotherapy 25 mg/day creeping to a target of 100 to 200 mg/day over about six weeks; never faster than recommended.
- **Valproate interaction:** valproate roughly doubles the lamotrigine level, so halve the titration and the target (start 25 mg on alternate days, target about 100 mg/day).
- **Enzyme inducer (carbamazepine):** lowers the level, so roughly double the schedule and target (start 50 mg/day, up to 400 mg/day).
- **Serious rash / Stevens-Johnson syndrome and toxic epidermal necrolysis:** highest risk with fast titration and valproate co-therapy; stop the drug at any serious or mucosal rash.
- **Monitoring:** no routine serum-level or blood monitoring is required; the safeguard is the slow titration and rash vigilance.

HOLD THIS

Lamotrigine is the mood stabiliser for bipolar depression and maintenance but weak for mania: titrate it slowly from 25 to 200 mg/day over about six weeks, halve the schedule and target with valproate (which doubles the level) and double it with an enzyme inducer, and stop the drug at any sign of a serious or mucosal rash because of Stevens-Johnson syndrome.

25 . Antipsychotics as mood stabilisers

The **atypical** second-generation antipsychotics are no longer bit-players in bipolar disorder: several are guideline first-line agents across one or more phases, and the whole modern algorithm for mania and bipolar depression is built on them (CANMAT 2018; Maudsley 2021). The examiner treats **antipsychotics as mood stabilisers** as a phase-matching problem. You are expected to know which atypical is first-line for mania, which for bipolar depression, which for

maintenance, why they work (a fast anti-manic effect plus, for some, a genuine antidepressant and relapse-prevention effect), and the price you pay for them (the metabolic, extrapyramidal and prolactin burden).

Organise the topic around one idea: **match the atypical to the phase, then monitor the metabolic cost for as long as the drug is used.** Every phase indication, dose and monitoring interval below is verified against the CANMAT and Indian Psychiatric Society rows, the Maudsley and Stahl (CANMAT 2018; IPS 2017; Maudsley 2021; Stahl 2021). The deep receptor pharmacology, the full adverse-effect detail and the metabolic-monitoring schedule are the property of the Schizophrenia: management, antipsychotics and adverse effects notes; this fragment carries only what is load-bearing for mood, and cross-refers the rest there. The neurobiology of mood and the wider guideline-anchored management PLAN belong to the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

25.1 Why antipsychotics stabilise mood: the mechanism and the trade-off

What they do at the synapse. Antipsychotics are not merely anti-psychotic: individual agents variously possess sedative, anxiolytic, anti-manic, mood-stabilising and antidepressant properties, and a few (quetiapine and olanzapine) show all of these (Stahl 2021). The shared anti-manic action is **dopamine D2 blockade or partial agonism** in the mesolimbic pathway, which rapidly damps the elevated dopaminergic drive of mania (Stahl 2021; Maudsley 2021). The antidepressant and mood-lifting actions of the broader agents come from additional targets: 5-HT2A antagonism, 5-HT7 antagonism, 5-HT1A partial agonism, alpha-2 blockade and, for quetiapine, potent noradrenaline-reuptake inhibition via its norquetiapine metabolite (Stahl 2021). The full receptor map is developed in the Schizophrenia: management, antipsychotics and adverse effects notes.

Why we reach for them, and what it costs. They are used because the anti-manic effect is fast (useful in an agitated, sleepless, high-risk manic patient) and because, unlike a pure antimanic anticonvulsant, several have real efficacy in bipolar depression and in maintenance (Maudsley 2021; CANMAT 2018). The trade-off is the class burden: **metabolic** harm (weight gain, dyslipidaemia, hyperglycaemia, worst with olanzapine), **extrapyramidal** effects and akathisia, sedation, and prolactin elevation (marked with risperidone and paliperidone) (Stahl 2021; Maudsley 2021). Because bipolar treatment is long-term, that burden is carried for years, which is exactly why the metabolic monitoring is non-negotiable.

RULE **Match the atypical to the phase.** Quetiapine is the broad one (mania, bipolar depression, maintenance); lurasidone and cariprazine are the bipolar-depression agents; aripiprazole and risperidone/paliperidone are mania and maintenance workhorses.

25.2 The FDA phase map: which atypical is licensed for which pole

The set-piece table. The cleanest way to hold this is the FDA-indication-by-phase map (Stahl 2021; Maudsley 2021). Aripiprazole covers mania, mixed episodes and maintenance; asenapine mania and mixed states; olanzapine mania, mixed episodes and maintenance, and (as the olanzapine-fluoxetine combination) bipolar depression; quetiapine spans mania, maintenance

and bipolar depression; risperidone mania and mixed episodes (and, as risperidone LAI, maintenance); cariprazine and lurasidone are the bipolar-depression agents (cariprazine also covers mania); ziprasidone mania and maintenance (Stahl 2021).

ATYPICAL (GENERIC)	MANIA / MIXED	BIPOLAR DEPRESSION	MAINTENANCE	SIGNATURE TRADE-OFF
Quetiapine (Qutipin)	**Yes**	**Yes (300 mg/day)**	**Yes**	Sedation, weight gain, moderate metabolic
Olanzapine (Oleanz)	Yes	Yes (with fluoxetine)	Yes	**Highest metabolic burden**
Aripiprazole	Yes	No (as monotherapy)	Yes (manic relapse)	Akathisia; weight-neutral
Risperidone (Sizodon)	Yes	No	Yes (as LAI)	**Prolactin elevation**
Paliperidone	Yes	No	LAI option	**Prolactin elevation**
Cariprazine	Yes	**Yes**	-	Akathisia; low metabolic
Lurasidone	No	**Yes**	-	Akathisia, nausea; low metabolic; take with food
Asenapine	Yes (incl. mixed)	No	-	Sublingual; oral hypoaesthesia

Atypical antipsychotics by bipolar phase (FDA-indication map, Stahl 2021; Maudsley 2021). The highlighted cells are the phase-defining facts to hold: quetiapine across all three poles, olanzapine's metabolic cost, the depression pair (cariprazine, lurasidone), and the prolactin pair (risperidone, paliperidone).

25.3 Quetiapine: the broadest, works across all phases

Why it is the broad one. Quetiapine (Qutipin, quetiapine) is the single atypical effective across all three bipolar phases: acute mania, acute bipolar I depression and maintenance (Stahl 2021; CANMAT 2018). Its breadth is mechanistic: D2 and 5-HT2A antagonism for the anti-manic and antipsychotic effect, and an active metabolite (norquetiapine) that is a potent noradrenaline-reuptake inhibitor and 5-HT2C antagonist, underpinning a genuine antidepressant action (Stahl 2021). CANMAT names quetiapine as a first-line monotherapy for acute mania, a first-line monotherapy for acute bipolar I depression at a target of **300 mg/day**, and a first-line maintenance monotherapy for bipolar I disorder (CANMAT 2018).

The dose and the cost. Mania and maintenance use higher divided doses (commonly around 400 to 800 mg/day); bipolar depression is treated at the lower **300 mg/day** (CANMAT 2018; Maudsley 2021). It carries moderate metabolic risk and is sedating, so it is often dosed at night (Stahl 2021). In India it is marketed as Qutipin (quetiapine), available as 25, 50, 100, 200 and 400 mg tablets (KDT 2019).

GOOD TO REMEMBER

- **Quetiapine (Qutipin):** D2/5-HT2A antagonist whose norquetiapine metabolite is a noradrenaline-reuptake inhibitor; signature cost is sedation and weight gain; the one to hold is that it is first-line across all three phases and bipolar depression is treated at 300 mg/day (CANMAT 2018; Stahl 2021).

25.4 Olanzapine: mania and maintenance, and the OFC for bipolar depression

Its place. Olanzapine (Oleanz, olanzapine) is effective in acute mania, mixed episodes and maintenance, and the **olanzapine-fluoxetine combination** (OFC) is a recognised treatment for bipolar I depression (Stahl 2021; CANMAT 2018). CANMAT places olanzapine as a first-line option for acute mania but downgrades it in maintenance and lists the OFC as a second-line option for acute bipolar I depression, both because of its metabolic profile (CANMAT 2018). It is a D2 and 5-HT2A antagonist; the fluoxetine partner adds the serotonergic antidepressant drive that olanzapine alone lacks.

The catch. Olanzapine carries the **highest metabolic** burden of the atypicals used in mood disorder, alongside clozapine: substantial weight gain, dyslipidaemia and hyperglycaemia (Stahl 2021). This is why guidelines that rank it first-line for the manic pole still demote it for long-term use. Indian brand: Oleanz (olanzapine), 2.5 to 20 mg tablets (KDT 2019).

TRAP **Ignoring the metabolic monitoring when an atypical is used long-term for mood.** Olanzapine on maintenance without weight, glucose and lipid tracking is the classic error; the drug that controlled the mania quietly builds the metabolic syndrome.

GOOD TO REMEMBER

- **Olanzapine (Oleanz):** D2/5-HT2A antagonist; signature cost is the highest metabolic burden of the mood atypicals; the one to hold is that it covers mania and maintenance, and bipolar depression only as the olanzapine-fluoxetine combination (CANMAT 2018; Stahl 2021).

25.5 Aripiprazole: mania and maintenance, weight-neutral

The mechanism that sets it apart. Aripiprazole (aripiprazole) is a **D2 partial agonist** (and 5-HT1A partial agonist, 5-HT2A antagonist), which gives it a fast anti-manic effect with a low metabolic and prolactin profile (Stahl 2021; KDT 2019). CANMAT lists it as a first-line agent for acute mania and, importantly, as a first-line maintenance monotherapy, available oral or as a once-monthly long-acting injectable, with the caveat that it prevents manic but not depressive episodes (CANMAT 2018). It is not a bipolar-depression monotherapy.

Dose and tolerability. The usual bipolar dose range is roughly **15 to 30 mg/day** (Indian dosing 5 to 30 mg/day; KDT 2019). It is essentially **weight-neutral** and carries low metabolic risk, but akathisia is its characteristic and often dose-limiting adverse effect (Stahl 2021).

GOOD TO REMEMBER

- **Aripiprazole:** D2 partial agonist; signature cost is akathisia (but weight-neutral and low prolactin); the one to hold is that it is first-line for mania and for maintenance (oral or once-monthly LAI) but prevents only the manic pole, not the depressive one (CANMAT 2018; Stahl 2021).

25.6 Risperidone and paliperidone: mania and the LAI option, at a prolactin cost

What they cover. Risperidone (Sizodon, risperidone) is a potent D2 and 5-HT2A antagonist, first-line for acute mania and mixed episodes; paliperidone (paliperidone), its active 9-hydroxy metabolite, is likewise used in mania (Stahl 2021; CANMAT 2018). Their standout maintenance role is as the **long-acting injectable** option: CANMAT recommends a long-acting injectable antipsychotic (risperidone LAI every two weeks or aripiprazole once-monthly) for the non-adherent bipolar patient to prevent relapse (CANMAT 2018).

The cost. Both are the class leaders for **prolactin elevation** (galactorrhoea, menstrual disturbance, sexual dysfunction) and carry moderate metabolic risk, more than the partial agonists (Stahl 2021). Risperidone is dosed around 1 to 6 mg/day in mania; Indian brands include Sizodon and Respidon (risperidone), 1 to 4 mg tablets (KDT 2019).

GOOD TO REMEMBER

- **Risperidone (Sizodon) and paliperidone:** potent D2/5-HT2A antagonists (paliperidone is risperidone's 9-OH metabolite); signature cost is prolactin elevation; the one to hold is mania first-line, and the long-acting injectable (risperidone LAI two-weekly) as the maintenance option for non-adherence (CANMAT 2018; Stahl 2021).

25.7 Cariprazine: mania and bipolar depression, the D3-preferring partial agonist

Why it reaches the depressive pole. Cariprazine (cariprazine) is a D2 and D3 partial agonist that is unique in being the **most potent available agent at the D3 receptor**, more potent than dopamine itself, together with 5-HT1A partial agonism (Stahl 2021). This D3-preferring profile is the presumed basis of its efficacy across both poles. CANMAT names cariprazine among the first-line options for acute mania, and lists cariprazine (with the olanzapine-fluoxetine combination) as a second-line option for acute bipolar I depression when a rapid response is desirable (CANMAT 2018).

Tolerability. It sits in the low-metabolic-risk tier (with lurasidone and aripiprazole) but, like the other partial agonists, akathisia is its characteristic adverse effect (Stahl 2021). Its long half-life and active metabolites mean effects and adverse effects accumulate over weeks.

GOOD TO REMEMBER

- **Cariprazine:** D3-preferring D2/D3 partial agonist (the most potent D3 agent available); signature cost is akathisia (low metabolic); the one to hold is that it works in both mania and bipolar depression, unusual for an anti-manic atypical (CANMAT 2018; Stahl 2021).

25.8 Lurasidone: the bipolar-depression agent

Its niche. Lurasidone (lurasidone) is a potent antagonist at 5-HT2A, D2 and 5-HT7 receptors and a 5-HT1A partial agonist (Kaplan and Sadock 2024; Stahl 2021). Its distinctive place is

bipolar depression: CANMAT lists it as a first-line treatment for acute bipolar I depression, as monotherapy or adjunctive to lithium or divalproex (CANMAT 2018). It is not licensed for acute mania. It sits with cariprazine and aripiprazole in the low-metabolic-risk tier (Stahl 2021).

The practical points. Its commonest adverse effects are sedation, akathisia and nausea, and it has a firm pharmacokinetic quirk: it must be **taken with food** (at least 350 kcal) to be adequately absorbed, and it is a CYP3A4 substrate, so it is contraindicated with strong CYP3A4 inhibitors and inducers (Kaplan and Sadock 2024; Stahl 2021). The receptor and interaction detail is developed in the Schizophrenia: management, antipsychotics and adverse effects notes.

RULE **Lurasidone and cariprazine for bipolar depression.** When the pole to treat is the depressive one, these two (plus quetiapine and the olanzapine-fluoxetine combination) are the atypicals with the evidence, not the pure anti-manic agents.

GOOD TO REMEMBER

- **Lurasidone:** 5-HT2A/D2/5-HT7 antagonist and 5-HT1A partial agonist; signature cost is akathisia and nausea (low metabolic) plus the take-with-food requirement; the one to hold is that it is first-line for bipolar depression and has no mania licence (CANMAT 2018; Kaplan and Sadock 2024).

25.9 Asenapine: mania, including mixed features

Its place. Asenapine (asenapine) is a high-affinity 5-HT2A and D2 antagonist (with broad serotonergic, dopaminergic and adrenergic actions) licensed for acute **mania and mixed states**, and it is one of the agents named first-line for acute mania by CANMAT (Kaplan and Sadock 2024; CANMAT 2018). Its usefulness in **mixed features** is the fact worth holding.

The formulation quirk. Asenapine is given **sublingually** because oral bioavailability is negligible; the patient must avoid food and drink for 10 minutes afterwards, and it commonly causes oral hypoaesthesia (Kaplan and Sadock 2024). It carries moderate metabolic risk (Stahl 2021).

GOOD TO REMEMBER

- **Asenapine:** high-affinity 5-HT2A/D2 antagonist given sublingually; signature cost is oral hypoaesthesia (and no food or drink for 10 minutes); the one to hold is mania first-line, particularly useful for mixed features (CANMAT 2018; Kaplan and Sadock 2024).

25.10 Phase-matching and the metabolic monitoring: pulling it together

The selection logic, previewing the choosing topic. The whole class resolves into a phase-matching decision (CANMAT 2018; Stahl 2021). For **acute mania**, CANMAT offers quetiapine, aripiprazole, risperidone, paliperidone, cariprazine or asenapine (alone or combined with lithium or divalproex), with an atypical-plus-mood-stabiliser combination first-line in severe presentations. For **acute bipolar I depression**, the atypical options are quetiapine, lurasidone (monotherapy or adjunctive to lithium or divalproex), the olanzapine-fluoxetine combination and cariprazine. For **maintenance**, quetiapine, aripiprazole and asenapine are first-line monotherapies, with olanzapine and paliperidone (and risperidone LAI) as second-line,

olanzapine downgraded for its metabolic risk. The **Indian Psychiatric Society** position aligns: the IPS guidelines name quetiapine, aripiprazole, risperidone, asenapine or cariprazine (with lithium or divalproex) among first-line monotherapies for acute mania and place olanzapine and ziprasidone second-line, name the olanzapine-fluoxetine combination, quetiapine, lurasidone or cariprazine as first-line for acute bipolar depression, and quetiapine and lamotrigine alongside lithium and divalproex as first-line maintenance agents, with olanzapine, carbamazepine, ziprasidone and risperidone second-line (IPS 2025). NICE recommends offering an antipsychotic (asenapine, aripiprazole, olanzapine, quetiapine or risperidone) where lithium is unsuitable for maintenance (NICE 2014). The full agent-versus-agent selection is developed in the choosing topic.

The monitoring headline. Whenever an atypical is used long-term for mood, the metabolic monitoring runs for as long as the drug does: CANMAT advises weight monthly for the first three months then every three months, with blood pressure, fasting glucose and a fasting lipid profile at 3 and 6 months then yearly, on top of the baseline metabolic and prolactin screen (CANMAT 2018). The receptor-level basis and the full adverse-effect and monitoring schedule are the property of the Schizophrenia: management, antipsychotics and adverse effects notes.

300	3	3 and 6
QUETIAPINE BIPOLAR DEPRESSION (MG/DAY)	WEIGHT CHECK FOR FIRST MONTHS (MONTHLY, THEN 3-MONTHLY)	GLUCOSE AND LIPIDS THEN YEARLY (MONTHS)

PEARL

The two atypicals that reach the depressive pole in bipolar I as first-line (lurasidone and, with quetiapine, cariprazine second-line) are exactly the ones in the low-metabolic-risk tier: the drugs you most want to keep a patient on long-term for the harder-to-treat depressive phase happen to be the metabolically kindest, which is a rare alignment of efficacy and tolerability (Stahl 2021; CANMAT 2018).

INDIA

Lead with the Indian brand where one is confirmed: quetiapine as **Qutipin** (25 to 400 mg), olanzapine as **Oleanz** (2.5 to 20 mg), risperidone as **Sizodon** or Respidon (1 to 4 mg) (KDT 2019). Aripiprazole, paliperidone, cariprazine, lurasidone and asenapine are all marketed in India but a specific brand could not be confirmed from the parsed library, so the generic is given for those (flagged under gaps). All of these are widely available and used as mood stabilisers in Indian bipolar practice.

GOOD TO REMEMBER

- **Mania (first-line atypicals):** quetiapine, aripiprazole, risperidone, paliperidone, cariprazine, asenapine, alone or with lithium/divalproex (CANMAT 2018).
- **Bipolar depression:** quetiapine and lurasidone are first-line; cariprazine and the olanzapine-fluoxetine combination are second-line (CANMAT 2018).
- **Maintenance:** quetiapine, aripiprazole, asenapine first-line; aripiprazole prevents manic (not depressive) relapse; risperidone LAI or aripiprazole once-monthly for non-adherence (CANMAT 2018).
- **The trade-off:** the metabolic burden (worst with olanzapine), extrapyramidal effects/akathisia (the partial agonists) and prolactin (risperidone, paliperidone) must be monitored for as long as the drug is used (Stahl 2021; CANMAT 2018).

HOLD THIS

Quetiapine works across all three phases; lurasidone and cariprazine are the bipolar-depression agents; and any atypical used long-term for mood earns lifelong metabolic monitoring.

26 . Choosing a mood stabiliser: the algorithms

Choosing a mood stabiliser is not a single decision, it is a decision that is remade at every phase of bipolar disorder: the agent that is first-line for **acute mania** is not the same agent that is first-line for the depressive pole, and the **maintenance algorithm** is anchored by yet another logic. This is the mood-block closer and a reliable theory question: the examiner rewards the guideline-anchored **phase-then-polarity** spine and the exact serum-level targets, not a recitation of side effects. The deep pharmacology, dosing, monitoring and teratogenicity of each agent are owned by the dedicated lithium, valproate, carbamazepine and lamotrigine topics in these notes; this topic carries the **selection algorithm**.

Lead the guideline answer with CANMAT, specifically the CANMAT and ISBD 2018 bipolar guidelines (Yatham 2018), then give the Indian Psychiatric Society (IPS 2025, Menon et al.), NICE (NICE 2014) and BAP (BAP 2016, Goodwin) positions. Across all four the organising principle the exam tests is one instruction: **pick the stabiliser by phase and by predominant polarity, with lithium anchoring maintenance and lamotrigine covering the depressive pole.**

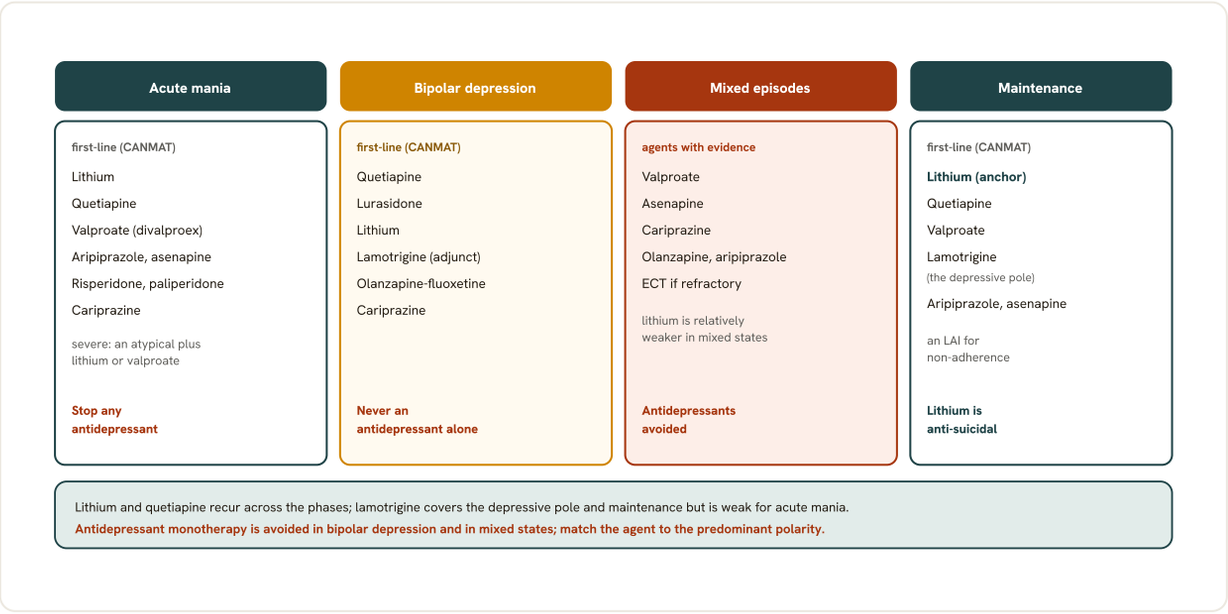

Fig 12.13 Choosing a mood stabiliser by phase, led by the CANMAT recommendations. Lithium, quetiapine and valproate anchor acute mania; quetiapine, lurasidone, lithium and lamotrigine cover bipolar depression; valproate and the atypicals (asenapine, cariprazine) with ECT cover mixed episodes; and lithium anchors maintenance with lamotrigine for the depressive pole. Antidepressant monotherapy is avoided in bipolar depression and mixed states, and any antidepressant is stopped in acute mania.

26.1 The selection logic: phase first, then predominant polarity

Phase before drug. The single most examinable idea is that you choose the agent by the phase you are treating, not by a generic label of "mood stabiliser". A drug that is genuinely first-line for mania (for example an antipsychotic or valproate) may be weak or useless for the depressive pole, and a drug that covers the depressive pole (lamotrigine) is weak for acute mania. Layered on top of phase is **predominant polarity**: a patient whose recurrences are mostly depressive is steered toward agents with depressive-pole efficacy (lamotrigine, quetiapine, lithium), whereas a mostly-manic course is steered toward lithium and the antimanic antipsychotics. The receptor-level pharmacology that underlies these differences is cross-referred to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

RULE **Pick the stabiliser by phase and predominant polarity.** Lithium anchors maintenance; lamotrigine covers the depressive pole; the antimanic antipsychotics and valproate cover mania.

26.2 ACUTE MANIA: the CANMAT first-line monotherapies

For **acute mania**, CANMAT offers a defined first-line monotherapy list (Yatham 2018): lithium (Licab or Intalith), quetiapine (Qutipin), divalproex (Valance or Valprol), asenapine, aripiprazole, paliperidone, risperidone and cariprazine, given alone or in combination. Note what is *not* on this list: lamotrigine, carbamazepine and the antidepressants. The choice among the first-line agents is individualised on prior response, tolerability, comorbidity and the need for sedation. The IPS names essentially the same set, listing lithium, divalproex, risperidone, quetiapine, aripiprazole, asenapine or cariprazine monotherapy as first-line for acute mania, with carbamazepine, olanzapine, ziprasidone and haloperidol second-line on grounds of a less favourable safety profile (IPS 2025). NICE, for a person not already on treatment, offers haloperidol, olanzapine, quetiapine or risperidone (NICE 2014).

RULE **Acute mania first-line = lithium, an antimanic atypical (quetiapine, asenapine, aripiprazole, paliperidone, risperidone, cariprazine) or divalproex.** Individualise on tolerability and comorbidity (CANMAT 2018).

26.3 ACUTE MANIA: the first-line combination and the antidepressant rule

For severe mania, CANMAT's **first-line combination** is an atypical antipsychotic (quetiapine, aripiprazole, risperidone or asenapine) plus lithium or divalproex, preferred in severe presentations over monotherapy (Yatham 2018). The IPS agrees: combine a mood stabiliser with a second-generation antipsychotic for severe mania (IPS 2017). Two selection rules sit alongside this. First, **discontinue any antidepressant** in a patient presenting with mania, and reassess the diagnosis before starting antimanic agents in a first-episode presentation (CANMAT 2018; IPS 2017). Second, if response to an optimally dosed first-line agent is inadequate after 2 weeks, optimise the dose and address non-adherence and substance use before switching to or adding another first-line agent (CANMAT 2018). The serum-level target for lithium in acute mania is **0.8 to 1.2 mEq/L** (Yatham 2018).

TRAP **Leaving an antidepressant running in acute mania.** Antidepressants are discontinued when a patient presents in mania; continuing one is a selection error.

WORKED EXAMPLE

A 27-year-old man presents with a first severe manic episode with psychotic features while taking sertraline for a presumed depression. The sertraline is discontinued. Because the mania is severe, he is started not on monotherapy but on the first-line combination: an atypical antipsychotic, risperidone (Sizodon or Risdone), plus a mood stabiliser, lithium (Licab or Intalith), titrated to an acute-phase serum lithium of 0.8 to 1.2 mEq/L. He is reviewed at 2 weeks; because the response is only partial, the dose is optimised and adherence checked before any switch. The diagnosis is reassessed as bipolar I disorder once the episode settles, which sets up the maintenance decision.

26.4 BIPOLAR DEPRESSION: a different first-line list

The depressive pole has its own first-line set, and it is the reason lamotrigine exists in this algorithm. For acute bipolar I depression, CANMAT's first-line options are quetiapine (Qutipin), lurasidone (as monotherapy or added to lithium or divalproex), lithium, and lamotrigine (Lamitor or Lametec) as monotherapy or adjunct (Yatham 2018). Lamotrigine is titrated slowly from **25 mg** to a minimum target of **200 mg/day** to limit the rash risk; the full titration schedule and the Stevens-Johnson syndrome caution are owned by the lamotrigine topic in these notes. The IPS names the olanzapine-fluoxetine combination, quetiapine, lurasidone and cariprazine as first-line for acute bipolar depression, and is explicit that lithium is not approved as a first-line treatment here and that lamotrigine is usually not preferred for the acute phase because of its prolonged titration (IPS 2025). NICE offers fluoxetine combined with olanzapine, quetiapine alone, olanzapine alone, or lamotrigine alone (NICE 2014). A hard rule governs the whole pole: **do not use an antidepressant as monotherapy in bipolar depression**; if one is used it is only on a background mood stabiliser, paroxetine is avoided, and bupropion is preferred (IPS 2017). The management of each bipolar phase in full is owned by the dedicated bipolar-management topics.

TRAP **An antidepressant alone in a bipolar patient.** Antidepressant monotherapy is not used in bipolar depression; cover it with a mood stabiliser, and never use lamotrigine to treat acute mania (it is weak there).

26.5 MAINTENANCE ALGORITHM: lithium leads, lamotrigine for the depressive pole

The **maintenance algorithm** is where lithium is the anchor. CANMAT's first-line maintenance monotherapies for bipolar I are lithium, quetiapine, divalproex, lamotrigine, asenapine and aripiprazole, alone or in combination (Yatham 2018). Two polarity facts drive the choice: **lamotrigine is the maintenance agent for the depressive pole** and is weak against manic recurrence, whereas **aripiprazole prevents manic but not depressive episodes**. Lithium is the broadest, preventing both poles, and carries specific anti-suicide evidence (IPS 2017). A rational default is to continue into maintenance the agent that worked in the acute phase (BAP 2016; IPS 2017). The maintenance serum-level target for lithium is **0.6 to 1.0 mEq/L** (Yatham 2018); NICE and BAP frame a slightly narrower **0.6 to 0.8 mmol/L** range (NICE 2014; BAP 2016). NICE is explicit that lithium is the first-line long-term treatment, with an antipsychotic (asenapine, aripiprazole, olanzapine, quetiapine or risperidone) if lithium is unsuitable (NICE 2014). The IPS guidelines name lithium and valproate as the best-evidenced maintenance agents (IPS 2017).

RULE **Lithium leads maintenance and prevents both poles; lamotrigine covers the depressive pole; aripiprazole covers the manic pole only.** Continue what worked acutely (CANMAT 2018; NICE 2014).

26.6 MAINTENANCE: the LAI option for non-adherence

Non-adherence is the commonest cause of maintenance failure, and the algorithm has a defined answer. In a non-adherent patient, CANMAT offers a **long-acting injectable** antipsychotic as first-line to prevent relapse, specifically risperidone LAI every 2 weeks or aripiprazole once-monthly (Yatham 2018). BAP frames the same option as depot antipsychotics for prophylaxis against manic recurrence when oral adherence is erratic or injection is preferred (BAP 2016). This is a selection rule the exam likes because it links a clinical problem (non-adherence) to a specific pharmacological form; the deep antipsychotic pharmacology behind these agents is cross-referred to the Schizophrenia: management, antipsychotics and adverse effects notes.

RULE **Non-adherence in maintenance = a long-acting injectable.** Risperidone LAI two-weekly or aripiprazole once-monthly is first-line for the non-adherent patient (CANMAT 2018).

26.7 The stabiliser-selection algorithm assembled by phase

The phases and their first-line agents assemble into one table. Learn the highlighted cell in each row: it is the first-line fact the examiner tests. Each phase links to the dedicated bipolar-management topics for the full plan.

0.8 to 1.2	0.6 to 1.0	200	2 wk
ACUTE-MANIA LITHIUM (MEQ/L)	MAINTENANCE LITHIUM (MEQ/L)	LAMOTRIGINE MINIMUM TARGET (MG/DAY)	REASSESS BEFORE SWITCHING IN MANIA

PHASE	CANMAT FIRST-LINE (LEAD)	FIRST-LINE COMBINATION / NEXT STEP	IPS / NICE / BAP HEADLINE
Acute mania	**Lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone, cariprazine (monotherapy) (CANMAT 2018)**	Atypical (quetiapine, aripiprazole, risperidone, asenapine) plus lithium or divalproex for severe mania; discontinue any antidepressant; lithium 0.8 to 1.2 mEq/L	IPS: lithium, divalproex, risperidone, quetiapine, aripiprazole, asenapine, cariprazine first-line, with olanzapine, ziprasidone and haloperidol second-line; NICE: haloperidol, olanzapine, quetiapine, risperidone (IPS 2025; NICE 2014)
Bipolar depression	**Quetiapine, lurasidone (plus lithium or divalproex), lithium, lamotrigine (CANMAT 2018)**	Lamotrigine titrated 25 to 200 mg/day; no antidepressant monotherapy; olanzapine-fluoxetine an option	IPS: olanzapine-fluoxetine, quetiapine, lurasidone or cariprazine first-line, lithium not first-line here; NICE: fluoxetine plus olanzapine, or quetiapine, or lamotrigine (IPS 2025; NICE 2014)
Mixed features	**Antimanic agents; antidepressants avoided (treat the manic pole) (CANMAT 2018)**	Lithium, valproate or an antimanic atypical; do not use an antidepressant in a mixed state (IPS 2017)	IPS: no antidepressant monotherapy in mixed episodes; consider ECT if severe (IPS 2017)
Maintenance	**Lithium, quetiapine, divalproex, lamotrigine, asenapine, aripiprazole (CANMAT 2018)**	Lamotrigine for the depressive pole; aripiprazole for the manic pole only; LAI (risperidone two-weekly or aripiprazole monthly) for nonadherence; lithium 0.6 to 1.0 mEq/L	NICE: lithium first-line long-term; IPS/BAP: lithium and valproate best-evidenced, continue what worked acutely (NICE 2014; IPS 2017; BAP 2016)

The mood-stabiliser selection algorithm by phase; first-line agents verified against CANMAT and ISBD 2018 (Yatham 2018), IPS 2017, NICE 2014 and BAP 2016. Each phase is owned in full by the dedicated bipolar-management topics.

INDIA

The Indian Psychiatric Society Clinical Practice Guidelines for bipolar disorder (IPS 2025, Menon et al.) are the guideline most likely to be named in Indian postgraduate examinations, and they map cleanly onto the phases: lithium, divalproex or a first-line antipsychotic (risperidone, quetiapine, aripiprazole, asenapine, cariprazine) for acute mania, with olanzapine, ziprasidone and haloperidol second-line; the olanzapine-fluoxetine combination, quetiapine, lurasidone or cariprazine first-line for bipolar depression; lithium and valproate as the best-evidenced maintenance agents with lithium first-line for preventing recurrence at both poles and specific anti-suicide evidence. Every agent named here is available as an inexpensive Indian brand: lithium carbonate (Licab or Intalith), sodium valproate (Valprol or Encorate), divalproex (Valance or Divaa), quetiapine (Qutipin), olanzapine (Oleanz), lamotrigine (Lamitor or Lametec) and carbamazepine (Tegretol or Mazetol). The IPS avoids antidepressant monotherapy in bipolar depression, prefers bupropion if an antidepressant is unavoidable, and avoids paroxetine.

GOOD TO REMEMBER

- **Lithium (Licab or Intalith):** broad-spectrum anchor; prevents both poles and has anti-suicide evidence; acute-mania target **0.8 to 1.2 mEq/L**, maintenance **0.6 to 1.0 mEq/L** (CANMAT 2018).
- **Quetiapine (Qutipin):** the one atypical that is first-line across mania, bipolar depression and maintenance; signature adverse effect is metabolic and sedation.
- **Divalproex / valproate (Valprol or Encorate):** first-line for acute mania and maintenance; teratogenic, so avoided in women of childbearing potential; not first-line for bipolar depression.
- **Lamotrigine (Lamitor or Lametec):** the depressive-pole agent for bipolar depression and maintenance; weak for acute mania; titrate slowly from 25 mg to a minimum of **200 mg/day** for rash risk.
- **Aripiprazole:** first-line for mania and maintenance but prevents the manic pole only, not the depressive; available as a once-monthly LAI for non-adherence.
- **The antidepressant rule:** discontinue an antidepressant in acute mania, and never use antidepressant monotherapy in bipolar depression (CANMAT 2018; IPS 2017).

PEARL

Read the algorithm as three lists that overlap but are not identical. Only a handful of agents (lithium, quetiapine, divalproex, aripiprazole, asenapine) appear on both the mania and the maintenance first-line lists; lamotrigine appears on the depression and maintenance lists but never on the mania list; lurasidone appears on the depression list. The overlap is why lithium is the safest single answer when a question does not specify the phase.

HOLD THIS

Choose the mood stabiliser by phase and predominant polarity: for acute mania give lithium, an antimanic atypical or divalproex and stop any antidepressant; for bipolar depression reach for quetiapine, lurasidone, lithium or lamotrigine and never an antidepressant alone; for maintenance lithium leads and prevents both poles while lamotrigine covers the depressive pole, with CANMAT 2018 as the lead guideline.

Treatment resistance, augmentation and special populations

27 . Treatment-resistant depression

Some depressions do not lift on the first, or even the second, well-chosen antidepressant. **Treatment-resistant depression** is the label for that clinical situation, and it is one of the highest-yield theory topics in the mood block because the examiner is testing a discipline, not a drug list: before you escalate treatment, you must prove the depression is genuinely resistant and not merely under-treated. This topic teaches the **definition** of treatment-resistant depression, how to **staging** the degree of resistance, and the evaluation that must precede the label. The augmentation ladder that follows a confirmed diagnosis (which agent, which line) is the next topic; this topic carries the definition, the staging and the pre-escalation work-up.

The single organising idea is that resistance is a matter of *degree*, not a binary switch, and that it is over-diagnosed. Most apparent resistance is **pseudoresistance**, an inadequate dose, an inadequate duration, poor adherence or the wrong diagnosis, and every guideline (CANMAT 2016; BAP 2015; IPS 2017) opens the treatment-resistant depression pathway with a mandatory review of adequacy and diagnosis before any escalation.

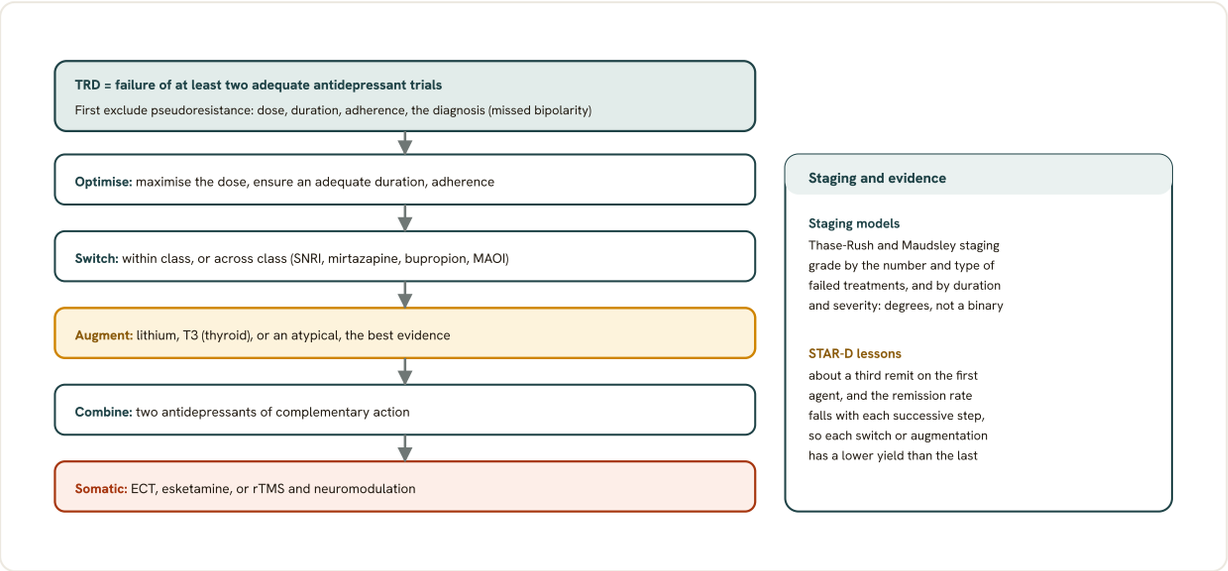

Fig 12.14 Treatment-resistant depression: staging and the augmentation ladder. Resistance means at least two failed adequate antidepressant trials, but pseudoresistance (inadequate dose or duration, non-adherence, missed bipolarity) is excluded first. The sequence then runs optimise, switch, augment (lithium, T3 or an atypical carry the best evidence), combine, and finally the somatic treatments. The STAR-D trial showed remission rates fall with each successive step.

27.1 The definition: two adequate failed trials in the current episode

The working definition. **Treatment-resistant depression** (**trd**) is conventionally defined as a failure to respond to at least **two** adequate antidepressant trials, each at an adequate dose for an adequate duration, in the current depressive episode (Tasman 2015; Maudsley 2021). Failure of a single trial is so common that it does not qualify as resistance; true resistance is better defined as failure to reach remission after two treatments given at adequate dosage and duration (Tasman 2015).

The definition is not settled. There is no universally accepted operational definition of treatment-resistant depression, which is precisely why comparisons across the literature are so difficult (Tasman 2015). Definitions vary in three ways: the *number* of failed trials required (some demand two, some more), the *outcome* threshold that counts as failure (non-response, usually less than a 50 percent symptom reduction, versus failure to reach full remission), and whether the failed trials must be of different pharmacological classes. Remission, not response, is the modern target, because response without remission carries a high relapse risk (Tasman 2015).

RULE **Two adequate antidepressant trials must fail in the current episode before the depression is called resistant.** Each trial must have been at an adequate dose for an adequate duration.

27.2 What "adequate" means: dose and duration

Adequacy is dose plus duration. A trial only counts toward resistance if it was truly adequate, meaning a therapeutic dose sustained for long enough to work. The BAP directs that before declaring a drug to have failed you must increase to a recommended therapeutic dose, and for a tricyclic aim for a dose-equivalence of at least **125 mg** if tolerated (BAP 2015). On duration, the guidelines assess response at **4 weeks** of adequate treatment and again at **6 to 8 weeks**; a marginal or low dose, or a trial cut short before this window, has not adequately tested the drug (BAP 2015; CANMAT 2016).

Optimise before you escalate. The first step in the treatment-resistant depression pathway is therefore not a new drug but optimisation: check the adequacy of the current treatment, and raise a low or marginal dose to a recommended therapeutic dose first (BAP 2015). Only a trial that was adequate in both dose and duration can be counted as a genuine failure.

2	4 to 8	50
ADEQUATE FAILED TRIALS TO DEFINE TRD	WEEKS TO JUDGE ONE ADEQUATE TRIAL	PERCENT SYMPTOM DROP DEFINING RESPONSE

27.3 Staging: resistance is a degree, not a binary

Why stage. Because resistance is a continuum, several **staging** systems quantify *how* resistant a depression is, which predicts outcome and guides how aggressively to treat (Tasman 2015). The two the board tests are the **thase-rush** five-stage model and the **maudsley staging** method; the Massachusetts General Hospital (MGH) staging method is a third. Each grades resistance by the number and type of failed treatments and, for the newer methods, the duration and severity of illness.

The clinical point of any staging system. All of them exist to make one point: neither doctor nor patient should be discouraged by a single failed trial, and good treatment demands persistence through multiple adequate trials (Tasman 2015). Staging turns "resistant or not" into a graded score that tracks the odds of remission.

27.4 The Thase-Rush five-stage model

Staged by class of drug failed. The Thase-Rush five-stage model grades resistance purely by non-response to sequential trials of antidepressants with differing mechanisms, culminating in

electroconvulsive therapy (Tasman 2015). It is the classic, examinable ladder.

STAGE	DEFINITION (CUMULATIVE)
Stage I	Failure of an adequate trial of one antidepressant
Stage II	**Stage I plus failure of a trial of an antidepressant of a different class**
Stage III	Stage II plus failure of a tricyclic antidepressant
Stage IV	Stage III plus failure of a monoamine oxidase inhibitor
Stage V	Stage IV plus failure of a course of electroconvulsive therapy

The Thase-Rush five-stage model, graded by non-response to antidepressants of progressively different mechanism and finally to ECT (Tasman 2015). Its weakness: it assumes a fixed hierarchy of drug classes and does not weigh dose, duration, augmentation or combination.

Its limitation. The Thase-Rush model presumes that a monoamine oxidase inhibitor is intrinsically superior to a tricyclic, and it cannot grade a trial by its dose or duration, nor does it credit augmentation or combination strategies (Tasman 2015). This is why the later staging methods were developed.

27.5 The Maudsley staging method

Multidimensional scoring. The Maudsley staging method (Fekadu et al. 2009) scores resistance across three separate dimensions rather than a single ladder: the *prior treatment* (number of failed antidepressants, plus augmentation and ECT), the *current symptom severity*, and the *duration* of the illness (Tasman 2015; Maudsley 2021). The points sum to a total that places the patient on a mild-to-severe resistance gradient.

Why it is preferred. By incorporating severity and chronicity, and by crediting augmentation and combination, the **maudsley staging** method predicts continuing treatment resistance and longer-term outcome better than the Thase-Rush ladder in inpatient samples (Fekadu et al. 2009; Tasman 2015). The MGH method, for comparison, assigns one point per adequate monotherapy trial of at least 6 weeks, adds 0.5 points for optimising, augmenting or combining, and adds 3 points for ECT (Petersen et al. 2005).

GOOD TO REMEMBER

- **Thase-Rush five-stage model:** grades resistance by failed drug *class* in sequence, ending at ECT (Stage V); ignores dose, duration and augmentation.
- **Maudsley staging method:** scores three dimensions, prior treatment, current symptom severity and duration of illness (Fekadu et al. 2009); better predicts persistence and outcome.
- **MGH staging method:** 1 point per adequate 6-week monotherapy trial, 0.5 for optimise/augment/combine, 3 for ECT (Petersen et al. 2005).
- **The shared message:** resistance is a degree, not a binary; do not be discouraged by one failed trial.

27.6 Before you label it resistant: reconsider the diagnosis

Resistance is often a wrong diagnosis. The first evaluation before calling any depression resistant is to reconsider the diagnosis. The BAP directs a formal diagnostic review, including the possibility of comorbid medical or psychiatric conditions and unrecognised bipolarity, psychosis or atypical features, using screening tools where helpful (BAP 2015). The commonest missed diagnoses are a missed bipolar disorder (the depression is a bipolar depression that will not respond to, and may be worsened by, an antidepressant alone), a missed psychotic depression (which needs an antipsychotic added), and a missed organic or substance cause (hypothyroidism, anaemia, alcohol or substance use) (Tasman 2015; IPS 2017).

And a comorbidity that sustains the depression. A coexisting personality disorder, a chronic medical illness, or an untreated anxiety or substance use disorder can hold a depression down and masquerade as pharmacological resistance. The Indian Psychiatric Society Clinical Practice Guidelines (Gautam et al.) make this explicit: the IPS treatment-resistant depression pathway reassesses the diagnosis to rule out bipolar disorder, substance use and medical contributors before escalating (IPS 2017). Where a finer IPS-specific staging or threshold cannot be confirmed against the guideline rows, it is flagged under gaps rather than invented.

TRAP **Calling a bipolar depression "treatment-resistant" and stacking on antidepressants.** An unrecognised bipolar depression will not respond to an antidepressant alone and can be destabilised by it; screen for bipolarity first.

27.7 Pseudoresistance: adherence, dose and duration

Confirm adherence. Once the diagnosis holds, confirm the patient actually took the drug. Non-adherence, whether from side effects, cost, or belief, is a leading cause of apparent non-response, and a depression that was never adequately dosed in the patient's body cannot be called resistant; the **ips guidelines** and the BAP both make confirming adherence a step before escalation (BAP 2015; IPS 2017). This is the essence of **pseudoresistance**: an apparent treatment resistance that is really an artefact of inadequate treatment.

The three checks that unmask pseudoresistance. Was the *dose* therapeutic? Was the *duration* long enough (at least 4 to 8 weeks at that dose)? Was *adherence* intact? If any answer is no, the depression is not resistant, it is under-treated, and the correct action is to optimise, not to escalate (BAP 2015; CANMAT 2016). A subtherapeutic or non-adherent trial simply does not count toward the two-trial definition.

RULE **Before labelling depression resistant, confirm the dose, the duration, adherence and the diagnosis.** Only then does a failed trial count.

INDIA

Pseudoresistance is disproportionately common in Indian outpatient practice, where largely out-of-pocket payment drives early self-discontinuation once the patient feels a little better or once side effects appear, and where a subtherapeutic dose may have been given to limit cost. Before any escalation, verify that a cheap generic SSRI such as escitalopram (Nexito or S-Citadep) or sertraline (Serta or Daxid) was actually taken at a therapeutic dose for an adequate duration; the commonest "resistant" case is a half-dose, half-taken first trial.

27.8 The STAR-D lessons: remission falls with each step

The landmark effectiveness trial. The STAR-D trial (the Sequenced Treatment Alternatives to Relieve Depression programme, Rush et al. 2006), a large NIH-funded practical trial highly applicable to real-world practice, gave the best available data on what happens across sequential steps (Tasman 2015). Patients who did not remit on the initial citalopram progressed through sequential, randomised steps of switching and augmentation.

Two lessons the examiner rewards. First, about a *third* of patients remit on the first agent: STAR-D reported first-step remission of roughly 28 percent by the Hamilton scale and 33 percent by the QIDS-SR, so lack of remission to a first antidepressant is common rather than exceptional (Tasman 2015). Second, remission rates *decline* with each successive step: the cumulative remission was about 37 percent after one trial, rising to 49 percent after two, but only to 50 percent after three and 51 percent after four (Tasman 2015). The small gains at steps three and four show how an increasingly resistant episode becomes progressively harder to treat.

STAR-D TREATMENT STEP	CUMULATIVE REMISSION (PERCENT)
After step 1 (citalopram)	37
After step 2	49
After step 3	50
After step 4	51

STAR-D cumulative remission by treatment step (Rush et al. 2006; Tasman 2015): about a third remit on the first agent, and each further step yields diminishing returns. Patients who need more steps to remit also relapse at a higher rate.

What STAR-D informs. These figures underpin the whole switch-versus-augment logic: because a first agent so often fails, a planned sequence of next steps is essential, and because returns diminish, staging and diagnostic review matter more with each failed step. STAR-D also showed that switching within class was no different in outcome from switching to another class (CANMAT 2016), and that patients needing more steps to remit relapse at a higher rate (Tasman 2015). The augmentation ladder that operationalises these next steps is the next topic.

TRAP **Reading STAR-D as evidence that antidepressants do not work.** A third remit on the first drug and roughly half by the second; the lesson is diminishing returns and the need for a planned sequence, not futility.

27.9 The pre-escalation checklist and where the ladder begins

The work-up before escalation, in order. Put the topic together as the checklist the examiner wants before any next-step drug: (1) reconsider the diagnosis, screening for missed bipolarity, psychosis, an organic or substance cause, and a medical or personality comorbidity; (2) confirm adherence; (3) confirm the dose was therapeutic; (4) confirm the duration was adequate (4 to 8 weeks); and only then (5) stage the resistance and move to the next-step algorithm (BAP 2015; IPS 2017; CANMAT 2016).

Then the ladder. Once genuine resistance is confirmed, the options are to switch antidepressant, augment or combine, or move to neurostimulation. At guideline level the first-line augmentation agents are aripiprazole or brexpiprazole (CANMAT 2016), with quetiapine, aripiprazole or lithium as the BAP first-line augmentation choices (BAP 2015); lithium augmentation has the best evidence in older people (BAP 2015). Electroconvulsive therapy is reserved for those who have not responded to other treatments (BAP 2015). The detail of that ladder, and the ECT and neurostimulation technique, belong to the next topic and to the ECT and neurostimulation notes.

HOLD THIS

Treatment-resistant depression is failure of two adequate antidepressant trials in the current episode, but most apparent resistance is pseudoresistance or a missed bipolar depression, so confirm dose, duration, adherence and diagnosis before you ever escalate.

MNEMONIC

DADD before you ESCALATE

Diagnosis (reconsider, screen for bipolarity), **A**dherence (confirm it), **D**ose (therapeutic?), **D**uration (4 to 8 weeks?). Only when all four are cleared do you stage the resistance and climb the augmentation ladder.

GOOD TO REMEMBER

- **Definition:** treatment-resistant depression is failure of at least two adequate antidepressant trials (adequate dose and duration) in the current episode; no single agreed definition exists.
- **Pseudoresistance:** most apparent resistance is a subtherapeutic dose, an inadequate duration, poor adherence or a wrong diagnosis; exclude it, and exclude missed bipolarity, first.
- **Staging:** Thase-Rush grades by failed drug class to ECT; the Maudsley staging method scores prior treatment, current severity and illness duration and predicts outcome better.
- **STAR-D:** about a third remit on the first agent (28 percent HAM-D, 33 percent QIDS-SR); cumulative remission is roughly 37, 49, 50, 51 percent across steps 1 to 4, so returns diminish.

28 . Augmentation and combination strategies

When an antidepressant has been pushed to an adequate dose for an adequate duration and the depression has still not remitted, the clinician has three moves: **switch** the antidepressant, **augment** it with a second agent of a different pharmacology, or **combine** it with a second antidepressant. This topic teaches how to choose between those moves and, once augmentation is chosen, which agent to add and in what order of evidence. It follows directly from the treatment-

resistant depression topic, which carries the definition, the staging and the pre-escalation work-up; here we climb the ladder itself. It is high-yield because the board tests a discipline, not a drug list: the examiner wants to see that you **augment a partial response** and **switch a non-response**, and that you reach for a proven **augmentation** agent rather than stacking antidepressants irrationally.

The organising principle, repeated across CANMAT (2016), the BAP (2015) and NICE (2014), is that **augmentation** and **combination** are for genuine, confirmed treatment resistance in which the diagnosis, dose, duration and adherence have already been checked. Of the augmentation options, **lithium augmentation** and the atypical antipsychotics carry the strongest and most modern evidence; **thyroid** augmentation with T3 is a real but second-line option; and combining two antidepressants is reserved, evidence-selective and never started from the outset.

28.1 The decision: switch versus augment versus combine

The response guides the move. The single decision that organises the whole ladder is the degree of response to the current antidepressant. If there has been *no* response at all, or the drug is intolerable, **switch** to another agent, because there is nothing to build on and no reason to expose the patient to a second drug. If there has been a *partial* response but not remission, and the current drug is well tolerated, **augment** or combine, because you keep a partly effective treatment and add to it (BAP 2015; CANMAT 2016). The BAP states it directly: consider a second agent for augmentation when there is partial or insufficient response with good tolerability of the current antidepressant, or after an unsuccessful switch (BAP 2015).

Switching first, then building. A rational sequence after one adequate failure is to switch to another first-line agent; switching within class is no different in outcome from switching to another class (CANMAT 2016). After more than one failure within a class, move to a different class (BAP 2015). Only once a partial response emerges, or once switching has been exhausted, does augmentation become the preferred next step.

RULE **Augment a partial response; switch a non-response.** Build on a partly effective, tolerated drug; abandon one that did nothing or cannot be tolerated.

TRAP **Stacking antidepressants irrationally instead of a proven augmentation.** Two antidepressants at the outset is not supported; a proven augmenter (lithium or an atypical) has far better evidence.

28.2 The guideline map of augmentation, at a glance

What the guidelines actually recommend. The lead guideline for this note is CANMAT: for an inadequate antidepressant response, add a first-line adjunct of aripiprazole 2 to 15 mg/day, quetiapine 150 to 300 mg/day, risperidone 1 to 3 mg/day, or brexpiprazole 1 to 3 mg/day; add lithium or triiodothyronine (T3) as a second-line adjunct with drug-level or thyroid monitoring (CANMAT 2016). The BAP ranks the same agents: add quetiapine, aripiprazole or lithium as first-line augmentation, and risperidone, olanzapine, triiodothyronine or mirtazapine as second-line (BAP 2015). NICE, where a combination of medications is chosen, positions adding a

second-generation antipsychotic (aripiprazole, olanzapine, quetiapine or risperidone) or lithium to the antidepressant, in or with advice from a specialist mental health setting (NICE 2022). The Maudsley collapses this to a headline: either lithium or quetiapine is the agent of first choice for augmenting the existing antidepressant (Maudsley 2021).

The Indian position. The Indian Psychiatric Society Clinical Practice Guidelines for depression (Gautam et al.) place augmentation within the treatment-resistant pathway, listing lithium augmentation among the recognised strategies alongside atypical antipsychotic and thyroid augmentation after two adequate trials have failed (IPS 2017). Where a precise IPS-specific ordering of augmenting agents cannot be confirmed against the guideline rows, it is flagged under gaps rather than invented; the IPS guidelines endorse augmentation as a strategy but the exact agent hierarchy is stated less rigidly than in CANMAT.

AUGMENTING AGENT	LINE / EVIDENCE	DOSE (PER DAY)	SIGNATURE CAVEAT
Lithium	First-line; strong, classic evidence; anti-suicidal	to level 0.6 to 1.0 mmol/L	Narrow window; renal, thyroid, level monitoring
Aripiprazole	First-line adjunct (CANMAT); VAST-D positive	2 to 15 mg	Akathisia, some weight gain
Quetiapine	First-line adjunct; agent of first choice (Maudsley)	150 to 300 mg	Sedation, metabolic, QTc
Brexpiprazole	First-line adjunct (CANMAT)	1 to 3 mg	Akathisia, weight gain
Risperidone	First-line adjunct (CANMAT); second-line (BAP)	1 to 3 mg	Prolactin, EPS, metabolic
Olanzapine	Second-line adjunct	2.5 to 10 mg	Highest metabolic burden
Triiodothyronine (T3)	Second-line; older evidence, well tolerated	25 to 50 mcg	Rare thyrotoxic symptoms above 25 mcg; TSH monitoring
Mirtazapine / mianserin	Second-line adjunct antidepressant	30 to 60 mg	A combination, not a true augmentation
Esketamine (intranasal)	Add to SSRI/SNRI after two failed trials	per protocol	Dissociation, blood-pressure rise; supervised dosing

Augmentation agents ranked by guideline evidence for inadequate antidepressant response (CANMAT 2016; BAP 2015; NICE 2022; Maudsley 2021). Lithium and the atypical antipsychotics carry the best modern evidence; T3 is a genuine second-line option. Doses in the header, bare figures in the cells.

28.3 Lithium augmentation: the classic, with anti-suicidal value

The evidence base. **Lithium augmentation** is the oldest and one of the best-evidenced augmentation strategies. Recent meta-analyses show robust efficacy for lithium alongside

quetiapine and the D2 partial agonists, and one meta-analysis found lithium to be the most effective augmenter (Maudsley 2021). The classic evidence derives from older RCTs combining lithium with tricyclics, which is why CANMAT positions it as a second-line adjunct even though it works (CANMAT 2016). It remains widely underused in resistant depression.

Dose to a plasma level, not a milligram target. Lithium augmentation is most effective at a lithium plasma level of **0.6 to 1.0 mmol/L** (Maudsley 2021); the CANMAT adjunctive dose range is **600 to 1200 mg/day** titrated to that therapeutic serum level (CANMAT 2016). As with any lithium prescription, check renal and thyroid function before starting and monitor the level, taking the sample 12 hours post-dose. In India the common carbonate brands are Licab and Intalith; the deeper lithium mechanism, pharmacokinetics and monitoring are carried in the lithium notes of this block.

The anti-suicidal signal. The feature that distinguishes lithium from every other augmenter is its specific effect on suicide. A meta-analysis of clinical trials concluded that lithium reduced the risk of both attempted and completed suicide by about 80 percent in patients with mood disorders, both unipolar and bipolar (Cipriani et al. 2013, BMJ), and the protective effect holds in unipolar depression, though the mechanism is unknown (Maudsley 2021). Clinical predictors of a good augmentation response include more severe depression, psychomotor retardation, weight loss, a family history of major depression, or more than three prior episodes (Maudsley 2021). The full suicide risk assessment and safety planning sit in the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

0.6 to 1.0	600 to 1200	80
LITHIUM AUGMENTATION LEVEL (MMOL/L)	CANMAT ADJUNCTIVE LITHIUM (MG/DAY)	PERCENT LITHIUM SUICIDE-RISK REDUCTION (BIPOLAR)

GOOD TO REMEMBER

- **Lithium augmentation:** add lithium to a partially responding antidepressant; the classic, strong-evidence augmenter, dosed to a plasma level of **0.6 to 1.0 mmol/L** (Maudsley 2021).
- **Signature value:** specific anti-suicidal effect, reducing attempted and completed suicide by about 80 percent in mood disorders, unipolar and bipolar (Cipriani et al. 2013).
- **The one to hold:** check renal and thyroid function before starting; monitor the level 12 hours post-dose. Indian brand Licab or Intalith (lithium carbonate).

28.4 Atypical augmentation: the best modern evidence

The strongest recent evidence. Atypical augmentation, adding a second-generation antipsychotic to an antidepressant, has the best modern evidence base of all the augmentation strategies and is the first-line adjunct in CANMAT (CANMAT 2016). Aripiprazole (Indian brand Arip or Asprito), quetiapine (Qutipin), brexpiprazole, risperidone (Sizodon or Risdone) and olanzapine (Oleanz) are the examinable agents; the D2 partial agonists aripiprazole and brexpiprazole are used at lower doses than in bipolar disorder or schizophrenia because their tolerability at these doses is favourable (CANMAT 2016).

The head-to-head data. Aripiprazole augmentation of an SSRI or venlafaxine is more effective than adding placebo, which won it FDA approval as an adjunct; in the 1,500-patient VAST-D trial aripiprazole augmentation achieved remission somewhat more often than switching to bupropion or augmenting with bupropion (Kaplan and Sadock 2024). Adding quetiapine **150 to 300 mg/day** to a standard antidepressant improved response in registration trials (Kaplan and Sadock 2024), and the Maudsley names quetiapine as an agent of first choice for augmentation (Maudsley 2021). The trade-off is the antipsychotic side-effect burden: akathisia and some weight gain with the partial agonists, sedation and metabolic effects with quetiapine, and the highest metabolic risk with olanzapine, which is why olanzapine is downgraded to second-line (CANMAT 2016).

WORKED EXAMPLE

A patient on escitalopram 20 mg (Nexito or S-Citadep) for eight weeks is 40 percent better but not remitted, and tolerates the drug well. This is a partial response to a tolerated drug: augment rather than switch. A reasonable first-line adjunct is aripiprazole 2 to 5 mg titrated to 10 mg, or quetiapine 150 mg titrated toward 300 mg, warning the patient about akathisia (aripiprazole) or sedation and weight (quetiapine), and monitoring metabolic parameters.

GOOD TO REMEMBER

- **Aripiprazole:** D2/5-HT1A partial agonist; first-line adjunct at **2 to 15 mg/day**; VAST-D beat switching to or augmenting with bupropion; signature effect akathisia (Kaplan and Sadock 2024). Indian brand Arip or Asprito.
- **Quetiapine:** broad antagonist with noradrenergic (norquetiapine) action; first-line adjunct at **150 to 300 mg/day**; the Maudsley agent of first choice; signature effect sedation and metabolic gain (Maudsley 2021). Indian brand Qutipin.
- **Brexpiprazole:** D2 partial agonist, chemically related to aripiprazole; first-line adjunct at **1 to 3 mg/day** (CANMAT 2016; NICE 2014); signature effect akathisia and weight gain.
- **Risperidone / olanzapine:** risperidone **1 to 3 mg/day** (prolactin, EPS); olanzapine **2.5 to 10 mg/day** is second-line, downgraded for the highest metabolic burden. Indian brands Sizodon/Risdone and Oleanz.

28.5 Thyroid augmentation with T3 (liothyronine)

The strategy. **Thyroid** augmentation adds triiodothyronine (T3), the synthetic form liothyronine, to an antidepressant in a nonresponder. It is the most widely studied thyroid strategy for depression; T4 (levothyroxine) has far fewer supporting data in refractory depression and is chiefly reserved as a mood-stabiliser adjunct in rapid-cycling bipolar disorder (Kaplan and Sadock 2024). CANMAT and the BAP both list T3 as a second-line adjunct with thyroid-level monitoring (CANMAT 2016; BAP 2015).

Evidence and dose. Open and controlled studies show that roughly 50 to 60 percent of tricyclic nonresponders respond within 2 to 3 weeks of adding T3, and patients augmented with T3 were about twice as likely to respond as controls (Kaplan and Sadock 2024). In the STAR*D trial, T3 augmentation had remission rates comparable to other augmentation options with a more favourable adverse-event and dropout profile (Kaplan and Sadock 2024). T3 is given as a single

morning dose of **25 to 50 mcg** to avoid insomnia; 25 mcg/day is below the replacement dose so thyrotoxic symptoms are rare, but 50 mcg/day approaches the daily production range and can cause thyroid excess, so doses above 25 mcg are used with caution and TSH is monitored. In responders, taper and stop by 12 weeks; avoid in pregnancy (Kaplan and Sadock 2024).

INDIA

Triiodothyronine (liothyronine) is not freely available in India and is used only occasionally (KDT 2019), so T3 augmentation is a more theoretical than practical option on the ground here; levothyroxine is the freely available thyroid preparation. Know T3 as an examinable second-line augmenter but recognise the supply constraint in Indian practice.

GOOD TO REMEMBER

- **Thyroid (T3, liothyronine):** thyroid hormone receptor agonist added as a second-line augmenter; single morning dose **25 to 50 mcg/day**; about 50 to 60 percent of tricyclic nonresponders respond within 2 to 3 weeks (Kaplan and Sadock 2024).
- **Signature caveat:** 25 mcg is subreplacement and safe; above 25 mcg can cause thyrotoxic symptoms, so monitor TSH and cap short courses; taper and stop by 12 weeks; avoid in pregnancy.
- **India:** liothyronine is not freely available in India; levothyroxine is. T3 is the option to name, not usually the one to reach for locally.

28.6 Combination antidepressant strategies and the polypharmacy caution

What a combination is. A **combination** strategy adds a second antidepressant with a complementary mechanism to the first, most classically an SSRI or SNRI plus mirtazapine (Indian brand Mirtaz), or plus bupropion (Bupron). CANMAT rates adding mirtazapine or mianserin 30 to 60 mg/day as a second-line adjunct and notes this combination is superior to other antidepressant combinations (CANMAT 2016). The rationale is pharmacological: mirtazapine's alpha-2 and 5-HT2/5-HT3 antagonism complements the reuptake block of an SSRI or SNRI, and bupropion's noradrenaline-dopamine action adds a different mechanism.

The evidence is modest and never from the outset. The discipline the board tests is that two antidepressants are never combined at the initiation of treatment (CANMAT 2016). The CO-MED trial found no benefit from starting escitalopram plus bupropion, or venlafaxine plus mirtazapine, over monotherapy from the outset (Kaplan and Sadock 2024). Even as a later strategy the yields are small: in STAR*D the venlafaxine plus mirtazapine combination achieved remission in only about 10 percent, no better statistically than the MAOI tranylcypromine though far better tolerated, and bupropion or buspirone augmentation of citalopram each remitted about 30 percent (Kaplan and Sadock 2024). This is the case against irrational polypharmacy: stacking antidepressants adds interaction and adverse-effect risk for a small, evidence-thin gain, whereas a proven augmenter does better.

COMMON TRAP

Adding a second, then a third antidepressant from different classes and calling it a "combination" when there was never a partial response to build on. This is irrational polypharmacy, not augmentation: it multiplies serotonergic load (raising serotonin syndrome risk, especially near an MAOI, covered in the Perinatal/women's mental health and emergency psychiatry notes) for a remission gain of around 10 percent (Kaplan and Sadock 2024). Use a proven augmenter instead.

GOOD TO REMEMBER

- **Mirtazapine combination:** alpha-2 and 5-HT2/5-HT3 antagonist added to an SSRI/SNRI at **30 to 60 mg/day**; superior to other antidepressant combinations (CANMAT 2016); STAR*D venlafaxine plus mirtazapine remitted only about 10 percent. Indian brand Mirtaz.
- **Bupropion combination:** noradrenaline-dopamine reuptake inhibitor added for a complementary mechanism; STAR*D bupropion augmentation of citalopram remitted about 30 percent (Kaplan and Sadock 2024). Indian brand Bupron.
- **The hold:** never combine two antidepressants at the outset (CO-MED negative); combination is a later, evidence-selective move, weaker than lithium or atypical augmentation.

28.7 When to move to esketamine or ECT

Esketamine and ketamine. For depression that has failed at least two adequate antidepressant trials, intranasal esketamine (Indian brand Spravato) is added to an ongoing SSRI or SNRI, monitoring blood pressure and for dissociative effects (CANMAT 2023). Intravenous racemic ketamine is a second-line adjunct for a rapid antidepressant effect, including rapid reduction of suicidal ideation, again with blood-pressure and dissociation monitoring; both act at the NMDA receptor and work within hours rather than weeks, which is their signature advantage over conventional augmenters. Non-esketamine racemic ketamine given orally, intramuscularly or intranasally is third-line given variable protocols (CANMAT 2023). The deeper esketamine and ketamine pharmacology is carried in its own fragment; here it is the escalation pointer.

ECT. When augmentation and combination have not delivered remission, or where the depression is severe, psychotic, or carries acute suicide risk, electroconvulsive therapy is the next step and remains the most effective acute treatment for severe depression (BAP 2015); the technique sits in the ECT and neurostimulation notes. The escalation logic is that the ladder runs optimise, switch, augment or combine, then esketamine or ECT, matched to the severity, the degree of resistance and the urgency.

PEARL

Two features push you past the augmentation ladder straight toward esketamine or ECT: *urgency* (acute suicide risk, food and fluid refusal, psychotic or catatonic depression) and *rapidity of effect needed*. Conventional augmenters take 2 to 6 weeks; ECT and ketamine/esketamine act far faster, which is precisely why they earn their place when time is the constraint.

GOOD TO REMEMBER

- **Esketamine (intranasal):** NMDA-receptor antagonist added to an SSRI/SNRI after at least two failed antidepressant trials; monitor blood pressure and dissociation (CANMAT 2023). Indian brand Spravato.
- **Ketamine (IV racemic):** second-line adjunct for rapid effect and rapid reduction of suicidal ideation; acts within hours; monitor blood pressure and dissociation.
- **ECT:** the step when augmentation and combination fail or when severity or suicide risk demands the fastest, most effective acute treatment (BAP 2015); technique in the ECT and neurostimulation notes.

HOLD THIS

Augment a partial response and switch a non-response: lithium (to a level of 0.6 to 1.0 mmol/L, and anti-suicidal) and the atypical antipsychotics have the best augmentation evidence, T3 is a second-line option, and two antidepressants are never combined from the outset.

29 . Depression in the elderly

Depression in later life is a high-frequency examinable topic because it looks different from depression in the young, it is dangerous (older men carry the highest completed-suicide rate of any group), and it is under-treated precisely when it is most treatable. **Depression in the elderly** (depression in the elderly, also termed geriatric depression) is tested as a triad: recognise the atypical presentation, exclude the organic mimic, and prescribe with geriatric caution. This fragment teaches the presentation and the assessment, then the pharmacology caveats that make prescribing in the old a different discipline from prescribing in the young (Kaplan & Sadock 2024; Maudsley 2021).

The organising phrase to hold is **start low and go slow**, but the trap it breeds is under-dosing to remission-failure, so the counter-phrase is equally examinable: reach an adequate dose despite starting low. Every dose, serum figure and monitoring interval below is verified against the CANMAT guideline rows, the Maudsley and the parsed textbooks; the wider frailty and cognitive workup cross-refers to the Consultation-liaison, geriatric and transcultural psychiatry notes (CANMAT 2016; Maudsley 2021).

29.1 The presentation: somatic and cognitive, not classically sad

More somatic and cognitive complaints. The older depressed patient frequently does not say they are sad. **Geriatric depression** presents disproportionately with somatic and cognitive complaints: bodily preoccupation, pain, fatigue, weight loss, sleep disturbance, agitation, and a subjective sense of memory failure, often with the affective core masked or denied (Kaplan & Sadock 2024; Shorter Oxford 2018). Anhedonia, psychomotor retardation and loss of drive are common, guilt is often absent, and the picture can be dominated by anxiety or by hypochondriacal fixation rather than low mood.

Why this matters. Because the mood complaint is muted and the somatic and cognitive complaints are loud, **late-life** depression is repeatedly misattributed to physical illness, to normal ageing, or to early dementia, and left untreated. Screening therefore has to be active, not reactive.

RULE **In the old, look for depression behind somatic and cognitive complaints, not behind a complaint of sadness.** The affective core is often masked or denied.

29.2 Pseudodementia: the depression-related cognitive impairment

The cognitive syndrome that mimics dementia. Depression in the old can produce cognitive impairment severe enough that the patient is misclassified as demented, historically termed pseudodementia (depressive pseudodementia), better called depression-related cognitive impairment. This is the most common potentially reversible cause of an apparent dementia, and missing it is catastrophic because a treatable, potentially fatal illness is passed off as an untreatable one (Companion 2010; Tasman 2015).

Discriminating it from true dementia. The examinable discriminators favour depression: a relatively abrupt, datable onset with the patient complaining loudly of memory loss, giving "don't know" answers, showing poor effort but preserved cued recall and orientation, and a personal or family history of mood disorder. True degenerative dementia is insidious, the patient conceals or is unaware of deficits, confabulates or near-misses rather than saying "don't know", and cued recall does not rescue performance (Companion 2010; Kaplan & Sadock 2024).

FEATURE	DEPRESSIVE PSEUDODEMENTIA	DEGENERATIVE DEMENTIA
Onset	**Relatively abrupt, datable**	Insidious, undatable
Complaint of memory loss	**Emphasised by patient**	Concealed or unaware
Typical answer	"Don't know", gives up	Near-miss or confabulation
Cued recall	Improves with cueing	Does not improve
Effort	Poor effort, distressed	Effortful, unconcerned
Mood history	Personal or family mood disorder	Usually absent

The classic discriminators between depression-related cognitive impairment and a degenerative dementia (Companion 2010; Kaplan & Sadock 2024). The picture can overlap, and depression can coexist with or herald a true dementia, so a therapeutic antidepressant trial and follow-up cognition are part of the workup.

TRAP **Writing off a reversible depressive pseudodementia as an untreatable dementia.** It is the commonest reversible cause of apparent dementia; treat the depression and reassess cognition.

29.3 The vascular depression concept

Cerebrovascular disease drives some late-onset depression. The vascular depression hypothesis (Alexopoulos 1997) holds that cerebrovascular disease predisposes to, precipitates or perpetuates some **late-life** depressive syndromes. It rests on the high comorbidity of depression with vascular risk factors, the excess of depression after stroke, and the burden of deep white-matter hyperintensities on MRI in late-onset depression (Kaplan & Sadock 2024).

The recognisable phenotype. Vascular depression tends to present with psychomotor retardation, anhedonia, prominent executive dysfunction, poor insight into the illness and disability, and relatively less guilt, on a background of hypertension and other vascular risk.

White-matter and microstructural disconnection of frontostriatal circuits predicts a poorer and slower response to antidepressants, which is one reason late-life depression is given a longer time to respond (Kaplan & Sadock 2024; Maudsley 2021).

PEARL

Late-onset first-ever depression in an older patient with vascular risk factors, executive slowing and white-matter change on imaging is the vascular-depression picture: expect a slower antidepressant response, treat the vascular risk factors alongside the mood, and do not mistake the executive slowing for early dementia.

29.4 The higher suicide risk in older men

The lethal edge of the topic. Completed suicide rates rise with age and are highest in older men, who use more lethal methods, give fewer warnings, are more often socially isolated and bereaved, and whose depression is more likely to be missed. An older man presenting with depression, physical illness, recent loss and alcohol use is a high-lethality combination that mandates explicit risk assessment at the first contact (Kaplan & Sadock 2024). The full structured suicide risk assessment and safety planning belong to the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

RULE **Ask every depressed older patient, and especially every older man, directly about suicide.** Older men have the highest completed-suicide rate and give the fewest warnings.

29.5 Assessment: screen, exclude an organic cause and drugs, test cognition

Screen. Use a structured instrument because the presentation is atypical: the Geriatric Depression Scale (self-report, yes or no, tolerated by the frail elderly) is the standard screen, with the PHQ-9 or a HAM-D also acceptable; whatever is chosen, repeat it to track response (measurement-based care).

Exclude an organic cause and drugs. Before attributing the picture to primary depression, exclude the medical and iatrogenic mimics that are common in the old. Screen and treat comorbid hypothyroidism and B12 or folate deficiency, look for occult malignancy, anaemia, renal or hepatic failure, Parkinson's disease, and covert cerebrovascular or neurodegenerative disease. Review the drug chart for depressogenic agents (corticosteroids, beta-blockers, some centrally acting antihypertensives, opioids, interferon) and for the anticholinergic and sedative burden that itself impairs cognition and mood.

Test cognition. Perform bedside cognitive testing (for example the MMSE or MoCA) to characterise the deficit, to establish a baseline before starting a drug, and to separate depression-related impairment from an evolving dementia over follow-up. The wider frailty, functional, falls-risk and comprehensive geriatric assessment frame is the Consultation-liaison, geriatric and transcultural psychiatry notes.

29.6 The drug caveats: start low and go slow, prefer an SSRI

The prescribing frame. Ageing changes pharmacokinetics (reduced renal and hepatic clearance, altered volume of distribution, longer half-lives) and pharmacodynamics (greater receptor sensitivity), and the old are on more concurrent drugs, so the **drug caveats** in the elderly all follow from one principle: **start low** and go slow (Maudsley 2021; CANMAT 2016). Begin at about half the usual adult starting dose (for example escitalopram **5 mg/day**, sertraline **25 mg/day**) and titrate slowly, watching tolerability at each step.

Prefer an SSRI. The first-line agent in the old is a well-tolerated SSRI, and the two workhorses are sertraline (Serta or Daxid) and escitalopram (Nexito or S-Citadep), chosen for a clean interaction profile, low anticholinergic load and cardiac safety (CANMAT 2016; Maudsley 2021). The specific geriatric hazards to manage are hyponatraemia, falls, the anticholinergic burden, drug interactions and the citalopram and escitalopram QTc cap.

CAVEAT IN THE ELDERLY	WHAT TO DO	WHY
Start low, go slow	Half the adult start (escitalopram 5, sertraline 25), titrate slowly	Reduced clearance, greater sensitivity, polypharmacy
Prefer an SSRI	Sertraline or escitalopram first-line	Clean interactions, low anticholinergic load, cardiac safety
Hyponatraemia (SIADH)	Check sodium at baseline and 2 to 4 weeks; recheck if drowsy, confused or falling	SSRIs cause SIADH; risk highest in the old, in women, on diuretics
Falls	Review at each visit; minimise sedatives and orthostatic-load drugs	Antidepressants raise fall and fracture risk in the old
Anticholinergic burden	Prefer low-anticholinergic agents; avoid the TCAs	Cumulative anticholinergic load worsens cognition and delirium
Drug interactions	Prefer escitalopram or sertraline over fluoxetine, paroxetine, fluvoxamine	The clean SSRIs are weak CYP inhibitors; the others are potent
Citalopram and escitalopram QTc cap	Citalopram maximum 20, escitalopram maximum 10, in the elderly	Dose-related QTc prolongation; caps are lower in over-65s
Avoid the TCAs	Not first-line; use only where unavoidable	Anticholinergic, orthostatic hypotension, cardiotoxic, lethal in overdose

The verified geriatric drug caveats (Maudsley 2021; CANMAT 2016). The three highlighted rows are the highest-yield: start low and go slow, watch hyponatraemia, and respect the citalopram and escitalopram QTc dose caps in the elderly.

The citalopram and escitalopram QTc cap. Citalopram and escitalopram cause a dose-related QTc prolongation and are the most cardiotoxic of the SSRIs (albeit modestly so), which is why the licensed maximum is reduced in the old: in the elderly, citalopram is capped at **20 mg/day** and escitalopram at **10 mg/day** (Maudsley 2021). Where QTc is a concern, sertraline is the cleaner cardiac choice.

TRAP **Titrating citalopram or escitalopram past the reduced elderly ceiling, or missing an SSRI-induced hyponatraemia.** Respect the QTc caps and check sodium at baseline and 2 to 4 weeks.

5	20	10
ESCITALOPRAM START IN ELDERLY (MG/DAY)	CITALOPRAM ELDERLY MAX (MG/DAY)	ESCITALOPRAM ELDERLY MAX (MG/DAY)

INDIA

In Indian practice the outpatient workhorses are the cheap generic SSRIs, led by sertraline (Serta or Daxid) and escitalopram (Nexito or S-Citadep), which suits a largely out-of-pocket, medically complex elderly population. The TCAs (amitriptyline as Tryptomer, imipramine as Depsonil) remain cheap and available and are still reached for, but their anticholinergic, orthostatic and cardiotoxic load makes them a poor first choice in the old; keep them off first line and prefer the clean SSRI.

29.7 Treatment: adequate dose despite starting low, and a longer wait

Reach an adequate dose. Starting low does not mean staying low. The commonest management error in the old is to under-dose out of caution and leave the patient at a homeopathic, sub-therapeutic dose that never reaches remission. Titrate up to a full adequate antidepressant dose as tolerated (for example sertraline toward **50 to 200 mg/day**, escitalopram toward the elderly ceiling of **10 mg/day**), and judge the trial only once an adequate dose has been given for an adequate time (CANMAT 2016; BAP 2015).

Allow a longer time to respond. In older people the antidepressant response may take longer, so allow more time before declaring failure, and continue treatment after remission because continued antidepressant treatment roughly halves the relapse rate (BAP 2015). For treatment resistance in the old, lithium augmentation has the best evidence, with about half of patients responding to a switch or augmentation (BAP 2015); the deep next-step ladder is the treatment-resistance topic.

The guideline position. At guideline level, CANMAT and the SSRI-first frame apply to the old as to the young, individualised to the patient with a lower start, and the **Indian Psychiatric Society** Clinical Practice Guidelines likewise place the SSRIs first-line for late-life depression with a reduced starting dose and slow titration (CANMAT 2016; IPS 2018). Beyond this SSRI-first-with-caution position, a finer elderly-specific IPS dose could not be confirmed from the parsed source and is flagged rather than invented.

RULE **Start low and go slow, but still reach an adequate dose in the elderly.** Judge the trial only at a full dose given for an adequate (and, in the old, longer) time.

29.8 ECT: a good response in severe or psychotic late-life depression

ECT works well in the old. Severe, psychotic, food-and-fluid-refusing or actively suicidal late-life depression responds well to electroconvulsive therapy, and age is not a contraindication; the elderly, particularly those with psychotic depression, are among the best responders to ECT

(Kaplan & Sadock 2024). It is the treatment of choice where a rapid, definitive response is needed, where the patient is not eating or drinking, or where drug options are exhausted or poorly tolerated. The technique, the anaesthetic considerations and the cognitive-side-effect management belong to the ECT and neurostimulation notes.

GOOD TO REMEMBER

- **Presentation:** somatic and cognitive complaints with the affective core masked; screen actively.
- **Pseudodementia:** depression-related cognitive impairment is the commonest reversible cause of apparent dementia; abrupt onset, "don't know" answers, cued recall improves; treat and reassess.
- **Vascular depression:** late-onset, executive slowing, vascular risk, white-matter change; slower antidepressant response.
- **Suicide:** highest completed-suicide rate is in older men; ask directly at first contact.
- **Sertraline (Serta or Daxid):** SSRI, clean and cardiac-safe, first-line in the old; start **25 mg/day**, target **50 to 200 mg/day**.
- **Escitalopram (Nexito or S-Citadep):** SSRI, clean, dose-related QTc; start **5 mg/day**, elderly maximum **10 mg/day**.
- **Citalopram:** SSRI, dose-related QTc; elderly maximum **20 mg/day**.
- **Drug caveats:** start low and go slow, prefer an SSRI, watch hyponatraemia and falls, mind the anticholinergic burden and interactions, respect the QTc caps, avoid the TCAs.
- **ECT:** a good response in severe or psychotic late-life depression; age is not a contraindication.

MNEMONIC

SAD-SAFE

The elderly prescribing caveats: **S**tart low, **A**dequate dose still reached, **D**rug interactions minimised; **S**odium (hyponatraemia) watched, **A**nticholinergic burden avoided (no TCAs), **F**alls guarded against, **E**CG-aware QTc caps on citalopram and escitalopram.

HOLD THIS

In late-life depression, start low and go slow with a clean SSRI (sertraline or escitalopram) but still reach an adequate dose over a longer trial, watching hyponatraemia, falls, anticholinergic burden and the elderly QTc caps of citalopram 20 mg and escitalopram 10 mg, and remember ECT works well in severe or psychotic late-life depression.

30 . Suicide risk in mood disorders: the pharmacological angle

Why this closes the mood block. Mood disorders carry the highest **suicide risk** in psychiatry, and the drugs a resident chooses either lower that risk, do nothing, or add a lethal means to a suicidal patient's cupboard. This note teaches only the **mood-specific** risk picture and the **pharmacological** angle: which agent has genuine anti-suicidal evidence, which drug not to hand over in bulk, and what to counsel and monitor at the start of treatment. The full clinical **suicide risk** assessment, the stratification interview and the safety-planning method are taught separately in the Somatic-symptom, sexual, impulse-control disorders and suicide notes; the acute serotonin-syndrome and NMS frame sits in the Perinatal/women's mental health and emergency psychiatry notes.

Exam framing is blunt: examiners want the one psychotropic with the strongest mortality evidence (lithium), the psychotic-overlap agent (clozapine), the early-treatment activation caveat, and the overdose-safety principle (never a large tricyclic antidepressant supply to a suicidal patient). Get those four and you have the topic.

30.1 The burden: where the risk concentrates

Highest risk in psychiatry. Lifetime suicide in bipolar disorder is estimated at around 15 percent, among the highest of any psychiatric condition (Maudsley 2021). The risk is not spread evenly across the illness course: it clusters in **severe depression**, in **mixed states**, in the **depressive phase** of bipolar illness, in the **early bipolar illness** (the first years after diagnosis, the first decade), and in the **early recovery phase** as psychomotor retardation lifts before mood and hopelessness do. Recurrent unipolar depression carries a substantial risk too. The mood-specific message: a mixed, agitated or early-course presentation is a higher-risk presentation.

~15	mixed / depressive	first years
LIFETIME SUICIDE IN BIPOLAR (PERCENT)	HIGHEST-RISK MOOD PHASES	EARLY ILLNESS, HIGHEST RISK WINDOW

RULE **Phase drives risk.** Severe depression, mixed states, early bipolar illness and the early recovery phase are the danger windows, screen and act hardest there.

30.2 Lithium: the anti-suicidal drug

The strongest evidence of any psychotropic. The **lithium anti-suicidal** effect is the single most important pharmacological fact in this topic. A meta-analysis of randomised trials concluded that lithium reduced the risk of both attempted and completed suicide by roughly 80 percent in patients with mood disorders, and lithium-treated patients are less likely to complete suicide than patients on other mood stabilisers (Cipriani 2005, Maudsley 2021). This is an effect on suicide and on **all-cause mortality**, not merely on mood-episode counts, and it holds in bipolar illness and appears to protect in unipolar depression too (mechanism unknown). Even naturally occurring lithium in drinking water is inversely related to population suicide rates. No antidepressant, anticonvulsant or antipsychotic has evidence of this strength for reducing suicide in mood disorders.

The clinical consequence. The anti-suicidal effect is a positive reason to weigh lithium in a high-risk bipolar or recurrent depressive patient, over an anticonvulsant stabiliser that lacks the mortality evidence. It runs partly independent of mood-episode prevention, so a patient at high suicide risk gains from lithium even where another agent might control episodes. Note the plasma targets from the mood-stabiliser topic: minimum effective prophylaxis around **0.4 mmol/L**, optimal prophylaxis **0.6 to 0.8 mmol/L**, and the CANMAT maintenance range **0.6 to 1.0 mEq/L** (Maudsley 2021, CANMAT 2018). Full initiation, monitoring and toxicity are taught in the lithium notes; here the point is the anti-suicidal indication.

~80	0.6 to 0.8	0.6 to 1.0
SUICIDE RISK REDUCTION ON LITHIUM (PERCENT)	OPTIMAL PROPHYLAXIS LITHIUM (MMOL/L)	CANMAT MAINTENANCE LITHIUM (MEQ/L)

RULE **Lithium reduces suicide.** In a high-risk bipolar or recurrent depressive patient, weigh lithium specifically for its anti-suicidal and all-cause mortality benefit.

PEARL

The anti-suicidal benefit is why an examiner asks "what would you add for a bipolar patient with repeated attempts" and expects lithium, not a switch to valproate. The evidence base is Cipriani 2005: attempted and completed suicide both cut by about 80 percent.

30.3 Clozapine: the psychotic-overlap anti-suicidal agent

The second drug with real anti-suicidal evidence. Where a mood disorder overlaps with a psychotic illness, or in schizophrenia and schizoaffective disorder, clozapine has a specific anti-suicidal effect. Roughly 5 to 10 percent of patients with schizophrenia eventually complete suicide, and clozapine treatment markedly reduces the suicide rate, demonstrated in the international suicide prevention trial (InterSePT, Meltzer 2003). Clozapine is therefore the antipsychotic to consider for suicidality in the psychotic overlap, remembering its haematological and cardiac monitoring burden (the deep antipsychotic pharmacology sits in the Schizophrenia: management, antipsychotics and adverse effects notes). Lithium remains the answer for the pure mood disorder; clozapine is the answer where a chronic psychotic illness drives the risk.

GOOD TO REMEMBER

- **Lithium:** the strongest anti-suicidal and all-cause mortality evidence of any psychotropic in mood disorders, roughly 80 percent risk reduction (Cipriani 2005); weigh it in high-risk bipolar or recurrent depression, prophylaxis target 0.6 to 0.8 mmol/L.
- **Clozapine:** specific anti-suicidal effect in schizophrenia and the psychotic overlap (InterSePT, Meltzer 2003); the antipsychotic to consider when a chronic psychotic illness drives suicidality, with its neutropenia and cardiac monitoring.

30.4 Early antidepressant activation and the paediatric suicidality signal

Counsel and monitor at the start. Antidepressant treatment has been associated with an increased risk of suicidal thoughts and acts in the early weeks, particularly in children, adolescents and young adults, the basis of the regulatory black-box warning (Maudsley 2021). Two mood-specific mechanisms matter: early **activation** or agitation before mood lifts, and the recovery-phase energising of a still-hopeless patient. The relative risk is raised above placebo in the young, but the **absolute risk stays very small**, and the most effective way to prevent suicide in depression is to treat the depression effectively. The practical rule is to warn the patient (and family for a young person) about early activation, tell them how to seek help, and review early. NICE advises review within 1 week if the person is aged 18 to 25 or there is particular concern about suicide risk, and within 2 weeks otherwise (NICE 2022). Rates also rise when antidepressants are stopped, so apply the same care on discontinuation.

The paediatric point. In children and adolescents the small antidepressant suicidality signal is why guidelines restrict prescribing largely to SSRIs, and why fluoxetine is the best-evidenced first

choice in this age group (BAP 2015). The signal is a reason to counsel and monitor, not a reason to withhold treatment from a depressed adolescent who needs it.

1 week	first weeks
REVIEW IF AGE 18 TO 25 OR HIGH SUICIDE CONCERN	PEAK ACTIVATION / SUICIDALITY WINDOW

TRAP **Starting and walking away.** Not counselling about early activation and not reviewing a young patient within a week or two of starting an antidepressant, when the suicidality signal peaks.

WORKED EXAMPLE

A 19-year-old with moderate depression is started on fluoxetine. You counsel him and a parent that the first two weeks can bring restlessness or worsened thoughts before improvement, agree a help-seeking plan, and book review at one week because he is under 25. This is the correct application of the early-activation and paediatric-signal rules: treat, but counsel and monitor early.

GOOD TO REMEMBER

- **Early antidepressant activation:** raised suicidality signal in the first weeks in the young (black-box), absolute risk small; the discriminator is treat-but-counsel, warn on activation and review within 1 week if aged 18 to 25 or high concern (NICE 2022).
- **Paediatric first choice:** restrict to SSRIs, fluoxetine best evidenced; the first management step is family counselling plus early review, not withholding treatment (BAP 2015).

30.5 Overdose safety: never a large TCA supply

The drug is the means. A suicidal mood-disorder patient may take a deliberate overdose of whatever you prescribe, so overdose lethality is a prescribing decision, not an afterthought. Guidelines advise choosing antidepressants that are **better tolerated and safer in overdose**: SSRIs and other newer antidepressants are first-line, partly for this reason (BAP 2015). The tricyclic antidepressant class is the danger. A tricyclic overdose of about 10 times the daily dose can be fatal, death is usually from **cardiac toxicity** (type I antiarrhythmic membrane effect, QRS widening, arrhythmia), and TCA mortality per ingestion runs roughly 25-fold higher than SSRIs (Kaplan and Sadock 2024). Amitriptyline (Tryptomer) is among the leading single-drug causes of death by overdose. Therefore **avoid a large TCA supply** in a suicidal or high-risk patient: if a TCA is genuinely needed, dispense small quantities, and prefer the safer-in-overdose SSRI wherever the choice is open. A pre-existing QTc of 450 ms or more is a contraindication to TCA treatment (Kaplan and Sadock 2024).

AGENT / CLASS	OVERDOSE PROFILE	SUICIDAL-PATIENT IMPLICATION
SSRIs, newer antidepressants	**relatively safe in overdose**	first-line choice on safety grounds (BAP 2015)
Tricyclic antidepressants (amitriptyline, Tryptomer)	**fatal at ~10x daily dose; cardiotoxic; ~25x SSRI mortality**	avoid a large supply; dispense small quantities; QTc >=450 ms contraindicates
Lithium (Licab, Intalith)	narrow therapeutic index, toxic > 1.5 mEq/L	anti-suicidal, but a means in overdose: dispense with care and monitor levels

Overdose lethality as a prescribing lens for the suicidal mood-disorder patient.

TRAP **Handing over a cardiotoxic overdose.** Giving a suicidal patient a large quantity of a cardiotoxic tricyclic when a safer-in-overdose SSRI would do.

INDIA

Amitriptyline (Tryptomer) and imipramine (Depsonil) are cheap, ubiquitous and often the default in general and non-psychiatric Indian practice for depression and pain. That very availability is the hazard in a suicidal patient: lead with an SSRI (escitalopram, Nexito or S-Citadep; sertraline, Serta or Daxid; fluoxetine, Fludac) and, if a TCA is unavoidable, dispense small quantities and enlist family means-restriction. Lithium carbonate (Licab, Intalith) is inexpensive and widely available, so the anti-suicidal option is realistic in Indian practice.

GOOD TO REMEMBER

- **Tricyclic antidepressants (amitriptyline, Tryptomer):** cardiotoxic membrane effect, fatal at roughly 10x the daily dose, about 25-fold the SSRI overdose mortality; never a large supply to a suicidal patient, QTc >=450 ms contraindicates (Kaplan and Sadock 2024).
- **Safer-in-overdose choice:** SSRIs and newer antidepressants are first-line partly because they are safer in overdose (BAP 2015); prefer them wherever the clinical choice is open.

MNEMONIC

LiCK the risk: Lithium, Clozapine, Keep TCAs small

The three pharmacological moves against suicide in mood disorders: Lithium (strongest anti-suicidal, weigh it in high-risk mood disorder), Clozapine (anti-suicidal in the psychotic overlap), and Keep TCA supply small (safer-in-overdose SSRI first, small quantities if a TCA is used).

GOOD TO REMEMBER

- **Where the risk sits:** highest in severe depression, mixed states, early bipolar illness and the early recovery phase; lifetime bipolar suicide around 15 percent.
- **Lithium is anti-suicidal:** the strongest evidence of any psychotropic (roughly 80 percent risk reduction, plus all-cause mortality); weigh it in high-risk bipolar or recurrent depression.
- **Clozapine:** anti-suicidal in the psychotic overlap (InterSePT).
- **Avoid a large TCA supply, counsel early-activation:** lead with a safer-in-overdose SSRI, dispense TCAs in small quantities, warn about early antidepressant activation and review the young patient early.

HOLD THIS

Of every psychotropic, lithium has the strongest evidence for reducing suicide and all-cause mortality in mood disorders, so weigh it in a high-risk patient; and never hand a suicidal patient a large supply of a cardiotoxic tricyclic when a safer-in-overdose SSRI will do.

31 · ECT in mood disorders: indications and place

Why this matters. This topic is about the **place in algorithm**, not the technique. Electroconvulsive therapy (ECT) is the single most effective and most rapid antidepressant treatment available, and the examiner wants to know exactly where it sits: which mood presentations make it a first-line emergency option, where it otherwise slots in behind the drugs, and the one selection trade-off (a powerful, fast response against a transient memory cost). The engineering of the seizure, the electrode placement, the electrical dosing and the anaesthetic all belong to the ECT and neurostimulation notes; what is held here is the selection logic in mood disorder.

Exam framing. The high-yield answer is the list of **indications for ect** in mood disorder and its **place in algorithm**. ECT is a first-line option in the mood emergencies (a life-threatening or immediately dangerous depression or mania) and otherwise sits after adequate pharmacological trials as a treatment for drug-refractory illness. The syndromal criteria and the guideline-anchored drug plan are in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; the full suicide-risk assessment is in the Somatic-symptom, sexual, impulse-control disorders and suicide notes; the acute-emergency and perinatal framing is in the Perinatal/women's mental health and emergency psychiatry notes.

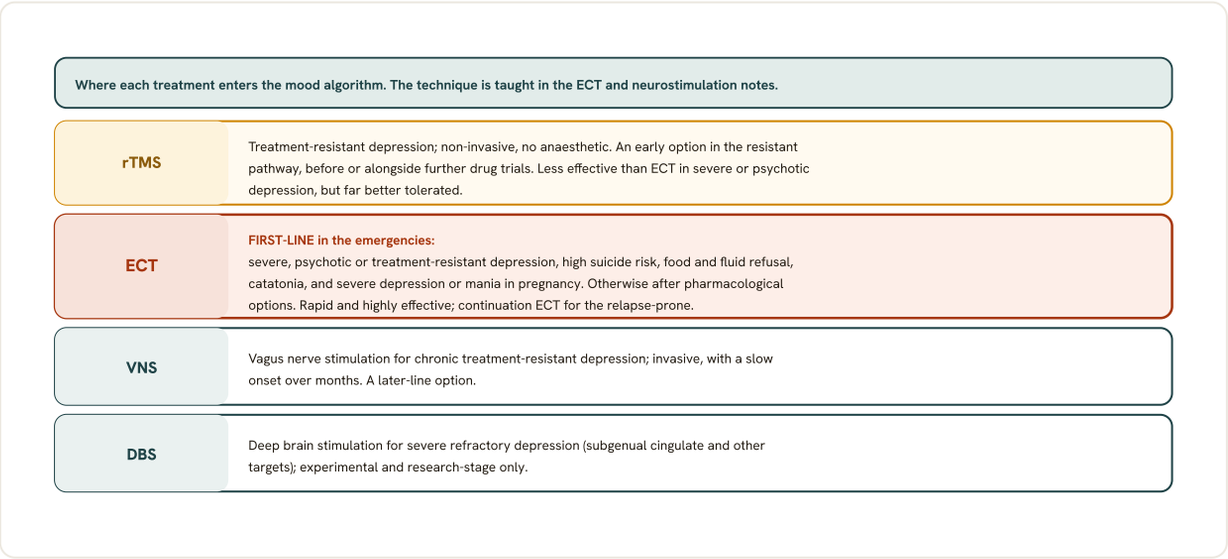

Fig 12.15 Where ECT and neuromodulation enter the mood-disorder algorithm. ECT is first-line in the emergencies (severe, psychotic or treatment-resistant depression, high suicide risk, food refusal, catatonia, pregnancy) and highly effective; rTMS is an early, non-invasive option in the treatment-resistant pathway; VNS is a slow, invasive later-line option; and DBS remains experimental. The technique of each is taught in the ECT and neurostimulation notes.

31.1 ect in mood disorders: strong efficacy and rapid onset

The property that drives every indication is that ECT is both highly effective and fast. In severe depressive illness the response rate is on the order of **70%** for real ECT against roughly **40%** for simulated (sham) treatment, giving a number-needed-to-treat of about **3 to 4** (UK ECT Review Group 2003; Shorter Oxford 2018), and under naturalistic conditions the response rate approaches **80%** (Companion 2010). In head-to-head comparisons ECT is at least as effective as, and works faster than, tricyclic antidepressants and MAOIs in severely depressed inpatients (UK ECT Review Group 2003; Shorter Oxford 2018). This combination of high response and rapid onset is precisely why ECT is reached for early whenever bringing about improvement quickly is essential rather than optional.

RULE **Use ECT mainly when it is essential to improve the patient quickly.** The strongest indications are an immediate high suicide risk, depressive stupor, and danger to physical health from food and fluid refusal (Shorter Oxford 2018).

31.2 The indications for ECT in mood disorder

The examiner wants the indication list held as a set. Combining the standard textbook indications (Shorter Oxford 2018) with the NICE and Royal College criteria, ECT in mood disorder is indicated for:

Severe depression needing a rapid response

severe depressive illness where quick improvement is essential, or when other treatments have failed (NICE 2009)

Psychotic depression

severe depression with mood-congruent delusions or hallucinations, one of the classic and best-responding ECT indications (Maudsley 2021)

Treatment-resistant depression

depression that has not responded to adequate trials of antidepressant drugs, with or without psychotic features (Shorter Oxford 2018)

High suicide risk or food-and-fluid refusal

an immediate high risk of suicide, or life-threatening refusal of food and fluids on the basis of extreme retardation or nihilism (RCPsych 2005)

Catatonia

severe non-organic catatonia, particularly with stupor and poor oral intake or drug non-response (NICE 2003)

Severe or treatment-resistant mania

a prolonged or severe manic episode, or mania unresponsive to pharmacotherapy or with life-threatening exhaustion (NICE 2003; IPS 2017)

Pregnancy where drugs are undesirable

severe depression or mania in pregnancy where medication is undesirable or has failed (CANMAT 2016; IPS 2017)

Across these, the unifying theme is severity plus urgency: the depressive picture that carries marked weight loss, early-morning waking, retardation and delusions is the one that responds best, and delusions and retardation are the features that most distinguish patients who respond to real ECT from those who respond to placebo (UK ECT Review Group 2003; Shorter Oxford 2018). Suicidal risk is named as the first and most important indication in the Indian standard text.

INDICATION IN MOOD DISORDER	CLINICAL TRIGGER	PLACE
Severe depression, rapid response needed	Life-threatening or where speed is essential	**First-line in the emergency**
Psychotic depression	Depression with delusions or hallucinations	**Early; strong ECT indication**
High suicide risk	Immediate, active suicidality	**First-line in the emergency**
Food and fluid refusal	Stupor, retardation, nihilism, dehydration	**First-line in the emergency**
Catatonia	Stupor, mutism, poor intake, drug non-response	**First-line / early**
Treatment-resistant depression	Failed adequate drug trials	After pharmacotherapy
Severe or treatment-resistant mania	Prolonged, exhausting, or drug-refractory mania	Emergency to after-drugs
Pregnancy, drugs undesirable	Severe perinatal depression or mania	**First-line where drugs avoided**

The mood-disorder indications for ECT and where each sits (Shorter Oxford 2018; NICE 2003/2009; IPS 2017; CANMAT 2016).

31.3 Its place in algorithm: first-line in the emergency, otherwise after drugs

The **place in algorithm** has two settings. In the mood emergencies, an immediate high suicide risk, depressive stupor with food and fluid refusal, life-threatening catatonia, and severe or exhausting mania, ECT is a **first-line option** that should be brought in without waiting for drugs to work or fail (Shorter Oxford 2018; IPS 2017). Outside those emergencies, ECT sits **after pharmacological options**: NICE positions it as a treatment for severe depression that is life-threatening or where a rapid response is required, or when other treatments have failed, and it is not used routinely for moderate depression (NICE 2009). For ordinary treatment-resistant depression, BAP places ECT among the next-step options for patients who have not responded to other treatments (BAP 2015). The Indian Psychiatric Society position is explicit that **modified ECT is first-line** for severe mania with food or fluid refusal or exhaustion, psychotic mania unresponsive to pharmacotherapy, severe bipolar depression with suicidality or stupor, mixed states with active suicidality, and catatonia, and that ECT should otherwise be considered for acute mania, mixed episodes or bipolar depression that is severe, refractory, suicidal, catatonic, psychotic, or in pregnancy (IPS 2017).

TRAP **Do not delay ECT through a sequence of failed drug trials in a life-threatening depression.** In a patient who is actively suicidal, in depressive stupor, or refusing food and fluids, ECT is first-line, not a last resort after every drug has failed.

31.4 Continuation and maintenance ECT for the relapse-prone

Response to an acute ECT course is high, but relapse rates after it are also high, especially in patients refractory to drugs (Shorter Oxford 2018). The answer for relapse-prone patients is **continuation and maintenance ECT**: after the acute course brings remission, further ECT sessions are given at spacing intervals (for example weekly, then fortnightly, then monthly) to hold the gain, usually alongside continuation pharmacotherapy. In psychotic depression, one small randomised controlled trial found maintenance ECT plus nortriptyline superior to nortriptyline alone at **2 years**, and ECT may be more protective against relapse in psychotic than in non-psychotic depression (Maudsley 2021). Maintenance ECT is therefore the tool reserved for patients who respond well to acute ECT but relapse rapidly on drugs alone. The dosing and scheduling of the maintenance course itself are in the ECT and neurostimulation notes.

31.5 Practical points relevant to choice: efficacy, memory, consent

Three practical facts drive the decision to use ECT and the conversation with the patient. First, **efficacy**: ECT is the most effective and most rapid treatment for severe mood disorder, and bilateral ECT is moderately more effective than unilateral (Companion 2010). Second, the **transient cognitive adverse effect**: both anterograde and retrograde memory disturbances are common, but they are usually mild and recovery occurs within about **1 to 6 months** of treatment, and unilateral ECT causes much less memory impairment than bilateral. This memory cost is the main reason patients hesitate and the main thing to weigh against ECT's speed and power. Third, **consent or the legal pathway**: ECT is always given after informed consent from the patient, or, where the patient lacks capacity, through the relevant legal pathway and local

statutory procedure. The technique, the electrode placement, the electrical dosing and the anaesthetic detail are all cross-referred to the ECT and neurostimulation notes.

70 vs 40	3 to 4	1 to 6
RESPONSE, REAL VS SHAM ECT (%)	NUMBER-NEEDED-TO-TREAT, ECT IN DEPRESSION	MEMORY RECOVERY AFTER ECT (MONTHS)

The three numbers a resident should hold: efficacy against sham, NNT, and time to memory recovery (UK ECT Review Group 2003).

INDIA

ECT is widely available and heavily used across Indian psychiatry, and the norm in current Indian practice is **modified ECT**, that is, ECT given under general anaesthesia with a muscle relaxant (usually succinylcholine) and oxygenation. Direct (unmodified) ECT, given without anaesthesia or muscle relaxation, is no longer standard and carries a fracture and dislocation risk; the Mental Healthcare Act 2017 restricts unmodified ECT. The Indian Psychiatric Society makes modified ECT first-line for the mania and bipolar-depression emergencies listed above (IPS 2017). The anaesthetic and modified-ECT technique itself is in the ECT and neurostimulation notes.

PEARL

The single feature that best predicts a good ECT response in depression is the presence of **psychotic features (delusions)**, followed by psychomotor retardation; these are the very features that separate real-ECT responders from placebo responders (UK ECT Review Group 2003).

TRAP **Do not quote a permanent memory loss as a reason to withhold ECT from a dying patient.** The memory effect is usually mild and recovers within 1 to 6 months, and unilateral placement minimises it; in a life-threatening depression the balance clearly favours treating.

HOLD THIS

ECT is the fastest and most effective treatment in severe mood disorder and is first-line, not last resort, in the emergencies: severe/psychotic depression, high suicide risk, food and fluid refusal, catatonia, severe or refractory mania, and severe mood illness in pregnancy where drugs are undesirable.

MNEMONIC

SPRINT

Suicide risk high, **P**sychotic depression, **R**esistant (treatment-resistant), **I**ntake refused (food and fluids), **N**ot-eating catatonia, **T**oo-severe mania or pregnancy where drugs are undesirable: the mood indications where ECT is reached for early.

GOOD TO REMEMBER

- **Indications for ect (mood):** severe depression needing rapid response, psychotic depression, treatment-resistant depression, high suicide risk or food-and-fluid refusal, catatonia, severe or treatment-resistant mania, and severe depression or mania in pregnancy where drugs are undesirable.
- **Place in algorithm:** first-line in the emergencies (high suicide risk, stupor, food/fluid refusal, catatonia, exhausting mania); otherwise after adequate pharmacotherapy for drug-refractory illness (NICE 2009; IPS 2017).
- **Efficacy and onset:** the most effective and most rapid treatment for severe mood disorder; about 70% real vs 40% sham response, NNT 3 to 4, roughly 80% naturalistic response (UK ECT Review Group 2003; Companion 2010).
- **Adverse effect to hold:** transient anterograde and retrograde memory disturbance, usually mild, recovering within 1 to 6 months; unilateral placement causes less.
- **Continuation/maintenance ECT:** spaced sessions after the acute course for relapse-prone patients; maintenance ECT plus nortriptyline beat nortriptyline alone at 2 years in psychotic depression (Maudsley 2021).
- **Consent and legality:** given after informed consent or through the legal pathway; the norm in Indian practice is modified ECT under anaesthesia with a muscle relaxant. Technique is elsewhere.

32 · Neuromodulation in depression

Why this matters. This topic is about the **place in algorithm**, not the technique. The examiner wants to know where each device sits in the treatment-resistant depression pathway: which is licensed and offered early, which is invasive and held back, and which is still research only. The engineering of coils, currents and electrodes belongs to the ECT and neurostimulation notes; what is held here is the selection logic. Three devices matter, in descending order of how routinely they are used: rtms (repetitive transcranial magnetic stimulation), vns (vagus nerve stimulation) and dbs (deep brain stimulation).

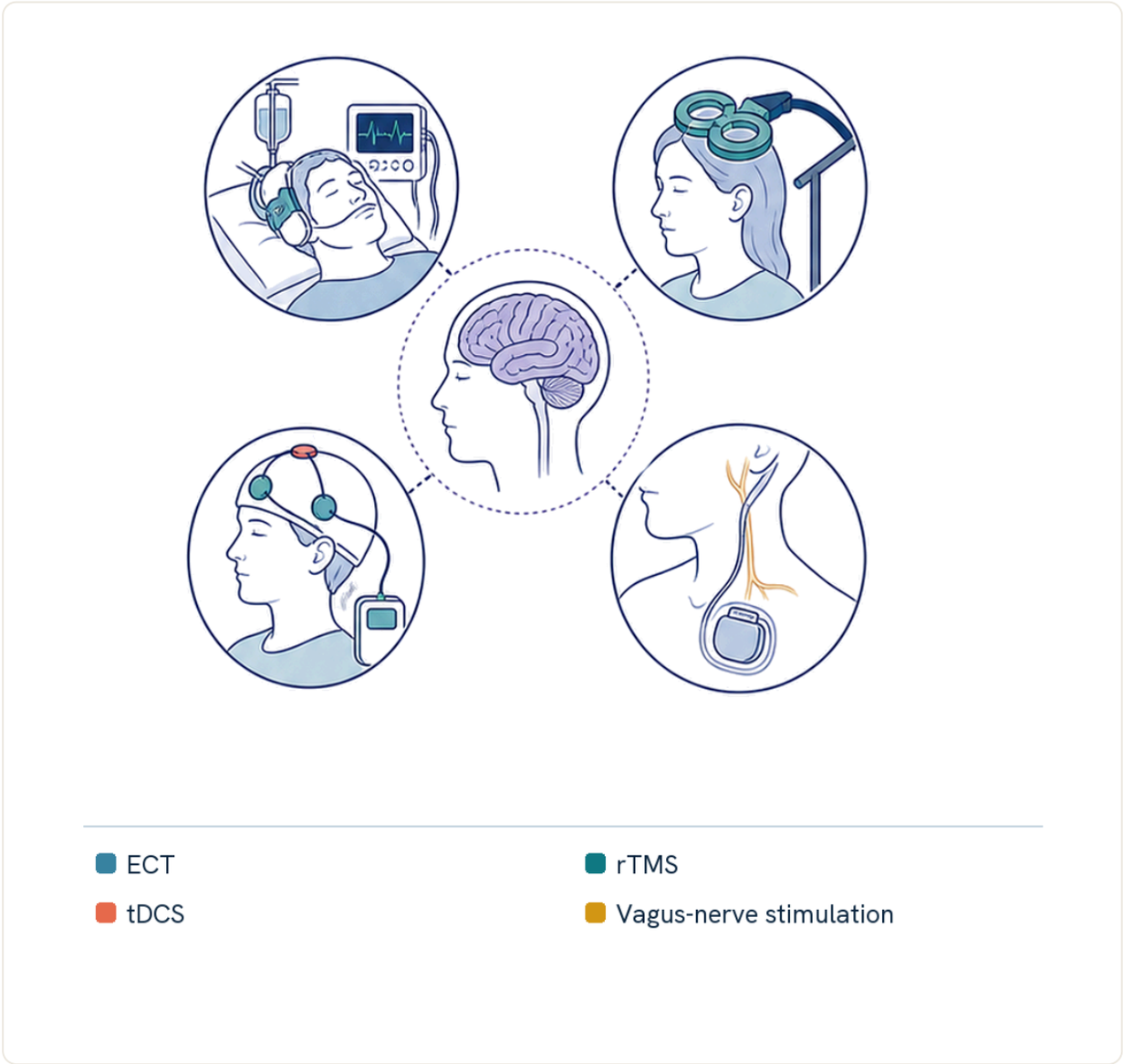

Fig 12.16 Major neuromodulation modalities differ in delivery: electroconvulsive therapy under anaesthesia, focal repetitive transcranial magnetic stimulation, transcranial direct-current stimulation and implanted vagus-nerve stimulation.

The frame is neuromodulation as a step in the pathway after antidepressants have underperformed. rTMS is a genuine guideline-supported option that can be brought in early; VNS and DBS are progressively more invasive and progressively less established, so they sit later in the ladder or outside routine practice altogether. The full technique of each device, the coil physics, the stimulation parameters and the surgery, is cross-referred to the ECT and neurostimulation notes; the wider acute-emergency and perinatal framing is in the Perinatal/women's mental health and emergency psychiatry notes.

32.1 rTMS: the licensed, non-invasive, early option in treatment-resistant depression

rtms is a non-invasive brain-stimulation technique delivered awake in an outpatient chair with no anaesthetic and no seizure induction, which is exactly why it earns an early place in the algorithm. CANMAT recommends rTMS as a **first-line** neuromodulation option for major depressive disorder that has not responded to at least one adequate antidepressant trial (CANMAT 2016), so it is a first-line-to-early option in the treatment-resistant pathway and can be offered before or

alongside further drug trials rather than being reserved for the very end. The standard protocol is high-frequency stimulation (**at least 5 Hz**) over the left dorsolateral prefrontal cortex, or low-frequency stimulation (**1 Hz or less**) over the right dorsolateral prefrontal cortex, delivered **20 to 40 min** per session, daily on 5 days a week for **4 to 6 weeks** (CANMAT 2016). It is non-invasive, well tolerated, and its commonest adverse effects are scalp discomfort and headache, with a rare seizure risk; this good tolerability, alongside the absence of anaesthetic and cognitive load, is the selling point that puts it ahead of the more invasive options.

RULE **rTMS is an evidence-based option in treatment-resistant depression, offered before or alongside further drug trials.** It is non-invasive, needs no anaesthetic, and is a first-line neuromodulation choice, not a last resort.

32.2 Theta-burst variants shorten the session

The practical evolution of rTMS is **theta-burst stimulation**. Intermittent theta-burst stimulation (iTBS) is offered as a first-line rTMS protocol that is non-inferior to conventional high-frequency rTMS but delivers the treatment in a much shorter session, on the order of **about 3 min** rather than 20 to 40 min (CANMAT 2023). Because each session is so short, accelerated protocols that pack several sessions into each day can compress a whole course into as little as **5 days** (CANMAT 2023). The theta-burst variants therefore make rTMS faster and more scalable without losing efficacy, which further supports its early place in the algorithm.

at least 5	20 to 40	about 3
HIGH-FREQUENCY RTMS, LEFT DLPFC (HZ)	STANDARD RTMS SESSION (MIN)	ITBS SESSION (MIN)

Verified rTMS parameters and the theta-burst session time (CANMAT 2023).

32.3 rTMS relative to ECT: less effective in severe or psychotic depression, better tolerated

The comparison the examiner wants is rTMS against ECT. For treatment-resistant patients the brain-stimulation alternatives to ECT, including rTMS, have **lower efficacy than traditional ECT**, so ECT remains the more powerful treatment for severe, psychotic or highly refractory depression (Kaplan & Sadock 2024). What rTMS offers instead is far better tolerability: it is non-invasive, needs no anaesthetic, and carries none of the anaesthetic and memory burden that makes many patients reluctant to accept ECT (Kaplan & Sadock 2024). The trade-off is the whole point of its place in algorithm, rTMS is the less effective but far better tolerated option, so it is preferred earlier and in less severe treatment-resistant pictures, while ECT is chosen when depth of response matters most, particularly in severe or psychotic depression. The device physics and the ECT technique itself are in the ECT and neurostimulation notes.

GOOD TO REMEMBER

- **rTMS mechanism:** non-invasive focal magnetic stimulation of the dorsolateral prefrontal cortex, awake, no anaesthetic, no induced seizure; signature adverse effects are scalp discomfort and headache with a rare seizure risk.
- **rTMS place:** CANMAT first-line neuromodulation for treatment-resistant depression; the one indication to hold is treatment-resistant depression that has failed at least one adequate antidepressant trial, offered before or alongside further drug trials.
- **rTMS vs ECT:** less effective than ECT in severe or psychotic depression, but better tolerated; the discriminator is tolerability (no anaesthetic, no memory load) traded against ECT's greater efficacy.
- **iTBS:** first-line theta-burst rTMS protocol, non-inferior to high-frequency rTMS, session about 3 min; the number to hold is that accelerated courses can be as short as 5 days.

32.4 VNS and DBS: the later-line and the experimental options

vns is an **invasive, later-line** option. It requires a surgically implanted pulse generator, with an electrode wrapped around the left cervical vagus nerve and the battery placed subcutaneously in the left chest wall (Kaplan & Sadock 2024). Its defining problem for the algorithm is a **slow onset**: only about **15%** of patients respond in the first 3 months, rising to roughly **30%** by 12 months, and response rates are lower than with ECT (Kaplan & Sadock 2024). VNS is approved as a long-term adjunctive treatment for chronic or recurrent treatment-resistant depression and is therefore worth considering only when patients have already failed less invasive treatments, so it sits late in the ladder rather than early (Kaplan & Sadock 2024).

dbs is **experimental** and research-stage for severe refractory depression. It involves surgical implantation of stimulating electrodes into a deep target, most studied at the **subgenual cingulate** cortex, with other targets under investigation (Kaplan & Sadock 2024; New Oxford 2020). The evidence base is still unsettled: small open-label and prospective studies of subgenual DBS were encouraging, but a large industry-supported controlled trial was stopped early on a futility analysis, and DBS for depression is not an approved routine treatment (Kaplan & Sadock 2024). Most of these newer neurostimulation therapies remain in an experimental phase of development (Kaplan & Sadock 2024), so DBS belongs to research protocols and last-resort refractory cases, not the routine algorithm. The neurosurgical technique and target physiology are in the ECT and neurostimulation notes.

DEVICE	INVASIVENESS	PLACE IN ALGORITHM	KEY CAVEAT
rTMS	Non-invasive, no anaesthetic	**First-line-to-early in treatment-resistant depression**	Less effective than ECT in severe/psychotic depression, better tolerated
VNS	Invasive, implanted generator	Later-line, chronic treatment-resistant depression	**Slow onset (about 15% at 3 months, about 30% at 12 months)**
DBS	Invasive, deep electrodes	Experimental, research-stage only	**Subgenual cingulate and other targets; controlled trial stopped for futility**

Place in algorithm of the three neuromodulation options in depression (CANMAT 2016; Kaplan & Sadock 2024; New Oxford 2020).

TRAP **Do not offer DBS or VNS as routine options.** DBS is experimental and research-stage; VNS is an invasive, slow-onset, later-line adjunct, not a mainstream step, and neither substitutes for rTMS or ECT in the ordinary pathway.

Guideline level. CANMAT names rTMS a first-line neuromodulation treatment for treatment-resistant depression and offers iTBS as a first-line rTMS protocol, with ECT reserved for severe, psychotic or refractory illness (CANMAT 2023). NICE similarly supports rTMS for depression as a recognised non-invasive option while positioning ECT for severe or life-threatening depression (NICE 2014). The Indian Psychiatric Society (IPS guidelines, Gautam et al. depression CPG) endorses ECT for severe and treatment-resistant depression, but a specific IPS position on rTMS, VNS and DBS in depression could not be confirmed against the parsed library and is flagged rather than invented; the IPS stance is named here and left as could-not-be-confirmed.

HOLD THIS

rTMS is a first-line, non-invasive, no-anaesthetic option in treatment-resistant depression (less effective than ECT but better tolerated); VNS is invasive, later-line and slow; DBS is experimental only.

GOOD TO REMEMBER

- **rtms:** non-invasive, no anaesthetic, first-line neuromodulation for treatment-resistant depression; hold high-frequency left DLPFC or low-frequency right DLPFC, 20 to 40 min per session, iTBS about 3 min.
- **vns:** invasive implanted generator on the left vagus nerve, later-line adjunct for chronic treatment-resistant depression; signature caveat is slow onset (about 15% respond at 3 months, about 30% at 12 months).
- **dbs:** invasive deep electrodes, experimental and research-stage for severe refractory depression; the target to hold is the subgenual cingulate, and a large controlled trial was stopped for futility.

33 . Psychotherapies for depression: the place

In a drug-focused chapter the drug is not the whole answer, and the board rewards the resident who knows exactly where a talking treatment sits in the depression algorithm. **Psychotherapy for depression** is not a soft alternative offered when medication fails; for mild-to-moderate illness a structured **first-line psychological** treatment is a genuine first-line option in its own right, and for moderate-to-severe illness combined treatment (medication plus psychotherapy) outperforms either alone (CANMAT 2016; Shorter Oxford 2018). This topic teaches the evidence-based *place* of psychotherapy for depression, the guideline-anchored algorithm; the *technique* of each therapy is cross-referred to the Psychotherapies, clinical assessment, MSE and nosology notes.

Ground the place in the guidelines. Lead with **CANMAT**: the Canadian Network for Mood and Anxiety Treatments names cognitive behavioural therapy, interpersonal therapy and behavioural activation as first-line psychological treatments for acute major depression, and directs that where feasible a psychological treatment (CBT or IPT) be combined with an antidepressant

because combined treatment is superior to either alone (CANMAT 2016). The place is then confirmed by the Indian Psychiatric Society, NICE and the BAP. Every first-line status below is verified against the CANMAT guideline rows and the Shorter Oxford (CANMAT 2016; Shorter Oxford 2018).

33.1 The three first-line psychological therapies

CBT, IPT and behavioural activation. The examinable list of **first-line psychological** treatments for acute major depression is three structured, time-limited, evidence-based therapies (CANMAT 2016). **cbt** (cognitive behaviour therapy) targets the depressive cognitive triad and maladaptive behaviour; **ipt** (interpersonal therapy) works on grief, role transitions, role disputes and interpersonal deficits; and **behavioural activation** uses scheduled activity and operant principles to re-engage the patient with rewarding behaviour. Head-to-head, none of the three is convincingly superior to the others, and each is as effective as pharmacotherapy in moderately depressed outpatients (Shorter Oxford 2018).

Each is first-line, alone, in mild-to-moderate depression. For a mild-to-moderate depressive episode, any one of CBT, IPT or behavioural activation may be offered as a stand-alone first-line treatment without medication (CANMAT 2016; Shorter Oxford 2018). Specific psychotherapies are more effective than treatment-as-usual in mild-to-moderate depression, particularly in primary care, and perform as well as drug treatment in the moderately depressed (Shorter Oxford 2018).

CBT

Cognitive behaviour therapy: restructures the depressive cognitive triad and reactivates behaviour; first-line for acute depression.

IPT

Interpersonal therapy: targets grief, role transitions, role disputes and interpersonal deficits; first-line for acute depression.

Behavioural activation

Scheduled, reward-linked activity using operant principles; first-line for acute depression and simple to train.

RULE **Offer an evidence-based psychotherapy first-line in mild-to-moderate depression, and combine it with medication in severe depression.** CBT, IPT and behavioural activation are all first-line for acute major depression.

TRAP **Treating every depression with medication alone when a psychological therapy is indicated.** In mild-to-moderate illness a structured psychotherapy alone is first-line; in severe illness the correct move is to add it, not to omit it.

33.2 The place in the algorithm: alone, combined, or for relapse prevention

Alone in mild-to-moderate; combined in moderate-to-severe. The place is a two-step rule. In a mild-to-moderate episode, offer a first-line psychological therapy (CBT, IPT or behavioural activation) as a first-line option alone, matching the efficacy of an antidepressant (CANMAT

2016; Shorter Oxford 2018). In more severe or recurrent illness, add the psychotherapy to medication rather than relying on either alone, because combined treatment is superior to pharmacotherapy alone for many patients (CANMAT 2016; Shorter Oxford 2018).

And for relapse prevention. After the acute phase, psychotherapy has a maintenance place: CANMAT names CBT and mindfulness-based cognitive therapy (MBCT) as first-line psychological treatments to prevent relapse (CANMAT 2016). Mindfulness-based cognitive therapy is the paradigm example, delivered in remission to patients with recurrent depression to reduce the relapse rate. Add adjunctive CBT to ongoing antidepressant treatment as a recognised next-step option in the patient who has not fully responded (BAP 2015).

ILLNESS SEVERITY / PHASE	THE PLACE OF PSYCHOTHERAPY	EVIDENCE-BASED OPTION
Mild-to-moderate, acute	**First-line, alone (no medication needed)**	CBT or IPT or behavioural activation
Moderate-to-severe, acute	**Add to medication (combined is superior)**	Antidepressant plus CBT or IPT
Partial response to an antidepressant	Add as a next-step to ongoing medication	Adjunctive CBT
Remission, recurrent illness	First-line for relapse prevention	CBT or mindfulness-based cognitive therapy (MBCT)

The place of psychotherapy for depression across severity and phase, verified against CANMAT (CANMAT 2016) and the BAP (BAP 2015): alone in mild-to-moderate illness, added to medication in more severe or recurrent illness, and first-line for relapse prevention.

WORKED EXAMPLE

A 30-year-old teacher presents with a first, mild-to-moderate depressive episode without suicidality, and asks to avoid tablets. Rather than defaulting to an SSRI, offer a first-line psychological therapy alone: a course of CBT, IPT or behavioural activation is a legitimate first-line treatment here and matches antidepressant efficacy in this severity band (CANMAT 2016). Contrast a 45-year-old with a severe, recurrent episode: here the correct move is combined treatment, an antidepressant plus CBT or IPT, because combined treatment is superior to medication alone, followed by CBT or MBCT in remission to prevent the next relapse.

33.3 Where the guidelines agree: CANMAT, the IPS, NICE and the BAP

CANMAT (lead). Offer CBT, interpersonal therapy or behavioural activation as first-line psychological treatments for acute major depression; where feasible combine a psychological treatment (CBT or IPT) with an antidepressant, as combined treatment is superior to either alone; and for maintenance offer CBT or MBCT first-line to prevent relapse (CANMAT 2016).

The Indian Psychiatric Society. The **indian psychiatric society** Clinical Practice Guidelines for depression (Gautam et al.) endorse structured psychotherapy, chiefly CBT and IPT, as a treatment for depression, offered alone in milder illness and combined with pharmacotherapy in moderate-to-severe illness (IPS 2017). The precise severity thresholds and the exact list of first-line psychotherapies in the current **ips guidelines** could not be confirmed from the parsed

library and are flagged under gaps rather than invented; the IPS is named and the position stated only to the level that is verified.

NICE and the BAP. NICE runs a stepped-care model: for less severe depression it prefers the least intrusive psychological options first (guided self-help, group CBT, group behavioural activation) and does not routinely start an antidepressant first-line, reserving combined psychotherapy-plus-antidepressant for more severe depression (NICE 2022). The BAP concurs that adding CBT to ongoing antidepressant treatment is a valid next-step option when response is incomplete (BAP 2015).

INDIA

In Indian practice the access barrier is real: trained CBT and IPT therapists are concentrated in cities and the private sector, so the guideline-ideal of psychotherapy alone for mild-to-moderate depression is often not deliverable, and a low-cost generic SSRI becomes the pragmatic first step. Behavioural activation is the most transportable of the three because, unlike CBT, therapist training in its techniques is claimed to be simple and quickly accomplished (Shorter Oxford 2018), which makes it well suited to task-shifted, non-specialist delivery in resource-limited settings.

33.4 The technique lives elsewhere; what to hold here

Cross-reference, do not duplicate. The actual technique of each therapy, the CBT thought record and cognitive triad, the IPT interpersonal inventory and four problem areas, and the behavioural activation activity schedule, is taught in the Psychotherapies, clinical assessment, MSE and nosology notes. For these notes, hold only the *place*: which therapies are first-line, when they stand alone, when they combine with medication, and where they prevent relapse.

The one line that answers the viva. When the examiner asks "what is the place of psychotherapy in depression?", answer with the two-step rule plus the maintenance rider: first-line alone in mild-to-moderate illness, added to medication in moderate-to-severe illness because combined treatment is superior, and CBT or MBCT for relapse prevention (CANMAT 2016).

3	Combined	MBCT
FIRST-LINE PSYCHOTHERAPIES (CBT, IPT, BA)	SUPERIOR TO MEDICATION ALONE (MODERATE-TO-SEVERE)	FIRST-LINE FOR RELAPSE PREVENTION

MNEMONIC

CIB, then M

CBT, **I**PT, **B**ehavioural activation are the three first-line psychotherapies for acute depression; **M**BCT (with CBT) is first-line for relapse prevention. Alone in mild-to-moderate, combined in severe.

GOOD TO REMEMBER

- **CBT, IPT and behavioural activation:** the three first-line psychological treatments for acute major depression; each may be offered alone in mild-to-moderate illness (CANMAT 2016).
- **Alone vs combined:** first-line alone in mild-to-moderate depression, added to medication in moderate-to-severe or recurrent illness because combined treatment is superior to either alone.
- **Relapse prevention:** CBT or mindfulness-based cognitive therapy (MBCT) is first-line to prevent relapse after remission (CANMAT 2016).
- **The technique:** the technique of each is cross-referred to the Psychotherapies, clinical assessment, MSE and nosology notes; hold only the place here.

HOLD THIS

Offer an evidence-based psychotherapy (CBT, IPT or behavioural activation) first-line and alone in mild-to-moderate depression, add it to medication in moderate-to-severe or recurrent depression because combined treatment is superior to either alone, and use CBT or mindfulness-based cognitive therapy for relapse prevention; the technique is taught elsewhere.

34 . Managing bipolar depression

The depressive pole is where most of the illness burden of bipolar disorder sits, and it is the phase the board most wants you to manage **differently** from unipolar depression. The single organising idea is a warning: the drugs that break a unipolar depression are not the drugs you reach for here, because an **antidepressant** given without anti-manic cover can flip a depressed bipolar patient into mania. This is a management topic, so the marks are in the guideline-anchored selection, the first-line agents, and the recognition and handling of a treatment-emergent switch, not in a recitation of side effects. The deep per-drug pharmacology (lithium, valproate, lamotrigine, quetiapine, the antidepressant classes) is owned by the earlier topics in these notes; this topic carries which agent, which phase, which line, and the manic-switch rule.

Lead the answer with CANMAT (Yatham 2018, the CANMAT/ISBD 2018 guideline), then give the Indian Psychiatric Society position, now carried by the 2025 IPS bipolar update (IPS 2025, Menon et al., which supersedes the 2017 Shah guideline), and the NICE and BAP positions. Every first-line agent, dose, serum level and switch fact below is verified against the CANMAT/ISBD guideline, the Indian Psychiatric Society clinical practice guideline, the Maudsley Prescribing Guidelines, Stahl and Kaplan and Sadock (Yatham 2018; Menon 2025; Shah 2017; Maudsley 2021; Stahl 2021; Kaplan and Sadock 2024). The full syndrome and the wider guideline-anchored management PLAN sit in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; the receptor pharmacology and CYP metabolism behind agent selection sit in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

34.1 Why bipolar depression is managed differently

It is not unipolar depression with a manic history bolted on. Episodes of bipolar depression, compared with unipolar depression, tend to be more rapid in onset, more frequent, shorter, and more likely to carry reverse neurovegetative features such as hypersomnia and hyperphagia and, at times, psychotic features (Maudsley 2021). Two facts drive the whole management plan. First,

the antidepressant response is different: unopposed antidepressants are relatively less effective (perhaps not effective at all) in bipolar than in unipolar depression (Maudsley 2021). Second, and decisively, giving an antidepressant alone risks a **manic switch** and destabilisation of the illness course. So the agents of choice are anti-manic mood stabilisers and specific atypical antipsychotics, not antidepressants.

RULE **Treat bipolar depression with quetiapine, lurasidone, lamotrigine or lithium, not an antidepressant alone.** The first-line agents are anti-manic mood stabilisers and specific atypicals, chosen to cover the depressive pole without flipping the patient into mania (Yatham 2018).

34.2 CANMAT: the first-line agents for bipolar I depression

Lead with CANMAT. For acute bipolar I depression the CANMAT/ISBD guideline names the **first-line** options as: quetiapine (Qutipin) monotherapy; lurasidone monotherapy or adjunctive to lithium or divalproex; lithium (Licab, Intalith) monotherapy; lamotrigine (Lamitor, Lametec) monotherapy or adjunctive; and lurasidone or adjunctive lamotrigine (Yatham 2018). The verified target doses are quetiapine to about **300 mg/day** (the licence and practice range for bipolar depression is **300 to 600 mg/day**), lurasidone **20 to 120 mg/day**, lithium to an acute serum level of **0.8 to 1.2 mEq/L**, and lamotrigine slowly titrated from 25 mg to a minimum of **200 mg/day** (Yatham 2018; Maudsley 2021). One mechanistic pearl the board likes: the antidepressant efficacy of these antipsychotics in bipolar depression is not a dopamine-blocking effect, since aripiprazole and most pure D2 blockers do not work in acute bipolar depression (Maudsley 2021).

The second-line rapid-response pair. When a rapid response is desirable, CANMAT places cariprazine and the **olanzapine-fluoxetine combination** as second-line for acute bipolar I depression (Yatham 2018). The olanzapine-fluoxetine combination (the fixed-dose OFC, olanzapine 6 or 12 mg with fluoxetine 25 or 50 mg) is genuinely effective and is the strongest single piece of evidence for any antidepressant helping in bipolar depression, but note the antidepressant is always paired with an anti-manic partner, never given alone (Maudsley 2021).

TRAP **Naming aripiprazole as a first-line agent for bipolar depression.** Aripiprazole works for mania and manic-relapse prevention but does not have efficacy in acute bipolar depression; the depression antipsychotics are quetiapine, lurasidone, cariprazine and olanzapine (Maudsley 2021).

34.3 NICE and the Indian Psychiatric Society position

NICE. To treat bipolar depression NICE recommends fluoxetine combined with olanzapine, or quetiapine on its own; if the patient prefers, consider olanzapine without fluoxetine, or lamotrigine on its own (NICE 2014; Maudsley 2021). NICE therefore treats lamotrigine as second-line, whereas BAP has lamotrigine and lurasidone as first-line options with the caveat that a mood stabiliser or antipsychotic will still be needed to protect against mania in the longer term (Goodwin 2016).

India. The **Indian Psychiatric Society** clinical practice guideline (IPS 2017, Shah et al.) for acute bipolar depression names quetiapine (**300 to 600 mg**) or the olanzapine-plus-fluoxetine combination as first-line, with lithium and lamotrigine as alternatives, particularly where the antipsychotic burden is undesirable. Crucially the IPS guidelines state that antidepressant monotherapy is contraindicated, and that antidepressants should not be used in rapid cycling or mixed episodes; if an antidepressant is used at all, paroxetine is avoided and bupropion is preferred (Shah 2017). This maps cleanly onto CANMAT, and the indian psychiatric society (IPS) position, as set out in the ips guidelines, is the guideline most likely to be named in an Indian postgraduate examination.

INDIA

The IPS bipolar guideline has been updated: the 2025 IPS bipolar update (IPS 2025, Menon et al., Indian J Psychiatry 2026;68:8-43) supersedes the 2017 Shah guideline and now names the first-line options for acute bipolar depression as the olanzapine-fluoxetine combination (Oleanz plus Fludac), quetiapine (Qutipin), lurasidone and cariprazine, with lithium (Licab, Intalith) and lamotrigine (Lamitor, Lametec) as further options. It keeps the core rule that antidepressant monotherapy or unopposed antidepressant use is not recommended in bipolar depression; where an antidepressant is judged necessary, an SSRI or bupropion (Bupron) is preferred, always under anti-manic cover. All first-line agents are inexpensive Indian brands.

34.4 The first-line bipolar-depression agents at a glance

The first-line and rapid-response agents assemble into one table. Learn the highlighted cell in each row: it is the fact the examiner tests, and it is the line or the caveat, not the side-effect list (which is owned by the per-drug topics).

300 to 600	20 to 120	0.8 to 1.2	200
QUETIAPINE BIPOLAR DEPRESSION (MG/DAY)	LURASIDONE RANGE (MG/DAY)	ACUTE LITHIUM LEVEL (MEQ/L)	LAMOTRIGINE MINIMUM TARGET (MG/DAY)

AGENT (INDIAN BRAND)	CANMAT LINE	DOSE / TARGET	THE BOARD-CRITICAL POINT
Quetiapine (Qutipin)	First-line monotherapy	300 mg/day target (300 to 600 mg/day range)	**Broadest agent: works across mania, bipolar depression and maintenance; not associated with switching to mania (Maudsley 2021)**
Lurasidone	First-line, monotherapy or adjunctive to lithium/divalproex	20 to 120 mg/day	**Metabolically favourable (minimal weight gain); signature adverse effects are nausea and akathisia; take with food (Maudsley 2021)**

AGENT (INDIAN BRAND)	CANMAT LINE	DOSE / TARGET	THE BOARD-CRITICAL POINT
Lithium (Licab, Intalith)	First-line monotherapy	Acute serum level 0.8 to 1.2 mEq/L	**The only agent with specific anti-suicide evidence; acute-depression efficacy is modest but relapse prevention is strong (Maudsley 2021)**
Lamotrigine (Lamitor, Lametec)	First-line, monotherapy or adjunctive	Slow titration 25 to a minimum of 200 mg/day	**Best for the depressive pole and prevention, weak against acute mania; does not induce switching or rapid cycling; slow titration for rash (Yatham 2018)**
Olanzapine-fluoxetine combination (Oleanz + Fludac)	Second-line (for rapid response)	Olanzapine 6 or 12 mg with fluoxetine 25 or 50 mg/day	**Strongest evidence for an antidepressant helping in bipolar depression, but the antidepressant is always paired with olanzapine, never alone (Maudsley 2021)**
Cariprazine	Second-line (for rapid response)	Per licence	**Efficacious in bipolar depression with low weight-gain propensity; smaller effect size than lurasidone (Maudsley 2021)**

First-line and second-line agents for acute bipolar I depression, CANMAT lead (Yatham 2018) with doses verified against the Maudsley Prescribing Guidelines. Indian brands lead each row, this being the chapter where brands belong. Highlighted cells are the examinable line-or-caveat, not the side-effect profile.

WORKED EXAMPLE

A woman with bipolar I disorder, well on maintenance divalproex, presents with a breakthrough depressive episode. The correct next step is not to add an SSRI: add or switch to a first-line bipolar-depression agent, for example lurasidone adjunctive to the divalproex, or quetiapine, or add lamotrigine (titrated at half the usual rate because valproate doubles the lamotrigine level, targeting about 100 mg/day). Reaching for an antidepressant alone here risks a manic switch and rapid cycling, and the antidepressant is relatively less effective in this setting anyway (Yatham 2018; Maudsley 2021).

34.5 The antidepressant-in-bipolar question

The default is: do not. An **antidepressant in bipolar** depression is avoided as monotherapy because of two linked hazards: the risk of a **manic switch** (a flip into hypomania or mania) and the risk of destabilising the illness into rapid cycling (Yatham 2018; Kaplan and Sadock 2024).

Unopposed antidepressants (that is, without mood-stabiliser protection) are generally to be avoided in bipolar depression, especially in bipolar I disorder (Maudsley 2021). If an antidepressant is used at all it is only **with an anti-manic mood stabiliser** as cover, it is **avoided in mixed features and in rapid cycling**, and the adjunctive evidence is weak. Indeed, controlled data suggest a mood stabiliser alone is about as effective as a mood-stabiliser-plus-antidepressant combination (Maudsley 2021).

The nuances the board rewards. Not all antidepressants carry equal switch risk. Venlafaxine (an SNRI) appears more likely than an SSRI or bupropion to induce a switch to mania (Leverich 2006; Maudsley 2021). Tricyclics and MAOIs are usually best avoided. Where an antidepressant is judged necessary, an SSRI (or bupropion) under mood-stabiliser cover is preferred, and the IPS specifically prefers bupropion and avoids paroxetine (Shah 2017). Some guidelines allow a more permissive use of antidepressants in bipolar II depression, where sertraline does not appear to increase switch rates, but bipolar I depression is where the prohibition is firmest (Altshuler 2017; Maudsley 2021).

TRAP **Giving antidepressant monotherapy in a bipolar depression and precipitating a switch or rapid cycling.** An antidepressant is only ever added under anti-manic cover, is avoided in mixed features and rapid cycling, and is never the first-line agent (Yatham 2018; Shah 2017).

34.6 Treatment-emergent mania: recognise it and manage it

What it is. **Treatment-emergent mania** (the treatment-emergent mania of the guidelines) is a switch into hypomania or mania that appears on treatment, classically driven by an antidepressant, sometimes within the first weeks of exposure. In a patient being treated for what looked like a unipolar depression, a treatment-emergent affective switch on antidepressant monotherapy reclassifies the diagnosis as bipolar disorder (Shah 2017; Kaplan and Sadock 2024). Recognise it as the emergence of elevated or irritable mood, reduced need for sleep, increased energy, pressured speech, overactivity or risk-taking against a background of antidepressant use (or a dose increase).

How to manage it. The steps are, in order: **stop (or reduce) the antidepressant**; **optimise the mood stabiliser** (raise lithium or valproate towards the anti-manic range, or add or up-titrate an **atypical antipsychotic**); and reassess the diagnosis and future prophylaxis. In a first-episode manic presentation, discontinue any antidepressant and reassess the diagnosis before starting antimanic agents (Yatham 2018; Shah 2017). One safety point sits alongside this: abruptly adding a serotonergic antidepressant to an existing regimen, or the accidental co-prescription during a switch, can precipitate serotonin syndrome, whose acute management is owned by the Perinatal/women's mental health and emergency psychiatry notes.

RULE **Treatment-emergent switch: stop the antidepressant, optimise the stabiliser, add or up-titrate an atypical.** A switch on antidepressant monotherapy reclassifies the depression as bipolar (Shah 2017).

PEARL

The manic switch is not just an adverse event, it is a diagnostic event. A first manic or hypomanic episode emerging on an antidepressant given for depression converts the working diagnosis from unipolar depression to bipolar disorder and changes the whole prophylaxis plan towards a mood stabiliser, not an antidepressant (Kaplan and Sadock 2024).

MNEMONIC

QuLLL

The four verified CANMAT first-line agents for bipolar depression, in one handle: **Qu**etiapine, **L**urasidone, **L**ithium, **L**amotrigine (Yatham 2018). If you can name only four things in the exam, name these four, and add that an antidepressant is never given alone.

HOLD THIS

Bipolar depression is treated first-line with quetiapine, lurasidone, lithium or lamotrigine (and the olanzapine-fluoxetine combination or cariprazine second-line for rapid response), and never with an antidepressant alone, because unopposed antidepressants risk a manic switch and rapid cycling.

GOOD TO REMEMBER

- **Quetiapine (Qutipin):** multi-acting atypical; the broadest bipolar agent (mania, depression, maintenance); first-line monotherapy for bipolar depression at **300 to 600 mg/day**; not associated with switching (Yatham 2018; Maudsley 2021).
- **Lurasidone:** atypical, metabolically favourable; first-line for bipolar depression, monotherapy or adjunctive to lithium/divalproex, **20 to 120 mg/day**; signature adverse effects nausea and akathisia; take with food (Yatham 2018; Maudsley 2021).
- **Lithium (Licab, Intalith):** first-line monotherapy; acute-depression target serum level **0.8 to 1.2 mEq/L**; the one agent with specific anti-suicide evidence; the full monitoring and toxicity detail is owned by the lithium topics in these notes (Yatham 2018).
- **Lamotrigine (Lamitor, Lametec):** best for the depressive pole and prevention, weak against acute mania; does not induce switching or rapid cycling; slow titration 25 to a minimum of **200 mg/day** for rash; halve the schedule with valproate (Yatham 2018; Stahl 2021).
- **Olanzapine-fluoxetine combination (Oleanz + Fludac):** second-line for rapid response; olanzapine 6 or 12 mg with fluoxetine 25 or 50 mg/day; strongest evidence for an antidepressant helping in bipolar depression, but the antidepressant is always paired, never alone (Yatham 2018; Maudsley 2021).
- **Antidepressant in bipolar:** never monotherapy; only with an anti-manic stabiliser; avoided in mixed features and rapid cycling; venlafaxine carries the higher switch risk, bupropion is preferred over paroxetine (Shah 2017; Leverich 2006).
- **Treatment-emergent mania (the discriminator and first step):** a switch into hypomania or mania on treatment; a switch on antidepressant monotherapy reclassifies the diagnosis as bipolar; first step is to stop the antidepressant, then optimise the stabiliser or add an atypical (Shah 2017; Yatham 2018).

35 . Managing bipolar mixed episodes

A **mixed state** is where depressive and manic or hypomanic symptoms co-occur, and it is the presentation that most often gets the pharmacology wrong. The examiner is testing one insight: a **mixed state does not behave like either pure pole,** it carries the highest suicide risk in the bipolar course, and the drug you reach for a "mixed depression" is not an antidepressant. This is a dedicated management topic. The mixed-episode and mixed-features SYNDROME, its criteria and its neurobiology, is owned by the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; this topic carries the guideline-anchored pharmacotherapy.

Lead the answer with CANMAT (CANMAT 2018, Yatham et al.), then give the Indian Psychiatric Society position, now carried by the 2025 IPS bipolar update (IPS 2025, Menon et al., which supersedes the 2017 Grover and Avasthi guideline and names divalproex first-line and carbamazepine second-line for acute mixed episodes), and the BAP (BAP 2016) and NICE (NICE 2014) positions. The agents with the best mixed-state evidence are the atypicals asenapine, cariprazine, olanzapine and aripiprazole, and valproate (divalproex); lithium is relatively weaker for classic mixed and dysphoric presentations; and antidepressants are avoided.

35.1 The principle: a mixed state responds differently from a pure pole

Define it first. A **mixed state** spans two things the exam wants named distinctly: a full **mixed episode** (co-occurring depressive and manic or hypomanic symptoms meeting threshold, the classic dysphoric mania and agitated mixed depression) and the milder DSM-5 **mixed features** specifier attached to a manic, hypomanic or depressive episode (Kaplan and Sadock 2024). Dysphoric mania is manic overactivity, pressured speech and reduced sleep carried on a dysphorically excited, irritable, anxious mood, often with agitation and suicidal ideation (Kaplan and Sadock 2024). **Why it matters.** The mixed state carries a **high suicide risk**, among the highest of any phase of the illness, because manic-level drive and energy sit on top of depressive despair (IPS 2017). It responds differently from a pure manic or a pure depressive episode, so it is managed as its own entity, not as "the mania" or "the depression" that happens to be present.

RULE **Treat the mixed state as its own high-suicide-risk entity.** It is not a pure pole with extra symptoms, and it does not respond like one.

35.2 Lithium is relatively weaker in classic mixed and dysphoric presentations

The single most tested selection fact: **lithium underperforms in mixed and dysphoric presentations.** Kaplan and Sadock is explicit that patients with concomitant depressive symptoms, that is dysphoric mania, respond more poorly to lithium, as do those with a high cumulative episode burden; and in subtype analyses the irritable manic subtype responded significantly better to divalproex than to lithium, while the classic euphoric manic subtype responded similarly to both (Kaplan and Sadock 2024). Lithium keeps its place as the anti-suicide agent of the illness and a first-line antimanic and maintenance drug, but it is not the drug you build a classic mixed or dysphoric-manic plan around. Its deep pharmacology, dosing and monitoring are owned by the lithium topics in these notes.

TRAP **Reaching first for lithium in a dysphoric mania.** Dysphoric and irritable presentations respond more poorly to lithium and better to divalproex or an atypical (Kaplan and Sadock 2024).

35.3 Valproate (divalproex): the mixed-state mood stabiliser of choice

Mechanism. Valproate broadens GABAergic inhibitory tone, blocks voltage-sensitive sodium channels and modulates T-type calcium currents, damping the excitatory drive that fuels the manic and agitated components of a mixed state (Stahl 2021). **Where it wins.** Valproate and divalproex have specific evidence in dysphoric mania, mixed affective episodes and rapid cycling, and outperform lithium in irritable and dysphoric presentations (Kaplan and Sadock 2024). CANMAT lists divalproex as a first-line monotherapy for acute mania (which includes mixed presentations) at a serum level of **350 to 700 micromol/L** (50 to 100 microg/mL) (CANMAT 2018). **Signature cautions.** Weight gain, tremor, hair loss, thrombocytopenia and hepatotoxicity; and the hard rule that it is **teratogenic** (neural tube defects, neurodevelopmental harm) and is not started in a woman of childbearing potential without a pregnancy-prevention programme (NICE 2014; IPS 2017). The full valproate pharmacology and teratogenicity are owned by the valproate topic in these notes.

GOOD TO REMEMBER

- **Valproate (divalproex; Valprol or Encorate, divalproex Valance or Divaa):** broadens GABA and blocks sodium channels; specific evidence in dysphoric mania, mixed and rapid-cycling states; acute-mania serum target **50 to 100 microg/mL** (CANMAT 2018). Signature: teratogenic, avoid in women of childbearing potential.

35.4 Asenapine: a first-line atypical for mixed states

Mechanism. Asenapine is a high-affinity 5-HT2A and D2 antagonist with a broad serotonergic, dopaminergic and adrenergic binding profile structurally related to mirtazapine (Stahl 2021; Kaplan and Sadock 2024). **Where it wins.** CANMAT names asenapine among the first-line agents for acute mania (alone or in combination), and it has a specific licensed indication for acute manic and mixed episodes of bipolar I disorder, making it one of the go-to atypicals when the presentation is mixed (CANMAT 2018; Stahl 2021). **Dose.** It must be given **sublingually** (about 35 percent bioavailable sublingually, under 2 percent if swallowed), typically **5 to 10 mg twice daily** (10 to 20 mg/day) for mania, with no food or drink for 10 minutes after dosing (Stahl 2021). **Signature effects.** Sublingual oral hypoaesthesia, sedation and a moderate metabolic burden.

GOOD TO REMEMBER

- **Asenapine:** sublingual 5-HT2A/D2 antagonist; first-line for acute manic and mixed episodes of bipolar I; dose **5 to 10 mg twice daily** sublingually, no food or drink for 10 minutes; signature is sublingual oral hypoaesthesia. Indian brand could not be confirmed from the library; prescribe by generic name.

35.5 Cariprazine: the atypical that spans the mixed spectrum

Mechanism. Cariprazine is a D3-preferring D2 and D3 partial agonist with 5-HT1A partial agonism; the D2 blockade in limbic areas treats mania and psychosis while D3 partial agonism in the midbrain enhances prefrontal dopamine to address the depressive and cognitive components, so it works across the bipolar mood spectrum in one agent (Stahl 2021). **Where it wins.** CANMAT names cariprazine among the first-line agents for acute mania, and it carries evidence across manic, mixed and bipolar-depressive presentations, which is exactly the coverage a mixed state needs (CANMAT 2018; Stahl 2021). **Dose.** Acute bipolar mania is **3 to 6 mg/day** once daily, titrated from 1.5 mg; Stahl notes the more manic the features, the higher the dose within range (Stahl 2021). **Signature effect.** Akathisia, which is dose-related and reduced by slower titration.

GOOD TO REMEMBER

- **Cariprazine:** D3-preferring D2/D3 partial agonist that spans the mixed spectrum in one agent; first-line acute mania at **3 to 6 mg/day**; signature is akathisia. Indian brand could not be confirmed from the library; prescribe by generic name.

35.6 Olanzapine and aripiprazole: the other evidenced atypicals

Two further atypicals round out the mixed-state toolkit. Olanzapine (Oleanz) is a first-line antimanic with evidence in mixed episodes, useful where rapid control of agitation is the priority, at the cost of the heaviest metabolic burden of the group, so weight, glucose and lipids are monitored (CANMAT 2018). Aripiprazole is a D2 and D3 partial agonist and 5-HT1A partial agonist, a first-line antimanic with a favourable metabolic profile, again with mixed-episode data (CANMAT 2018; Stahl 2021). CANMAT also endorses combination therapy, an atypical (quetiapine, aripiprazole, risperidone or asenapine) added to lithium or divalproex, as a first-line option for acute mania, especially in severe presentations, and that combination logic carries into severe mixed states (CANMAT 2018). The deep antipsychotic pharmacology and the shared adverse-effect set are owned by the Schizophrenia: management, antipsychotics and adverse effects notes.

GOOD TO REMEMBER

- **Olanzapine (Oleanz):** first-line antimanic with mixed-episode evidence; signature is the heaviest metabolic burden of the group; monitor weight, fasting glucose and lipids (CANMAT 2018).
- **Aripiprazole:** D2/D3 and 5-HT1A partial agonist; first-line antimanic, mixed-episode data, favourable metabolic profile; signature is akathisia (CANMAT 2018).

35.7 The critical caution: antidepressants are avoided in the mixed state

This is the crux of the topic. **Antidepressants are avoided** in a mixed state: they worsen the manic pole and drive the agitation, so a mixed "depression" is not treated with an antidepressant, and any antidepressant already running is discontinued (IPS 2017; CANMAT 2018). The IPS guidelines are unusually direct here: do not use antidepressants as monotherapy in bipolar depression, nor in rapid cycling disorder or mixed episodes; if an antidepressant is unavoidable, avoid paroxetine and prefer bupropion, and never as monotherapy (IPS 2017). CANMAT

reserves antidepressants for pure, non-mixed bipolar depression only, and instructs that antidepressants be discontinued in patients presenting with mania (CANMAT 2018). The mechanistic reason is simple: adding a pro-monoaminergic drug to a state that already contains manic activation pours fuel on the exact symptoms driving the risk.

RULE **Treat a mixed state with valproate or an atypical (asenapine, cariprazine) and stop antidepressants.** The mixed pole is managed from the manic side, not the depressive side.

TRAP **Treating the depressive symptoms of a mixed episode with an antidepressant.** It worsens the manic pole and the agitation and raises the suicide risk; discontinue any antidepressant instead.

35.8 ECT for severe or refractory mixed episodes

When the mixed episode is severe, treatment-refractory, or dominated by active suicidality, catatonia or psychosis, ECT is the answer. The IPS names modified ECT as first-line for mixed states with active suicidality and endorses ECT for a mixed episode that is severe, refractory, associated with suicidality, catatonia or psychosis, or occurring in pregnancy (IPS 2017). It is the fastest route to control when pharmacotherapy is too slow or has failed, and it side-steps the antidepressant problem entirely because it is not pole-specific. The ECT technique, electrode placement and cognitive monitoring are owned by the ECT and neurostimulation notes; the wider acute-emergency and perinatal frame is owned by the Perinatal/women's mental health and emergency psychiatry notes.

GOOD TO REMEMBER

- **ECT in a mixed state:** first-line for severe or refractory mixed episodes and for mixed states with active suicidality, catatonia, psychosis or in pregnancy; not pole-specific, so it avoids the antidepressant problem (IPS 2017).

35.9 The mixed-state options at a glance

The whole selection assembles into one table. Learn the highlighted cell in each row, and learn that antidepressants are the row you do not add.

50 to 100	5 to 10	3 to 6
ACUTE-MANIA VALPROATE (MICROG/ML)	ASENAPINE PER DOSE, TWICE DAILY (MG)	CARIPRAZINE ACUTE MANIA (MG/DAY)

OPTION	LINE AND ROLE	DOSE OR SERUM TARGET	SIGNATURE CAUTION
Valproate (divalproex)	**First-line mood stabiliser for dysphoric mania, mixed and rapid-cycling states; beats lithium here**	Acute-mania serum **50 to 100 microg/mL** (350 to 700 micromol/L)	Teratogenic; avoid in women of childbearing potential
Asenapine	**First-line atypical, licensed for acute manic and mixed episodes of bipolar I**	**5 to 10 mg twice daily** sublingually (10 to 20 mg/day)	Sublingual oral hypoaesthesia; no food or drink for 10 minutes

OPTION	LINE AND ROLE	DOSE OR SERUM TARGET	SIGNATURE CAUTION
Cariprazine	**First-line atypical spanning manic, mixed and depressive poles in one agent**	Acute mania **3 to 6 mg/day**, titrate from 1.5 mg	Akathisia (dose-related; slower titration reduces it)
Olanzapine	First-line antimanic with mixed-episode evidence; rapid agitation control	Standard antimanic dosing	**Heaviest metabolic burden of the group**
Aripiprazole	First-line antimanic, mixed-episode data, metabolically favourable	Standard antimanic dosing	Akathisia
Lithium	Anti-suicide agent and first-line antimanic overall, but relatively weaker for classic mixed and dysphoric presentations	Acute-mania serum 0.8 to 1.2 mEq/L	**Underperforms in dysphoric and irritable mania versus divalproex**
ECT	For severe or refractory mixed episodes, active suicidality, catatonia, psychosis or pregnancy	Acute course per protocol	Not pole-specific; avoids the antidepressant problem
Antidepressant	**Avoided: worsens the manic pole and agitation; discontinue any that is running**	Not indicated in the mixed state	Reserved only for pure, non-mixed bipolar depression, never as monotherapy

The mixed-state pharmacotherapy options, CANMAT-led, with the antidepressant row shown as the one you remove; doses and serum targets verified against CANMAT 2018, Stahl 2021 and Kaplan and Sadock 2024.

INDIA

The IPS bipolar guideline is now the 2025 update (IPS 2025, Menon et al.), which keeps divalproex first-line and carbamazepine second-line for acute mixed episodes; the earlier 2017 guideline (Grover and Avasthi et al.) still gives the sharpest examinable line for the mixed state: antidepressants are not used as monotherapy in bipolar depression, rapid cycling or mixed episodes, and if an antidepressant is unavoidable, avoid paroxetine and prefer bupropion (IPS 2017). The IPS also flags that suicide risk in bipolar disorder is among the highest of any psychiatric condition (lifetime around 15 to 20 percent) and is greatest in mixed states and the depressive phase, and names modified ECT as first-line for mixed states with active suicidality (IPS 2017). Valproate (Valprol or Encorate; divalproex Valance or Divaa) and olanzapine (Oleanz) are widely and cheaply available in India. Asenapine and cariprazine are the newer atypicals here and a confirmed Indian brand could not be verified from the library, so prescribe them by generic name.

WORKED EXAMPLE

A 29-year-old man is brought in agitated, sleepless for four nights, speaking rapidly and irritably, but voicing hopelessness and a plan to end his life; he has been on an SSRI for a presumed depression for three weeks. This is a dysphoric mania, a mixed state, and the suicide risk is high. The SSRI is **stopped**, not increased. He is started on a mixed-state agent, divalproex titrated to an acute-mania serum level of 50 to 100 microg/mL, or an atypical such as asenapine or cariprazine, with lithium a weaker choice for this dysphoric picture. If agitation, suicidality or refusal of oral medication makes control urgent, or the episode is refractory, ECT is first-line. Nobody adds an antidepressant to this presentation.

COMMON TRAP

Labelling the presentation "bipolar depression" because the mood is low and the patient is suicidal, then reaching for an antidepressant. If manic-side symptoms co-exist, agitation, racing thoughts, reduced sleep, pressured speech, irritability, it is a mixed state, and the antidepressant is the wrong drug. Manage it from the manic side with valproate or an atypical and stop any antidepressant.

PEARL

Read the drive, not just the mood. A suicidal patient who is also energised, sleepless and pressured has the lethal combination the mixed state is famous for: the despair supplies the intent and the manic activation supplies the capacity to act. That is why the mixed state is the highest-risk phase and why you treat it from the manic pole.

HOLD THIS

A mixed state is high-suicide-risk and does not respond like a pure pole: treat it with valproate or an atypical such as asenapine or cariprazine (olanzapine or aripiprazole also work, lithium is weaker for dysphoric mania), use ECT for severe or refractory cases, and stop antidepressants rather than treating the depressive symptoms with one.

36 . Maintenance and prophylaxis of bipolar disorder

Bipolar disorder is a lifelong, recurrent illness, so the acute episode is only half the task: the harder, higher-yield half is the **maintenance treatment of bipolar** disorder, the long-term relapse prevention that keeps a patient euthymic between episodes. The examiner wants a guideline-anchored answer built around one anchor drug and one organising idea: **lithium is the backbone of maintenance, and you match the agent to the patient's predominant pole.** A resident who can name the first-line maintenance agents, quote the maintenance lithium level, and justify continuing treatment long-term after multiple episodes has the marks.

This is a selection topic, so it is **guidelines**-first. The lead guideline is CANMAT (Yatham 2018); the **Indian Psychiatric Society** position (the **IPS guidelines**, Shah/Grover et al. IPS 2017), the BAP (Goodwin 2016) and NICE (NICE 2014) are corroborating. The acute-episode drug pharmacology sits in the lithium and valproate topics; the neurobiology of mood and the wider guideline-anchored management PLAN belong to the Mood disorders: classification, depressive

and bipolar syndromes, neurobiology notes; the perinatal and acute-emergency frame to the Perinatal/women's mental health and emergency psychiatry notes.

36.1 The goal of maintenance: prevent both poles, not just the last one

What maintenance is for. Maintenance (also called continuation-plus-prophylaxis) aims to prevent recurrence of both manic and depressive episodes, reduce sub-syndromal symptoms, lower suicide risk, and preserve function (Yatham 2018; Maudsley 2021). Bipolar disorder spends more time in the depressive than the manic pole, so an agent that only blocks mania leaves the commonest source of morbidity untreated.

Prophylaxis as the frame. The word **prophylaxis** captures the core intent: because relapse is the rule, treatment is preventive rather than reactive, and the default assumption is that an effective agent is continued well beyond symptomatic recovery (Maudsley 2021).

RULE **Maintenance protects both poles.** Judge a maintenance agent by whether it prevents the depressive pole as well as mania, since depression dominates the bipolar course.

36.2 CANMAT first-line maintenance: lithium the anchor

The verified first-line set. CANMAT names, as first-line maintenance monotherapy for bipolar I disorder: lithium, quetiapine, divalproex, lamotrigine, asenapine, and aripiprazole, alone or in combination (Yatham 2018). Lithium (Licab, Intalith) is the anchor: it is the single best-evidenced prophylactic agent and the only psychotropic with a dedicated anti-suicidal signal (Maudsley 2021; Yatham 2018). The target **maintenance treatment of bipolar** lithium level is **0.6 to 1.0 mEq/L** (Yatham 2018).

The anti-suicidal evidence. Lithium reduces the risk of suicide and of relapse requiring hospitalisation (relative risk about 0.34 in one analysis), and this mortality benefit is specific to the ion and not shared by valproate (Maudsley 2021). This is why lithium is preferred in a bipolar patient with any suicide-risk history; the full suicide risk assessment belongs to the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

AGENT (INDIAN BRAND)	MECHANISM / CLASS	POLE IT BEST PREVENTS	KEY MAINTENANCE NUMBER	SIGNATURE CAUTION
Lithium (Licab, Intalith)	Monovalent cation; GSK3-beta and inositol effects	Both poles; best anti-manic and anti-suicidal	Level 0.6 to 1.0 mEq/L	Renal, thyroid, calcium; narrow window
Quetiapine (Qutipin)	Atypical antipsychotic; D2 and 5-HT2A, norquetiapine NET	Both poles (broad-spectrum)	Continue effective acute dose	Metabolic gain, sedation
Divalproex (Valance, Divaa)	Anticonvulsant; enhances GABA, blocks Na channels	Manic pole predominantly	Level about 50 to 100 mcg/mL	Teratogen; avoid in childbearing potential

AGENT (INDIAN BRAND)	MECHANISM / CLASS	POLE IT BEST PREVENTS	KEY MAINTENANCE NUMBER	SIGNATURE CAUTION
Lamotrigine (Lamitor, Lametec)	Anticonvulsant; blocks Na channels, cuts glutamate	Depressive pole (weak for mania)	Target about 200 mg/day; slow titration	Rash / Stevens-Johnson; titrate from 25 mg
Asenapine	Atypical antipsychotic; broad D2 and 5-HT2A	Manic pole predominantly	Sublingual; continue effective dose	Oral hypoaesthesia, sedation
Aripiprazole (oral or LAI)	D2 partial agonist	Manic pole (does not prevent depression)	Once-monthly LAI option	Akathisia; poor for depressive pole

CANMAT first-line maintenance monotherapy agents for bipolar I disorder, mapped to predominant pole and the one maintenance number to hold (Yatham 2018; Maudsley 2021). Lithium and lamotrigine highlighted as the two polarity anchors.

TRAP **Using aripiprazole or asenapine alone in a depression-predominant patient.** These prevent mania but not the depressive pole; the patient keeps relapsing into depression on apparently adequate maintenance.

36.3 The polarity index: matching the agent to the predominant pole

The concept. The **polarity index** (Popovic et al. 2012) quantifies whether a maintenance drug is more anti-manic or more anti-depressive: it is the ratio of the number-needed-to-treat to prevent depression over the NNT to prevent mania (New Oxford 2020; Tasman 2015). A polarity index above 1 marks a manic-predominant agent; below 1 marks a depressive-predominant agent. This gives the clinical **match the polarity** heuristic a number.

The values to hold. Lithium sits close to balanced at **1.39** (mildly manic-predominant but effective both ways); lamotrigine is the strongly depressive-predominant agent at **0.40**; quetiapine is near-balanced at 1.14; olanzapine 2.98 and risperidone LAI 12.09 are strongly manic-predominant (Popovic et al. 2012; Tasman 2015). So a patient whose recurrences are mostly depressive is anchored on lithium and lamotrigine; one whose recurrences are mostly manic leans to an antipsychotic or divalproex.

1.39	0.40	12.09
LITHIUM POLARITY INDEX	LAMOTRIGINE POLARITY INDEX	RISPERIDONE LAI POLARITY INDEX

PEARL

Read the polarity index as a compass: above 1 points to mania-prevention (antipsychotics, divalproex), below 1 points to depression-prevention (lamotrigine at 0.40). Lithium near 1.39 is the all-rounder you build around and then add a pole-matched partner if one pole keeps breaking through.

36.4 Lamotrigine for the depressive pole

Its niche. Lamotrigine (Lamitor, Lametec) is the maintenance agent for the depressive pole: it prevents depressive recurrence well but is weak against mania, so it is rarely used as the sole agent in a mania-predominant patient (Yatham 2018; Maudsley 2021). It is added or substituted when depression is the recurring problem.

The titration rule. Because of the risk of rash and Stevens-Johnson syndrome, lamotrigine must be titrated slowly, starting at **25 mg/day** and building over weeks to a target near **200 mg/day** (Yatham 2018; Maudsley 2021). Valproate roughly doubles lamotrigine levels and mandates a halved lamotrigine dose and even slower titration.

TRAP **Titrating lamotrigine too fast, or forgetting the valproate interaction.** Rapid escalation, or full-speed titration alongside valproate, sharply raises the Stevens-Johnson risk.

36.5 The LAI option for non-adherence

When to reach for a depot. Non-adherence is the leading modifiable driver of relapse, so in a repeatedly non-adherent patient CANMAT offers a long-acting injectable antipsychotic to prevent recurrence: risperidone LAI every 2 weeks or aripiprazole once-monthly (Yatham 2018). The BAP concurs, recommending a depot antipsychotic for prophylaxis against manic recurrence when oral adherence is erratic (Goodwin 2016). Mirror-image data show fewer admissions and bed-days after switching to an LAI of aripiprazole or paliperidone (Maudsley 2021).

The polarity caveat. LAI antipsychotics are strongly manic-predominant (risperidone LAI polarity index 12.09), so they protect against mania far more than depression; a depression-prone non-adherent patient still needs a pole-matched agent alongside (Popovic et al. 2012).

36.6 What IPS, BAP and NICE recommend

The Indian Psychiatric Society. The **IPS guidelines** (the **Indian Psychiatric Society** bipolar CPG, Shah/Grover et al. IPS 2017) keep lithium as the first-choice long-term prophylactic agent, valued for its prophylactic and anti-suicidal evidence, with valproate, carbamazepine, lamotrigine and atypical antipsychotics as alternatives, and psychoeducation as the non-pharmacological base (IPS 2017). The IPS agrees the drug that controlled the acute episode is the rational one to continue long-term. Note: the IPS bipolar CPG is not in the guideline database used for this note, so its first-line ranking is stated here as consistent with the parsed sources rather than DB-verified.

BAP. Continue the lithium or valproate that treated the acute manic episode as a rational long-term choice, and consider a depot antipsychotic where adherence is poor (Goodwin 2016).

NICE. NICE positions lithium as the first-line long-term pharmacological treatment for bipolar disorder, with valproate second-line (avoided in women of childbearing potential), and olanzapine or quetiapine as further options (NICE 2014).

INDIA

Lead with the Indian brand: lithium carbonate is Licab or Intalith, divalproex is Valance or Divaa, sodium valproate is Valprol or Encorate, lamotrigine is Lamitor or Lametec, quetiapine is Qutipin, olanzapine is Oleanz. Lithium remains cheap and widely stocked, which matters for a lifelong prophylactic; the IPS and CANMAT positions converge on lithium as the maintenance anchor.

36.7 Choice and duration: how long to continue

The duration rule. This is the **choice and duration** question the examiner presses on. Maintenance is long-term and often indefinite: after multiple episodes, or after even one severe episode (for example with high suicide risk, psychosis, or major functional damage), prophylaxis is continued for years and frequently for life (Maudsley 2021; Yatham 2018). There is no fixed stop point analogous to the 6-to-9-month continuation rule in unipolar depression; the recurrent nature of the illness means treatment is not routinely withdrawn after a good year.

Choosing the agent. Choose by (i) what worked acutely (continue it), (ii) the predominant polarity (lithium or lamotrigine for depressive-predominant; antipsychotic or divalproex for manic-predominant), (iii) suicide risk (favour lithium), and (iv) childbearing potential (avoid valproate) (Yatham 2018; Maudsley 2021).

RULE **Anchor on lithium, match the polarity, continue long-term.** After multiple or severe episodes, maintenance is indefinite, not a one-year course.

TRAP **Stopping maintenance after one good year and inviting relapse.** Withdrawing a prophylactic mood stabiliser after a single well year, especially abruptly, sharply raises recurrence risk (rebound mania is a particular hazard with abrupt lithium withdrawal).

36.8 Relapse prevention: predictors and the psychosocial base

The evidence. The **relapse prevention** evidence is strongest for lithium among pharmacological agents, and adding a structured psychosocial intervention lowers relapse further (Yatham 2018). CANMAT makes adjunctive psychoeducation a first-line relapse-prevention intervention in euthymic patients (for example the Barcelona or Life Goals programmes, at least 5 sessions) (Yatham 2018).

The predictors of relapse. The modifiable and non-modifiable predictors a resident should list: non-adherence (the single biggest modifiable driver), residual or sub-syndromal symptoms, comorbid substance use, sleep and circadian disruption, high expressed emotion in the family, and stressful life events (Yatham 2018; Maudsley 2021). The **psychoeducation** and lifestyle base (regular sleep and routine, mood monitoring, early-warning-sign action plans, substance avoidance) targets exactly these.

WORKED EXAMPLE

A 30-year-old woman with bipolar I, three lifetime episodes (two depressive, one manic) and one past suicide attempt, is euthymic on lithium (Licab) at a level of 0.7 mEq/L. Because her recurrences are depression-predominant and she has a suicide history, lithium is the correct anchor (anti-suicidal, near-balanced polarity index 1.39); lamotrigine (Lamitor) is added for the depressive pole given its polarity index of 0.40. She joins a psychoeducation group, keeps a sleep and mood chart, and treatment is planned as long-term rather than time-limited.

36.9 Flibanserin: a note at the mood-sexual interface

What it is and is not. Flibanserin is included here only to fix its place at the **sexual-interface**: it is a **flibanserin** agent for **hypoactive sexual desire** disorder (HSDD) in premenopausal women, a 5-HT1A agonist and 5-HT2A antagonist that in the prefrontal cortex lowers serotonin and raises noradrenaline and dopamine (Kaplan and Sadock 2024). It was originally trialled as an antidepressant and failed, so it is emphatically not a mood stabiliser and has no maintenance role in bipolar disorder.

The one fact to hold. Flibanserin is FDA-approved (2015), dosed at **100 mg** at night, with dizziness, sedation and fatigue as its common adverse effects and a historical caution about alcohol and hypotension (Kaplan and Sadock 2024). It matters for the exam as a discriminator: a serotonergic mood/sexual-interface drug for female HSDD, distinct from any bipolar prophylactic.

HOLD THIS

Bipolar maintenance is anchored on lithium (level 0.6 to 1.0 mEq/L, anti-suicidal), lamotrigine is added for the depressive pole, you match the agent to the predominant polarity, and you continue long-term after multiple or severe episodes.

MNEMONIC

LQ-DLAA

The six CANMAT first-line maintenance agents: Lithium, Quetiapine, Divalproex, Lamotrigine, Asenapine, Aripiprazole. Lead the list with Lithium (the anchor) and remember Lamotrigine is the one for the depressive pole.

GOOD TO REMEMBER

- **Lithium (Licab, Intalith):** monovalent cation (GSK3-beta and inositol effects); best prophylactic and only anti-suicidal mood stabiliser; maintenance level 0.6 to 1.0 mEq/L, polarity index 1.39. First-line maintenance anchor.
- **Quetiapine (Qutipin):** atypical antipsychotic (D2 and 5-HT2A, norquetiapine NET); broad-spectrum, near-balanced polarity index 1.14; metabolic gain and sedation are the signature caution. First-line maintenance.
- **Divalproex (Valance, Divaa):** anticonvulsant (GABA enhancement, Na-channel block); manic-predominant; teratogen, so avoid in women of childbearing potential. First-line maintenance.
- **Lamotrigine (Lamitor, Lametec):** Na-channel blocker cutting glutamate; the depressive-pole agent (polarity index 0.40), weak for mania; rash / Stevens-Johnson signature, titrate from 25 mg to about 200 mg/day. First-line for depression-predominant maintenance.
- **Asenapine:** sublingual atypical antipsychotic (broad D2 and 5-HT2A); manic-predominant; oral hypoaesthesia is the signature. First-line maintenance.
- **Aripiprazole (oral or once-monthly LAI):** D2 partial agonist; prevents mania but not depression; akathisia signature; the once-monthly LAI is the non-adherence option. First-line maintenance monotherapy.
- **Flibanserin:** 5-HT1A agonist / 5-HT2A antagonist for female hypoactive sexual desire disorder; 100 mg nocte; NOT a mood stabiliser, no bipolar maintenance role. The mood-sexual-interface discriminator.

Apply and consolidate

37 . Apply: four worked pharmacotherapy vignettes

The mood-block pharmacotherapy syllabus is easiest to hold when it is rehearsed as clinical decisions rather than drug lists, and the exam frequently poses exactly that: a short case, a demand for the next drug, and an implied demand for the reasoning behind it. This closing topic runs **four** short worked vignettes that each fuse a scenario, the reasoning and the resolution, so that the antidepressant-selection, lithium-initiation, emergency and treatment-resistance chapters are exercised together as they will be at the bedside.

How to read each vignette. Every vignette below is presented as a worked example: it starts with the case (each opens with the literal marker "case:"), states the reasoning against a named guideline or a verified dose, and ends with the resolution and the trade-off. The class detail behind each is developed in the parent topics; here the skill is **application**. Doses, serum levels and first-line agents are verified against the Maudsley Prescribing Guidelines, Stahl, CANMAT, the BAP and the Indian Psychiatric Society CPGs (Maudsley 2021; Stahl 2021; CANMAT 2016; Malhi 2015; Gautam 2017). Where a brand is named it leads with the Indian brand.

37.1 Vignette 1: an antidepressant choice in comorbid depression with chronic pain and prior SSRI sexual dysfunction

The decision. This vignette is a **selection** problem: two patient-specific factors, a comorbid pain syndrome and an intolerable adverse effect on the previous drug, should steer the choice off the default SSRI. The reasoning turns on matching the drug's secondary pharmacology to the comorbidity, and its adverse-effect profile to what the patient could not tolerate before. Both

candidates below are CANMAT first-line agents, so the choice is a trade-off, not a hierarchy (CANMAT 2016).

WORKED EXAMPLE

Case: a 46-year-old man with a moderate depressive episode and long-standing diabetic neuropathic pain. A prior trial of an SSRI (escitalopram) helped his mood but caused marked sexual dysfunction that he found intolerable, and he stopped it. Reasoning: the SSRI class as a whole causes sexual dysfunction through serotonin-transporter blockade, so simply swapping to another SSRI is likely to reproduce the problem; the comorbid neuropathic pain is a positive reason to choose a drug that treats both targets. The two rational off-SSRI choices are an SNRI, duloxetine (Duzela), which is CANMAT first-line for major depression at 60 mg/day and separately licensed for diabetic neuropathic pain and fibromyalgia because of its noradrenergic action on descending spinal pathways; or bupropion (Bupron), a noradrenaline-dopamine reuptake inhibitor that is CANMAT first-line at 150 to 300 mg/day and carries the lowest sexual-dysfunction rate of the common antidepressants. Resolution: duloxetine is the sharper choice here because it treats the depression and the neuropathic pain with one drug, and it does not aggravate the previous problem the way another SSRI would; the trade-off is that duloxetine, like the SSRIs, can itself cause some sexual dysfunction, whereas bupropion would spare sexual function most fully but does nothing for the pain. If the sexual adverse effect were the single dominant concern and there were no pain, bupropion would be the first pick.

The trade-off stated cleanly. Duloxetine (Duzela) 60 mg/day wins on the pain comorbidity; bupropion (Bupron) 150 to 300 mg/day wins on sexual tolerability. A third option, mirtazapine (Mirtaz) 15 to 45 mg/day, also spares sexual function and aids sleep and appetite but does not treat pain (Stahl 2021; CANMAT 2016). Both duloxetine and bupropion require the standard adequate-trial window before they can be judged: response is assessed at 4 weeks and again at 6 to 8 weeks (BAP 2015; CANMAT 2016). The SSRI-versus-SNRI class detail and the full antidepressant-selection algorithm are set out in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

RULE **Let the comorbidity and the prior intolerance pick the antidepressant.** Comorbid pain points to duloxetine; prior sexual dysfunction points to bupropion or mirtazapine, never to a second SSRI.

TRAP **Swapping one SSRI for another after SSRI-induced sexual dysfunction.** The adverse effect is a serotonin-transporter class effect, so a second SSRI usually reproduces it; switch class, not molecule.

37.2 Vignette 2: lithium initiation, target level, the twelve-hour trough and the no-NSAID counselling

The decision. This vignette is an **initiation and monitoring** problem: the baseline work-up, the target serum level for the phase being treated, the sampling rule, and the interaction counselling that keeps the patient out of toxicity. Every figure below is verified (Maudsley 2021; Yatham 2018; Shah 2017).

WORKED EXAMPLE

Case: a 30-year-old woman with bipolar I disorder, recovering from an acute manic episode, for whom lithium is chosen for maintenance. Reasoning: before the first tablet, establish the two organs lithium threatens and the cardiac baseline. The baseline work-up is renal function (eGFR, creatinine, urea and electrolytes), thyroid function (TSH), serum calcium, weight or BMI, an ECG where there are cardiovascular risk factors, and, because lithium is a human teratogen (Ebstein anomaly), a pregnancy test with contraception counselling in a woman of child-bearing potential (Maudsley 2021; Yatham 2018). Start lithium carbonate (Licab, or the controlled-release Intalith CR) and titrate to a maintenance target of 0.6 to 1.0 mmol/L, drawing the level as a twelve-hour trough: the blood is taken 12 hours (ideally 10 to 14 hours) after the last dose, which for a bedtime dose means the next morning before the day's tablet. Recheck the trough 5 to 7 days after each dose change, then roughly 3-monthly once stable, with renal and thyroid function about 6-monthly. Resolution: counsel the patient that anything reducing renal lithium clearance raises the level and can cause toxicity, so she must avoid NSAIDs (ibuprofen, diclofenac) for pain and tell any doctor she is on lithium before starting a thiazide diuretic or an ACE inhibitor; she should keep well hydrated, and report tremor, ataxia, slurred speech, vomiting or diarrhoea at once as toxicity signs.

The phase sets the target. In acute mania the target trough is higher, 0.8 to 1.2 mmol/L, and it steps down to 0.6 to 1.0 mmol/L for maintenance; toxicity appears reliably above 1.5 mmol/L (Yatham 2018; Maudsley 2021). The twelve-hour trough and the 5-to-7-day recheck after a dose change are the two most-tested sampling facts, developed in full in the lithium-monitoring topic of these mood-block notes.

0.6 to 1.0	0.8 to 1.2	12	1.5
MAINTENANCE LITHIUM (MMOL/L)	ACUTE MANIA TARGET (MMOL/L)	TROUGH SAMPLING (HOURS POST-DOSE)	TOXICITY THRESHOLD (MMOL/L)

RULE **Draw lithium as a twelve-hour trough and counsel against NSAIDs.** The **12-hour** post-dose sample is the only interpretable level; NSAIDs, thiazides and ACE inhibitors raise the level toward toxicity.

TRAP **Checking a lithium level at the wrong time.** A non-trough sample drawn a few hours post-dose reads falsely high and invites a wrong dose cut; standardise to 12 hours every time.

INDIA

Lithium carbonate is cheap and heavily prescribed in India as Licab and the controlled-release Intalith CR, and the serum assay is inexpensive and widely available. The practical failure point is the twelve-hour trough discipline in a busy outpatient department, so counsel the patient to attend fasting in the morning before the day's dose and to note the time of the last tablet. Over-the-counter NSAID use for musculoskeletal pain is common and unsupervised, which makes the no-NSAID counselling a genuine safety instruction, not a formality.

37.3 Vignette 3: suspected serotonin syndrome on an SSRI plus tramadol, reasoned through the Hunter criteria

The decision. This vignette is a **recognition and emergency-management** problem: identify the syndrome from a combination of a serotonergic antidepressant and a serotonergic analgesic, apply the diagnostic rule, take the first management step, and separate it from its dopamine-blocker mimic. The management sequence and the discriminator are verified (Maudsley 2021; Kaplan and Sadock 2024).

WORKED EXAMPLE

Case: a 52-year-old man on sertraline (Serta) for depression is given tramadol for acute back pain and within hours becomes agitated, sweaty and febrile at 39 degrees Celsius, with dilated pupils, a tachycardia of 130, brisk lower-limb reflexes and sustained ankle clonus. Reasoning: sertraline plus tramadol is a two-drug serotonergic combination, and tramadol is itself weakly serotonergic, so this is the classic precipitant of serotonin syndrome. Apply the Hunter Serotonin Toxicity Criteria: in a patient on a serotonergic agent, the diagnosis is met by any one of spontaneous clonus; inducible clonus with agitation or diaphoresis; ocular clonus with agitation or diaphoresis; tremor plus hyperreflexia; or hypertonia plus temperature above 38 degrees Celsius plus ocular or inducible clonus. This patient has spontaneous clonus, which alone satisfies the Hunter criteria. Resolution: the first and most important step is to stop all serotonergic agents at once (both the sertraline and the tramadol); then give supportive care with intravenous fluids and active cooling for the hyperthermia, sedate with a benzodiazepine for agitation and neuromuscular hyperactivity, and in this moderate-to-severe case give cyproheptadine (Ciplactin, or Practin), a 5-HT2A antagonist, orally as the serotonin-antagonist antidote, a common regimen being an initial 12 mg then 2 mg every two hours if symptoms persist, to a ceiling around 32 mg in 24 hours. Most cases resolve within about 24 hours of stopping the trigger.

The NMS differential is the point. Serotonin syndrome and neuroleptic malignant syndrome share hyperthermia, rigidity, autonomic instability and altered consciousness, so the examiner rewards the one discriminator: serotonin syndrome follows a serotonergic drug, comes on rapidly over hours, and shows clonus with hyperreflexia; neuroleptic malignant syndrome follows a dopamine-blocker, comes on slowly over days, and shows lead-pipe rigidity with hyporeflexia and a markedly raised creatine kinase, often above 1000 units per litre (Maudsley 2021). The wider acute-emergency management frame is set out in the Perinatal/women's mental health and emergency psychiatry notes.

clonus	hours	12 then 2
THE HUNTER ANCHOR AND NMS DISCRIMINATOR	SEROTONIN-SYNDROME ONSET AFTER TRIGGER	CYPROHEPTADINE (MG, INITIAL THEN Q2H)

RULE **Stop the serotonergic drugs first, then support, sedate and give cyproheptadine.** Clonus with hyperreflexia in a patient on a serotonergic agent is serotonin syndrome until proven otherwise.

TRAP **Missing serotonin syndrome when an SSRI meets tramadol, or mislabelling it as NMS.** Tramadol is serotonergic; clonus and hyperreflexia (not lead-pipe rigidity) separate serotonin syndrome from its dopamine-blocker mimic.

INDIA

Tramadol is casually co-prescribed for musculoskeletal pain across Indian practice, so the highest-risk everyday scenario is a patient already on an antidepressant who is given tramadol. Cyproheptadine is freely available in India as an oral antihistamine (commonly stocked as Ciplactin or Practin), which makes the specific antidote easy to obtain once moderate-to-severe serotonin syndrome is recognised.

37.4 Vignette 4: treatment-resistant depression up the augmentation ladder

The decision. This vignette is an **escalation-discipline** problem: before augmenting, prove the depression is genuinely resistant and not merely under-treated, then climb the augmentation ladder in the guideline order. Every guideline opens the treatment-resistant depression pathway with a mandatory review of adequacy and diagnosis before any escalation (CANMAT 2016; BAP 2015; Gautam 2017).

WORKED EXAMPLE

Case: a 40-year-old woman with a major depressive episode that has not remitted despite an SSRI (escitalopram) followed by an SNRI (venlafaxine). Reasoning: first confirm this is true resistance, defined as failure of at least two adequate antidepressant trials in the current episode, each at an adequate dose for an adequate duration (response judged at 4 weeks and again at 6 to 8 weeks). Confirm each trial actually reached a therapeutic dose and was taken long enough, and confirm adherence, because most apparent resistance is pseudoresistance from an inadequate dose, an inadequate duration, poor adherence or a wrong diagnosis; review the diagnosis for a missed bipolar disorder, psychotic depression, or an organic or substance cause. Resolution: with two genuinely adequate failures confirmed, augment rather than endlessly switch. The first-line augmentation moves are to add lithium (Licab) 600 to 1200 mg/day titrated to a therapeutic serum level, or to add an atypical antipsychotic such as aripiprazole 2 to 15 mg/day or quetiapine (Qutipin) 150 to 300 mg/day (CANMAT 2016; BAP 2015). If augmentation fails, the next tier is the glutamatergic and neurostimulation options: add intranasal esketamine (Spravato) to an SSRI or SNRI for patients who have failed at least two adequate antidepressant trials, monitoring blood pressure and dissociation, or refer for electroconvulsive therapy, which is considered for patients who have not responded to other treatments and is the treatment of choice in severe, psychotic or high-suicide-risk depression.

The ladder in order. Optimise and confirm adequacy and adherence, review the diagnosis, then augment with lithium or an atypical (first-line augmentation), then move to esketamine or ECT. Lithium augmentation has the best evidence in older people, and CANMAT places aripiprazole, brexpiprazole, quetiapine and lithium among the first-line adjuncts, with esketamine reserved for at least two failed trials (BAP 2015; CANMAT 2016). The staging systems (Thase-Rush, Maudsley staging method) and the full ladder are developed in the treatment-resistant depression topic; the ECT technique itself is in the ECT and neurostimulation notes.

STEP	ACTION	AGENT / DOSE (VERIFIED)
1	**Confirm adequacy and adherence, review diagnosis**	Two adequate trials at therapeutic dose, judged at 4 and 6 to 8 weeks; exclude bipolar, psychotic, organic and substance causes
2	Optimise the current antidepressant	Raise a low or marginal dose to a recommended therapeutic dose first
3	**First-line augmentation: lithium or an atypical**	Lithium 600 to 1200 mg/day (to therapeutic serum level); aripiprazole 2 to 15 mg/day; quetiapine 150 to 300 mg daily
4	Glutamatergic or neurostimulation	Intranasal esketamine added to an SSRI/SNRI after 2 failed adequate trials; or ECT

The treatment-resistant depression ladder as applied in the vignette: confirm resistance and adherence, optimise, augment with lithium or an atypical, then esketamine or ECT (CANMAT 2016; BAP 2015). Highlighted steps are the board-critical moves.

RULE **Prove adequacy and adherence before you augment.** Two adequate trials must fail in the current episode; then augment with lithium or an atypical before moving to esketamine or ECT.

TRAP **Stopping at response instead of remission, or escalating over pseudoresistance.** Response without remission relapses; an inadequate dose, an inadequate duration or a missed bipolar diagnosis is under-treatment, not resistance.

GOOD TO REMEMBER

- **Vignette 1, antidepressant choice:** comorbid pain plus prior SSRI sexual dysfunction reasons to duloxetine (Duzela) 60 mg/day (treats pain and mood, CANMAT first-line SNRI) or bupropion (Bupron) 150 to 300 mg/day (lowest sexual-dysfunction rate); never a second SSRI for a class-effect adverse event.
- **Vignette 2, lithium initiation:** baseline renal (eGFR/creatinine), thyroid (TSH), calcium, weight, ECG where indicated, and pregnancy test; maintenance target 0.6 to 1.0 mmol/L (acute mania 0.8 to 1.2); draw a twelve-hour trough; counsel no NSAIDs, and caution with thiazides and ACE inhibitors.
- **Vignette 3, serotonin syndrome:** SSRI plus tramadol, Hunter criteria met by spontaneous clonus; stop all serotonergic agents first, then support and cool, benzodiazepine, then cyproheptadine (Ciplactin/Practin) 12 mg then 2 mg every 2 hours; clonus and hyperreflexia (not lead-pipe rigidity) distinguish it from NMS.
- **Vignette 4, treatment-resistant depression:** confirm two adequate failed trials and adherence, review the diagnosis, then augment with lithium 600 to 1200 mg/day or an atypical (aripiprazole 2 to 15 mg/day, quetiapine 150 to 300 mg/day), then esketamine (Spravato) or ECT.

HOLD THIS

The four clinical moves: match the antidepressant to the comorbidity and the prior intolerance (duloxetine for pain, bupropion for sexual sparing); start lithium on a full baseline work-up with a twelve-hour trough and no-NSAID counselling; in serotonin syndrome stop the serotonergic drugs first and give cyproheptadine; and in resistant depression prove adequacy and adherence before augmenting with lithium or an atypical and then esketamine or ECT.

38 . Consolidate: mnemonic, retrieval and synthesis

This is the closing topic of the mood pharmacotherapy block, and its job is not to add new drug facts but to **consolidate** the ones already taught into a form you can retrieve cold in an examination. Two evidence-based study moves do the heavy lifting: a single master **mnemonic** that chains the whole chapter into four movements so nothing is dropped, and **active recall** against a map you can redraw from memory. The pharmacology and the algorithms are all upstream; here they are re-indexed for retrieval.

The board does not reward a resident who can recognise a fact when prompted; it rewards one who can **generate** it under time pressure. That is why this topic is built around retrieval, not re-reading: the mnemonic is the retrieval cue, the recall prompts are the practice, and the synthesis map is the whole chapter compressed to one page you rebuild without looking. Everything below points back to a topic taught in full elsewhere in these notes.

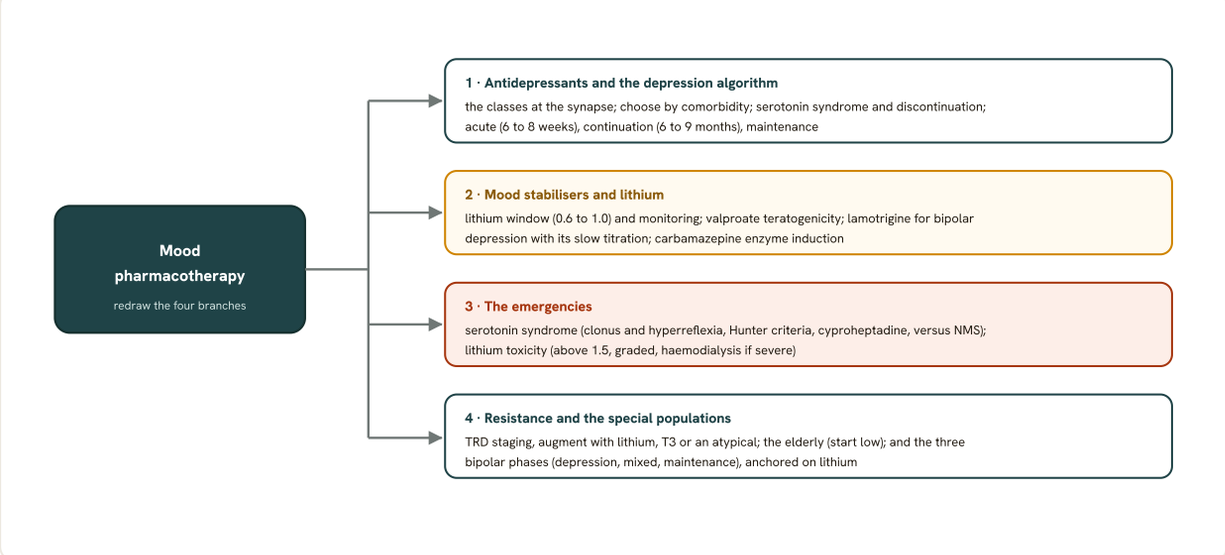

Fig 12.17 The whole chapter at a glance, framed for retrieval: cover the branches and redraw them from memory. The four branches are the antidepressants and the depression algorithm; the mood stabilisers and lithium with their monitoring and teratogenicity; the emergencies (serotonin syndrome and lithium toxicity); and treatment resistance with the special populations and the three bipolar-management phases.

38.1 The master mnemonic: chaining the whole chapter

One handle, four movements. The entire pharmacotherapy block hangs on the Step-2 seed you planted at the outset, and this is its payoff. Hold the whole chapter as **"A SNoM LiVeS, then CALM the STORM, then climb the LADDER"**. The first beat is the antidepressant classes and the depression algorithm; the second is lithium and the mood stabilisers with their monitoring and teratogenicity; the third is the two pharmacological emergencies; the fourth is treatment

resistance, augmentation and the bipolar-phase management. Each capitalised letter is a slot that expands into a full topic, and every fact chained below is verified against the source that owns it (Maudsley 2021; Stahl 2021; CANMAT 2016; CANMAT 2018; Yatham 2018).

MNEMONIC

A SNoM LiVeS, then CALM the STORM, then climb the LADDER

A SNoM is the antidepressant classes and the depression algorithm. **A**ntidepressants classify by synaptic action: SSRIs (SERT block, first-line, escitalopram **10 to 20 mg/day**), **S**NRIs (SERT plus NET, venlafaxine **75 to 225 mg/day** with dose-related blood-pressure rise), **N**aSSA/**N**DRI (mirtazapine, an alpha-2 antagonist that sedates; bupropion, a noradrenaline-dopamine reuptake inhibitor that spares sexual function and lowers the seizure threshold), the **o**lder tricyclics and **M**AOIs (reserved, dangerous, the tyramine and serotonergic hazards), and the **M**ultimodal and glutamatergic agents (vortioxetine, ketamine/esketamine). The depression algorithm is treat by phase to **remission**: acute review every **1 to 2 weeks**, judge by **2 to 4 weeks**, continuation at the same acute dose for **6 to 9 months**, maintenance **2 years or longer** if recurrent (CANMAT 2016). **LiVeS** is the mood stabilisers: **Li**thium (maintenance level **0.6 to 1.0 mmol/L**, twelve-hour trough, specific anti-suicide effect, first-trimester Ebstein signal), **V**alproate (serum **50 to 100 microg/mL**, the highest-risk teratogen: neural-tube defects, major-malformation rate around **10 percent**, dose-related IQ and autism harm, avoided in women of childbearing potential), lamotrigine (the depression pole, titrate **25 to 200 mg/day** slowly for the rash), the Stabiliser antipsychotics and carbamazepine (serum **4 to 12 mg/L**, enzyme induction, HLA-B*1502). **CALM the STORM** is the two emergencies: serotonin syndrome (clonus, hyperreflexia, autonomic instability, altered mental state, rapid over hours; stop the drug and give cyproheptadine) and lithium toxicity (coarse tremor and ataxia, toxic above **1.5 mmol/L**; stop, rehydrate with saline, dialyse if severe). **The LADDER** is treatment resistance and the bipolar phases: prove adequacy first (dose, duration, adherence, diagnosis), then switch, augment (lithium to **0.6 to 1.0 mmol/L**, or an atypical), combine, neuromodulate (ECT); and treat bipolar by phase (mania: lithium/valproate/an atypical, stop the antidepressant; bipolar depression: quetiapine, lurasidone, lithium, lamotrigine, never an antidepressant alone; maintenance: continue what worked, lithium level **0.6 to 1.0 mmol/L**).

RULE **Classify first, then treat by phase and polarity.** A SNoM LiVeS names the drug; CALM the STORM and the LADDER name what to do when it goes wrong or fails.

TRAP **Reciting the mnemonic without the numbers.** The letters are a scaffold; the exam marks fall on the doses, the serum levels and the monitoring intervals hung on each letter, so rehearse the figures, not just the acronym.

38.2 Retrieval practice, cover the answers

Practise generating, not recognising. The single most efficient consolidation move is **active recall**: close the notes and force the fact out, then check. What follows is a set of answer-free prompts spanning the four bands of the chapter. Use them as **retrieval practice**: read a prompt, say or write the full answer aloud from memory, and only then reveal the source topic to mark yourself. The prompts print no answers by design; that is the point of **cover the answers** practice. Space the repetitions across sittings rather than massing them.

RETRIEVAL PRACTICE, COVER THE ANSWERS

1. Name the primary synaptic action of each antidepressant class (SSRI, SNRI, TCA, MAOI, NaSSA, NDRI, multimodal, glutamatergic), and the one signature adverse effect or interaction that belongs to each.
2. State the four phases of the unipolar depression algorithm with the review interval, the response-judging point, the continuation duration and the maintenance duration, and say what defines the end of the acute phase.
3. Give the first-line agents for bipolar depression and state the one thing you never do with an antidepressant in bipolar disorder.
4. Recite the tyramine (cheese-reaction) food list for a patient on an irreversible MAOI, and the two washout intervals when switching to and from an MAOI or fluoxetine.
5. State lithium's molecular target and mechanism, its maintenance and acute serum ranges, the sampling rule (when the level is drawn), and the two anti-suicide claims attached to it.
6. List the lithium monitoring schedule: the trough timing, the recheck interval after a dose change, the ongoing level interval once stable, and the thyroid and renal monitoring intervals.
7. Give the drugs that raise and the drugs that lower the lithium level, and name the teratogenic signal and the trimester it belongs to.
8. State valproate's serum range, its full adverse-effect set, and the complete teratogenicity picture (structural, neurodevelopmental and its dose-dependence) with the prescribing rule that follows.
9. Give the lamotrigine titration and the one drug interaction that forces you to halve the schedule, and name the pole and phase lamotrigine is best for.
10. State carbamazepine's serum range, its three signature hazards, and the effect of its autoinduction on the level.
11. Recite the serotonin syndrome triad, the one sign that discriminates it from neuroleptic malignant syndrome, and the four-step management sequence.
12. Give the lithium toxicity level bands (mild, moderate, severe), the matching clinical features, the classic precipitants, and the four-step management including the dialysis indication.
13. State the definition of treatment-resistant depression, the four adequacy checks you clear before escalating, and the order of the switch-augment-combine-neuromodulate ladder.
14. Name the best-evidenced augmentation agents and the target lithium level for lithium augmentation.
15. Lay out the three bipolar phases (mania, depression, maintenance) with the first-line agents for each and the maintenance lithium level.

TRAP **Re-reading the notes and mistaking familiarity for mastery.** Recognising a fact on the page is not the same as retrieving it under a stem; only cover-the-answers recall trains the generation the board tests.

38.3 The synthesis map: redraw from memory

Rebuild the chapter on one page. The final consolidation move is to draw the whole-chapter **synthesis map** and then **redraw from memory** until it comes out clean. The map is a single

node, the mood pharmacotherapy block, with four branches, each a movement of the master mnemonic. Branch one is the antidepressants and the depression algorithm (the class map keyed to synaptic action, and the acute-continuation-maintenance phases). Branch two is the mood stabilisers and lithium (lithium initiation, monitoring, toxicity and teratogenicity, then valproate, carbamazepine, lamotrigine and the stabiliser antipsychotics). Branch three is the emergencies (serotonin syndrome and lithium toxicity, each with its discriminator and first management step). Branch four is treatment resistance and the special populations (the adequacy work-up and the augmentation ladder, the three bipolar phases, and prescribing in pregnancy and old age). Draw the four branches from the central node, hang the two or three load-bearing numbers on each leaf, and repeat the exercise cold until nothing is missing; the leaves you cannot fill are exactly the topics to revisit.

HOLD THIS

A SNoM LiVeS, then CALM the STORM, then climb the LADDER: four movements, four branches, one page you can redraw from memory.

GOOD TO REMEMBER

- **Branch 1 (antidepressants and the algorithm):** classify by synaptic action, then treat by phase to remission, continuation **6 to 9 months**, maintenance **2 years or longer** if recurrent (CANMAT 2016).
- **Branch 2 (stabilisers and lithium):** lithium maintenance **0.6 to 1.0 mmol/L** at a twelve-hour trough; valproate **50 to 100 microg/mL**, the highest-risk teratogen; lamotrigine for the depressive pole, titrated slowly (CANMAT 2018; Maudsley 2021).
- **Branch 3 (emergencies):** serotonin syndrome is clonus plus hyperreflexia (stop the drug, cyproheptadine); lithium toxicity is coarse tremor and ataxia above **1.5 mmol/L** (stop, saline, dialyse if severe) (Maudsley 2021).
- **Branch 4 (resistance and special populations):** prove adequacy (dose, duration, adherence, diagnosis) before you switch, augment, combine or neuromodulate; treat bipolar by phase and never give an antidepressant alone in bipolar depression (CANMAT 2016; Yatham 2018).
- **The retrieval rule:** generate the fact from a cue and space the repetitions; recognition on re-reading is not the skill the examination tests.

INDIA

For the Indian postgraduate examination, lead every management answer with CANMAT (CANMAT 2016 for depression, CANMAT 2018 and Yatham 2018 for bipolar disorder), then name the Indian Psychiatric Society position (Gautam et al. 2017 for depression, Grover and Avasthi 2017 for bipolar disorder), then note BAP and NICE where they converge (BAP 2015; NICE 2014). The Indian brands are learnt one drug at a time in the individual topics, Indian brand first: for example escitalopram (Nexito or S-Citadep), sertraline (Serta or Daxid), lithium carbonate (Licab or Intalith), sodium valproate (Valprol or Encorate), lamotrigine (Lamitor or Lametec) and quetiapine (Qutipin). Lithium remains a mainstream first-line stabiliser in Indian practice.

Previously asked

Mood pharmacotherapy is examined heavily and at the level of the individual drug: the SSRIs, the SNRIs, lithium, ketamine and the newer antidepressants have each come as standalone short notes, and the management of resistant depression and of refractory bipolar illness recurs as both a short note and the tail of a long essay. The reliable pattern is that every long mood question ends in a guideline-anchored drug plan, and a drug-specific note (a class, an agent, a monitoring rule, an adverse effect) can be asked on its own. The genuine questions on record are grouped by band below. The classification, the clinical syndromes and the neurobiology that these drugs treat are developed in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

HOW THIS TERRITORY IS ACTUALLY TESTED

- **Antidepressant classes and agents.** "SSRI antidepressants", "SNRI antidepressants" and "newer antidepressants" have each been asked as 10-mark notes, and "the recent advances in depression and development of antidepressants" as a longer question, so each class must be ready with its mechanism, its representative agents, its adverse-effect signature and its place. "Antidepressants in epilepsy with depression" tests the drug choice in a comorbidity. Prepare the class map, the individual agents and the comorbidity-driven selection. short note and essay, recurring

- **Serotonin syndrome and drug-induced states.** A case of a patient on an antidepressant and an antipsychotic who develops involuntary movements has been asked as a diagnose-investigate-manage question, and serotonin syndrome sits behind any antidepressant-combination scenario. Prepare serotonin syndrome (the Hunter criteria, the discrimination from NMS, the management) and the drug-induced movement disorders by cross-reference. case question, recurring

- **Rapid-acting and novel agents.** "The use of ketamine in depression" has come as a standalone note, so the NMDA mechanism, the rapid effect, the esketamine indication and the monitoring must be exam-ready, and the glutamatergic and other novel agents are worth a line. short note

- **Lithium and the mood stabilisers.** "Lithium" is a classic 10-mark note (mechanism, indications, the therapeutic range, monitoring, toxicity and the organ effects), and "carbamazepine" recurs across the papers. Prepare lithium in full, and valproate, carbamazepine and lamotrigine with their monitoring and their signature risks (valproate teratogenicity, lamotrigine and Stevens-Johnson). short note, recurring

- **Treatment resistance and bipolar management.** "The management of resistant depression" and "the management of treatment-resistant depression" have both come as standalone questions, and "the conceptual overview of bipolar spectrum disorder with the management of treatment-refractory bipolar II" and "the clinical features, differential diagnosis and management of bipolar depression" as essays. Prepare the TRD staging and augmentation ladder, and the three dedicated bipolar-management topics (bipolar depression, mixed episodes and maintenance), guideline-first. essay and short note, recurring

Prepare this material to be prescribed and monitored, not just recited: the class map, the dose-anchored good-to-remember boxes, the lithium monitoring and toxicity figures, the serotonin-syndrome differential and the guideline-anchored selection and management topics in these notes are built to the way the block is examined. The mood classification, the clinical syndromes and the neurobiology live in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; the ECT and neurostimulation technique lives in the ECT and neurostimulation notes; the full clinical suicide risk assessment lives in the Somatic-symptom, sexual, impulse-control disorders and suicide notes; and the wider perinatal and emergency frames live in the Perinatal/women's mental health and emergency psychiatry notes.

Quick review

The whole subject in one table	
ANTIDEPRESSANT CLASSES	Classify by the primary synaptic action: reuptake inhibitors (SSRI at SERT, SNRI at SERT and NET, TCA at both plus H1/M1/alpha-1 blockade), enzyme inhibitors (irreversible MAOI, reversible moclobemide), receptor-acting (mirtazapine NaSSA, bupropion NDRI), multimodal (vortioxetine, agomelatine, trazodone) and glutamatergic (ketamine, esketamine). The site predicts the tolerability and the dangerous interactions.
SSRIS	First-line, broadly equal in efficacy; differ in half-life, interactions and adverse-effect emphasis. Fluoxetine (long half-life, activating), sertraline (broadest), escitalopram and citalopram (cleanest, dose-dependent QTc, citalopram capped at 40 mg/day), paroxetine (short half-life, anticholinergic, worst discontinuation, avoid in pregnancy), fluvoxamine (OCD, CYP1A2). Class effects: GI upset, sexual dysfunction, hyponatraemia/SIADH in the elderly, bleeding with NSAIDs, early activation.
SNRIS AND TCAS	SNRIs: venlafaxine (dose-dependent noradrenergic effect and blood-pressure rise, marked discontinuation), desvenlafaxine, duloxetine (neuropathic pain). TCAs: reuptake blockade plus off-target H1/M1/alpha-1 (the adverse effects); dangerous in overdose (quinidine-like cardiotoxicity, QRS widening, seizures), so weigh the suicide risk; amitriptyline, imipramine, clomipramine (OCD), nortriptyline (best tolerated).
MAOIS	Irreversible non-selective (phenelzine, tranylcypromine) or reversible RIMA (moclobemide, safer). Tyramine (cheese) reaction gives a hypertensive crisis; never combine with a serotonergic drug (serotonin syndrome). Washout: at least two weeks off an MAOI before a serotonergic drug; about one week off most SSRIs/SNRIs (two off a TCA) before an MAOI; five weeks off fluoxetine before an MAOI.
MIRTAZAPINE, BUPROPION, NEWER	Mirtazapine (NaSSA): sedation and weight gain (more at low dose), minimal sexual dysfunction, for depression with insomnia and poor appetite. Bupropion (NDRI): activating, low sexual dysfunction, smoking cessation, lowers the seizure threshold (avoid in seizure and eating disorders). Newer: vortioxetine and vilazodone (multimodal), agomelatine (melatonergic, needs LFT monitoring), trazodone (SARI, priapism), tianeptine.

The whole subject in one table	
SEROTONIN SYNDROME VS NMS	Serotonin syndrome: rapid onset from a serotonergic combination; clonus, hyperreflexia, tremor, hyperthermia, hyperactive bowel sounds, mydriasis; Hunter criteria; stop the agent, supportive care, cyproheptadine. NMS: slow onset from a dopamine blocker; lead-pipe rigidity, hyporeflexia, marked CK rise; dantrolene, bromocriptine. The pivot is clonus and hyperreflexia (serotonin) versus lead-pipe rigidity (NMS).
KETAMINE, DISCONTINUATION	Ketamine and esketamine (NMDA antagonists): rapid effect within hours via AMPA and synaptogenesis; esketamine (intranasal) for treatment-resistant depression and MDD with acute suicidality, given under observation for dissociation and blood pressure; effect is transient. Discontinuation syndrome (FINISH: flu-like, insomnia, nausea, imbalance, sensory zaps, hyperarousal): worst with paroxetine and venlafaxine, least with fluoxetine; taper slowly, it is not addiction.
CHOOSING AND THE PHASES	First-line agents are equal in efficacy, so choose by comorbidity, adverse-effect profile, past response, safety and cost (CANMAT lead; IPS and NICE agree). Acute phase: treat to remission over 6 to 8 weeks, review by 2 to 4 weeks. Continuation: the SAME acute dose for 6 to 9 months. Maintenance: 2 years or longer for recurrent or high-risk depression. Psychotic depression needs an antidepressant plus an antipsychotic, or ECT.
LITHIUM: DOSE AND MONITORING	Mechanism: inositol depletion and GSK-3 inhibition; renally excreted, sodium-linked, narrow therapeutic index. Range: acute mania 0.8 to 1.0 (up to 1.2), maintenance 0.6 to 0.8 (up to 1.0), elderly 0.4 to 0.6 mmol/L. Sample as a 12-hour trough; recheck 5 to 7 days after a dose change; renal and thyroid function 6-monthly. Baseline: renal, thyroid, calcium, ECG, pregnancy, weight.
LITHIUM: TOXICITY AND ORGANS	Toxicity (dehydration, NSAIDs, thiazides, ACE inhibitors precipitate): mild 1.5 to 2.0 (coarse tremor, GI, lethargy), moderate 2.0 to 2.5 (confusion, ataxia, dysarthria), severe above 2.5 (seizures, coma, renal failure); stop, saline, haemodialysis for severe. Organs: nephrogenic DI and long-term CKD (watch eGFR trend), hypothyroidism and goitre (thyroxine, keep lithium), hypercalcaemia, benign T-wave changes, acne and psoriasis, fine tremor. Ebstein anomaly first-trimester (small but raised). Interactions that RAISE the level: NSAIDs, thiazides, ACE inhibitors and ARBs.
VALPROATE, CARBAMAZEPINE, LAMOTRIGINE	Valproate: anti-manic and maintenance (not bipolar depression alone); hepatotoxicity and PCOS; CRITICAL teratogenicity (neural-tube and neurodevelopmental risk), so avoid in women of childbearing potential without a pregnancy-prevention programme. Carbamazepine: potent CYP3A4 autoinducer (oral-contraceptive failure), hyponatraemia, blood dyscrasias, HLA-B*1502 SJS screen. Lamotrigine: for bipolar depression and

The whole subject in one table	
	maintenance (weak for mania); slow titration, HALVED with valproate; stop for a serious or mucosal rash (Stevens-Johnson).
TRD AND AUGMENTATION	TRD: failure of at least two adequate antidepressant trials, but exclude pseudoresistance first (dose, duration, adherence, missed bipolarity); Thase-Rush and Maudsley staging; STAR-D showed remission falls with each step. Ladder: optimise, switch, augment (lithium the classic and anti-suicidal, T3, an atypical, the best evidence), combine, then ECT, esketamine or neuromodulation.
BIPOLAR MANAGEMENT BY PHASE	Acute mania: stop any antidepressant; first-line lithium, quetiapine, valproate, or an atypical (aripiprazole, asenapine, risperidone, cariprazine), combination for severe. Bipolar depression: quetiapine, lurasidone, lithium, lamotrigine, olanzapine-fluoxetine, cariprazine; never an antidepressant alone (manic switch). Mixed episodes: valproate, asenapine, cariprazine, olanzapine, ECT; antidepressants avoided; lithium relatively weaker. Maintenance: lithium anchors (anti-suicidal), quetiapine, valproate, lamotrigine for the depressive pole, LAI for non-adherence.
ECT, NEUROMODULATION, PSYCHOTHERAPY	ECT: first-line in the emergencies (severe, psychotic or treatment-resistant depression, high suicide risk, food refusal, catatonia, pregnancy), rapid and effective; technique elsewhere. rTMS: non-invasive, for treatment-resistant depression. VNS: later-line, slow. DBS: experimental. Psychotherapy: CBT, IPT and behavioural activation are first-line in mild-to-moderate depression alone and combined with medication in severe depression.
SPECIAL POPULATIONS AND SUICIDE	Elderly: somatic and cognitive presentation, vascular depression; start low and go slow but still reach an adequate dose; prefer an SSRI (watch hyponatraemia, falls, the QTc cap), avoid TCAs; ECT works well in severe late-life depression. Suicide: mood disorders carry the highest risk (severe, mixed, early illness, early recovery); lithium is anti-suicidal; avoid a large TCA supply; counsel early antidepressant activation.

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The pharmacology is grounded in the standard prescribing and psychopharmacology sources (the source hierarchy below), with the Maudsley Prescribing Guidelines and Stahl as the depth bar for the mechanisms, doses, serum levels and monitoring, and the management is guideline-first (CANMAT leading, with the Indian Psychiatric Society, the British Association for Psychopharmacology and NICE). Every dose, serum level, therapeutic range, monitoring interval, teratogenicity fact, drug interaction and first-line recommendation has been checked against these sources; anything that could not be confirmed was omitted and flagged rather than guessed. Each journal PMID here was verified against PubMed this build, matched on title, first author

and year; identifiers that resolved to the wrong paper were corrected or dropped. The classic sources seeding the field (Cade's 1949 report of lithium in mania, Schou's lithium work) are named in the prose by author and year.

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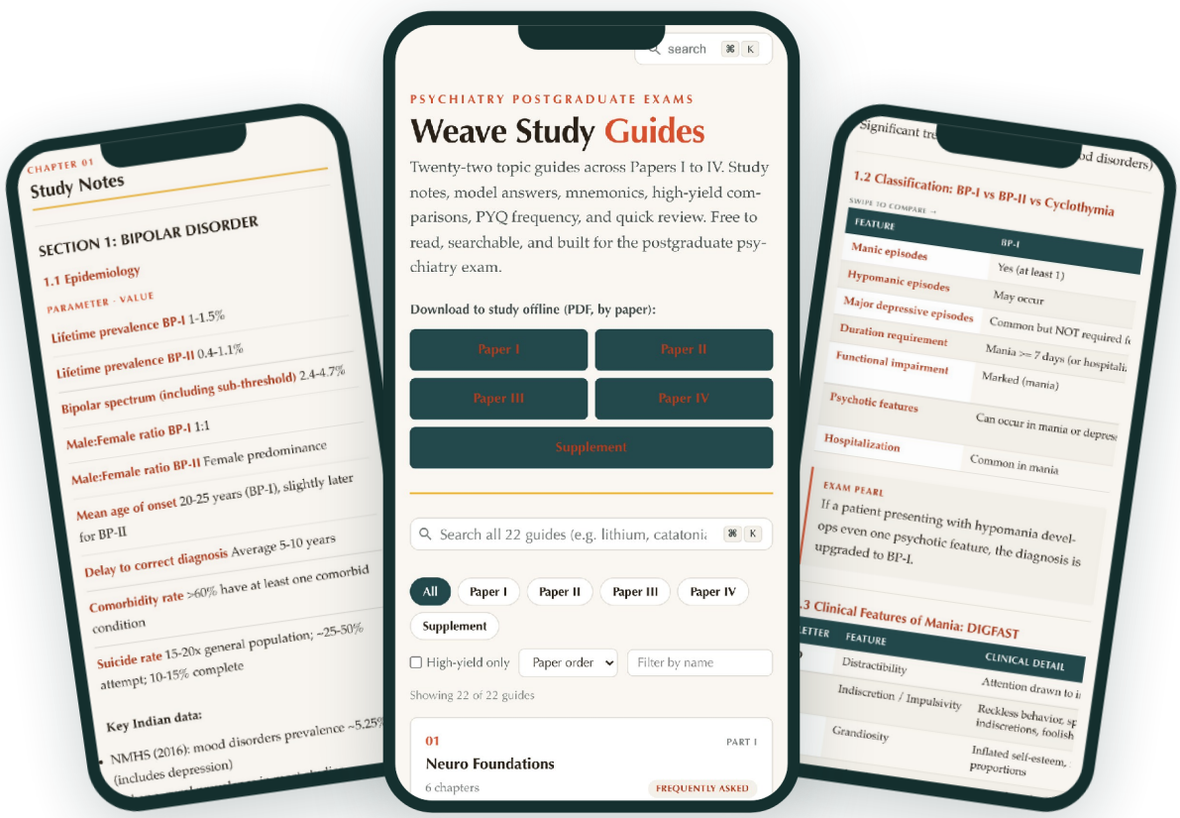

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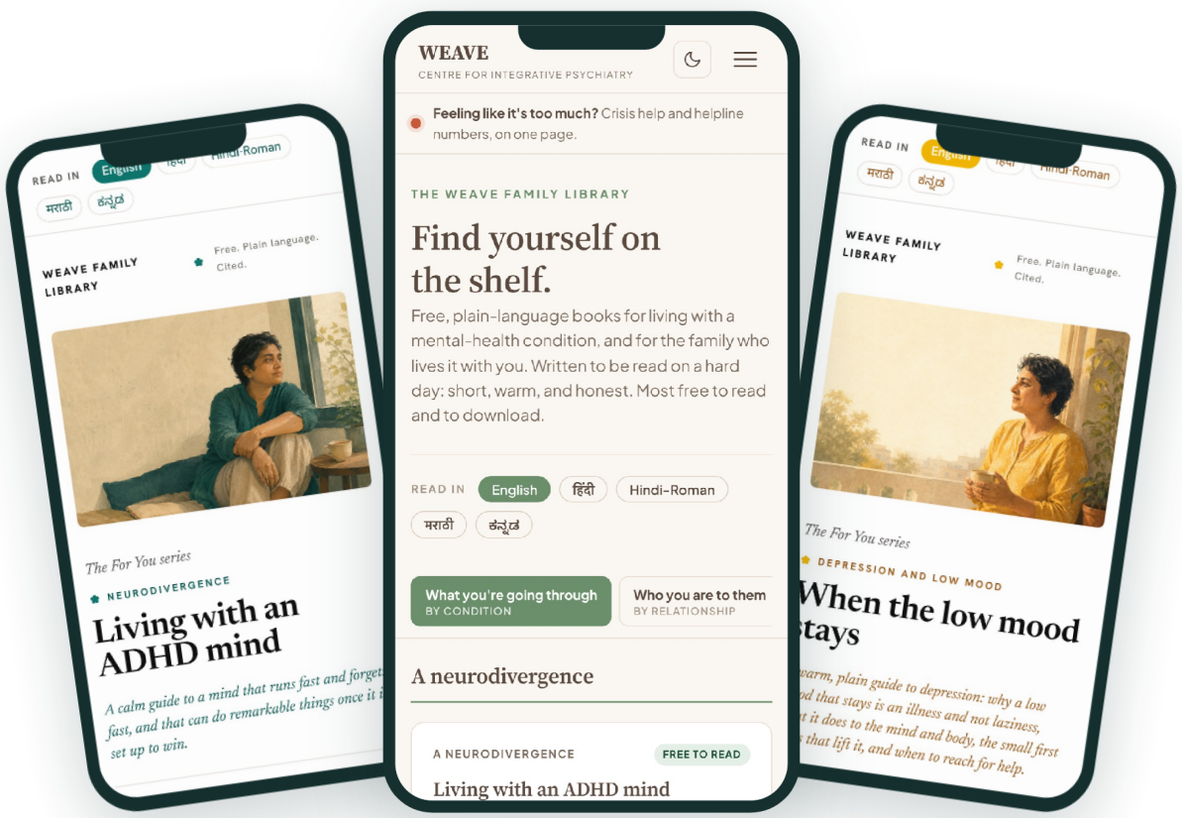

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