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Mood Disorders

The mood block in one document: how the depressive and bipolar disorders are classified and told apart, every depressive and bipolar syndrome and subtype with its criteria, the guideline-anchored management of each, and the neurobiology of mood from the monoamine hypothesis to the limbic-cortical circuit.

CONTENTS

- Mood disorders: classification and nosology
- Depressive disorders: clinical syndromes
- Bipolar and related disorders
- Mood disorders: neurobiology and aetiology
- Discriminate, apply and consolidate

Dr. Wilfred D'souza · Dr. Niharika Reddy

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Dr. Niharika Reddy and Dr. Wilfred D'souza, Consultant Psychiatrists. Runwal Forests Clinic, Kanjurmarg West, Mumbai, and online.

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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.

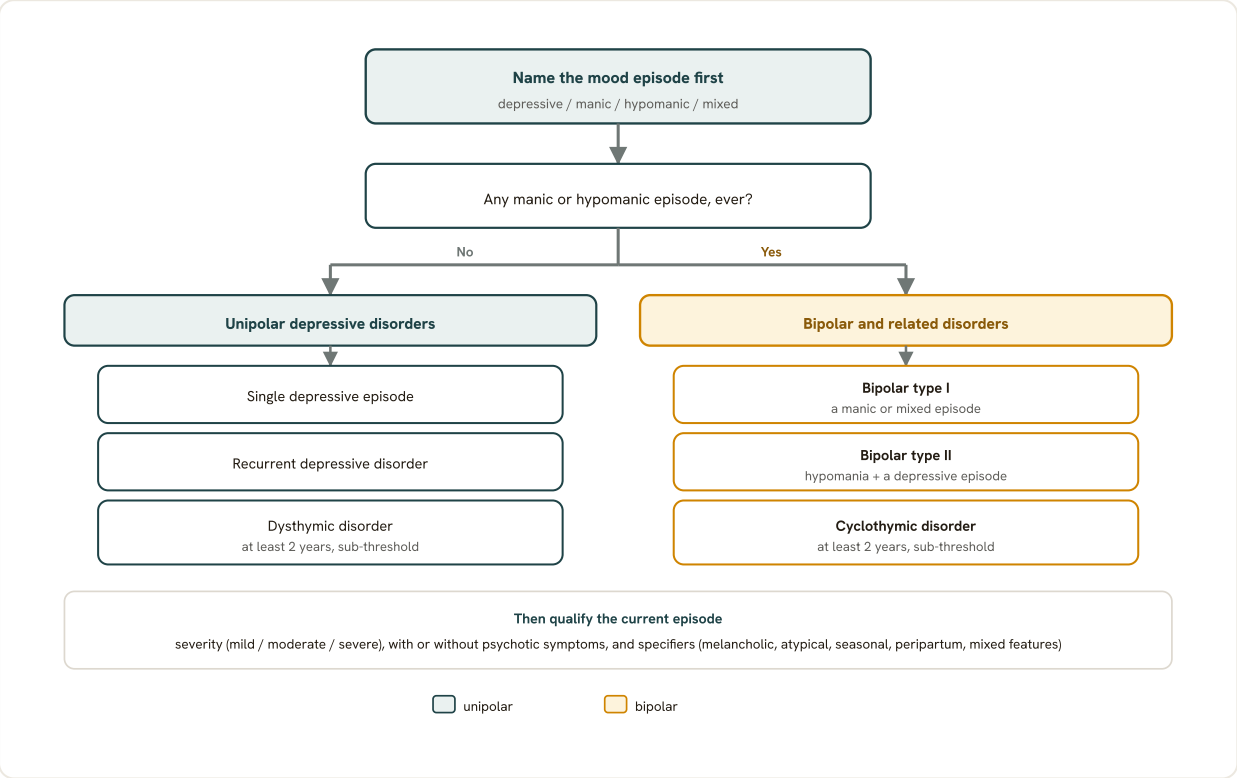


Fig 11.1 The ICD-11 episode-based mood-classification map. Name the current mood episode first, then split on polarity: any lifetime manic or hypomanic episode moves the patient into the bipolar column permanently, otherwise the illness is unipolar. The lifetime pattern of episodes then names the disorder,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

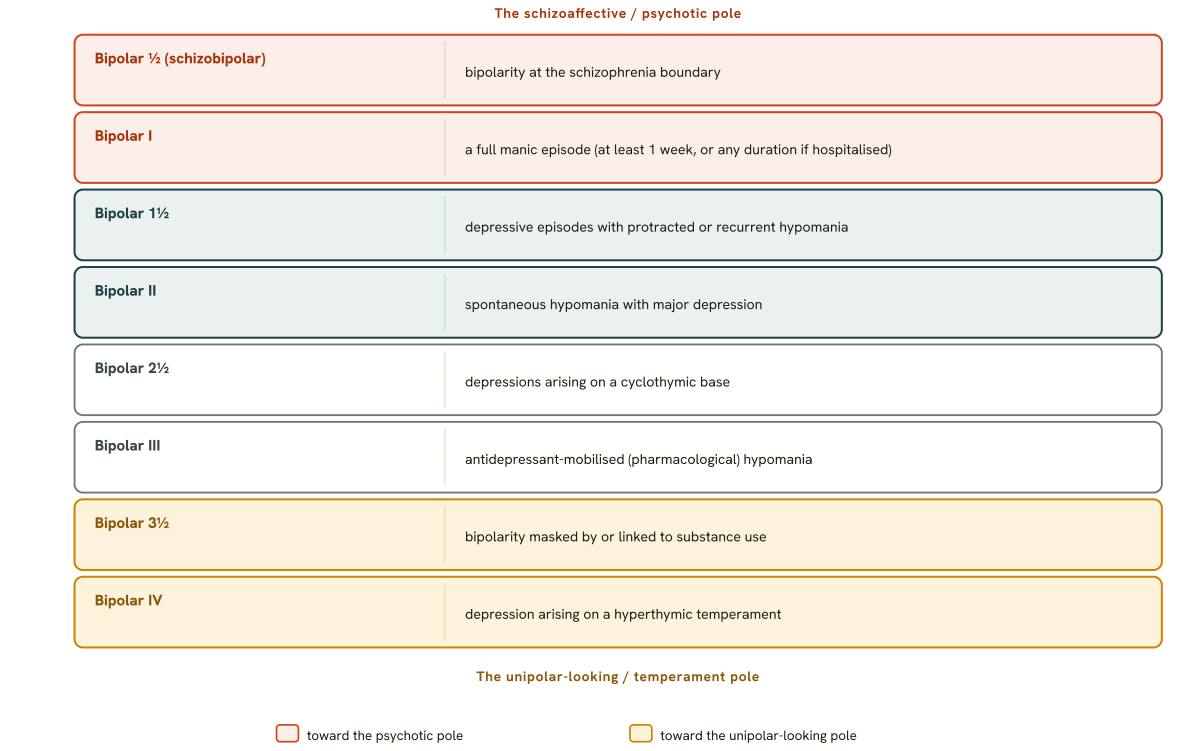


Fig 11.2 Akiskal's soft-bipolar spectrum, laid out before bipolar I proper. Read the fractions as rungs from the schizoaffective and psychotic pole at the top (bipolar one-half, then classic bipolar I) down through the temperament- and trigger-defined softer forms (protracted hypomania, spontaneous hypomania, 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.

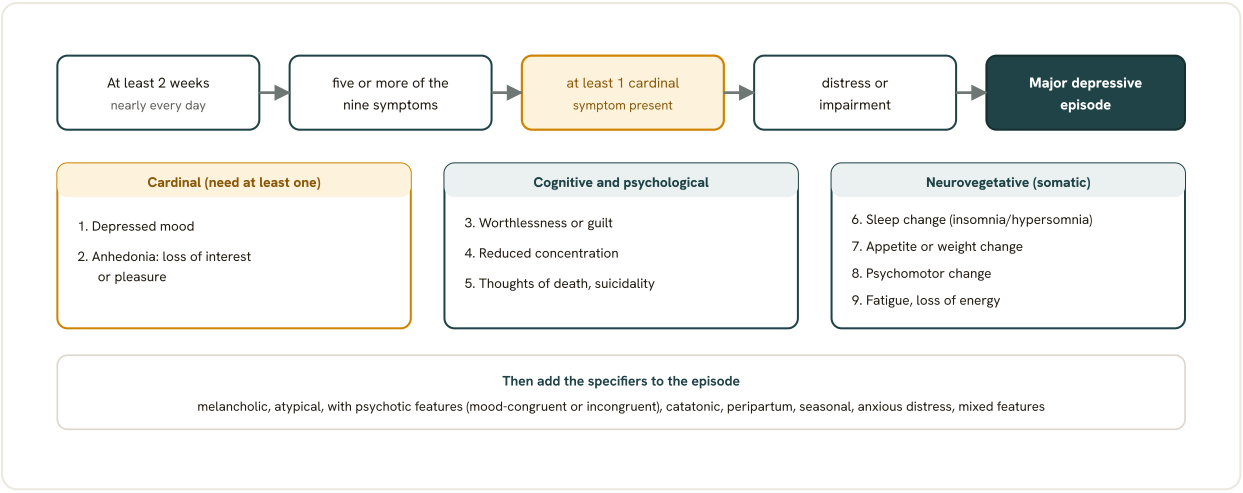


Fig 11.3 Major depressive disorder: the criteria gate and the specifier set. The episode needs at least two weeks, five or more of the nine symptoms including at least one cardinal symptom (depressed mood or anhedonia), and distress or impairment. The nine symptoms fall into a cardinal, a cognitive and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

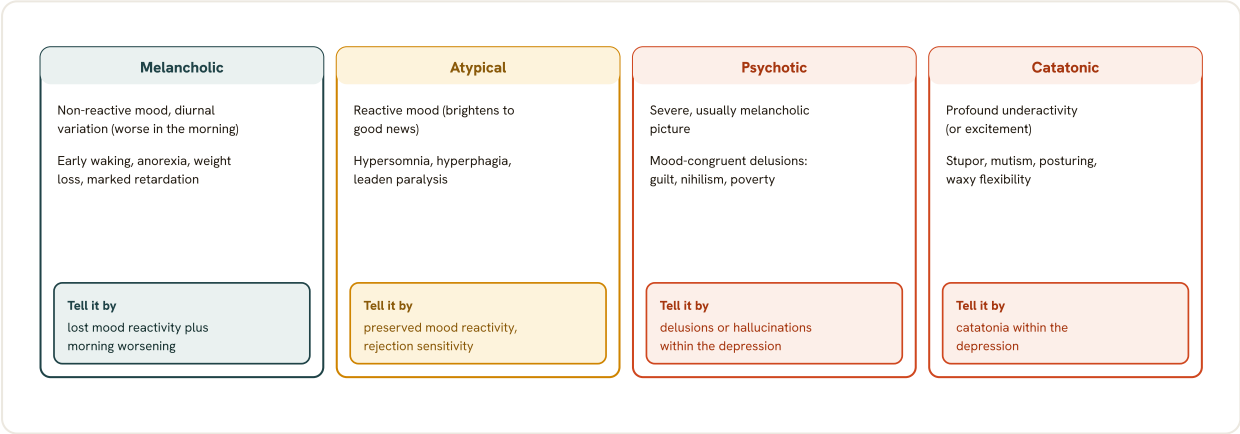


Fig 11.4 The depressive subtypes, keyed on the one feature that tells each apart. The pivotal contrast is mood reactivity: melancholic depression loses it (with morning worsening and early waking), atypical depression keeps it (with reversed vegetative signs and rejection sensitivity). Psychotic depression 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.

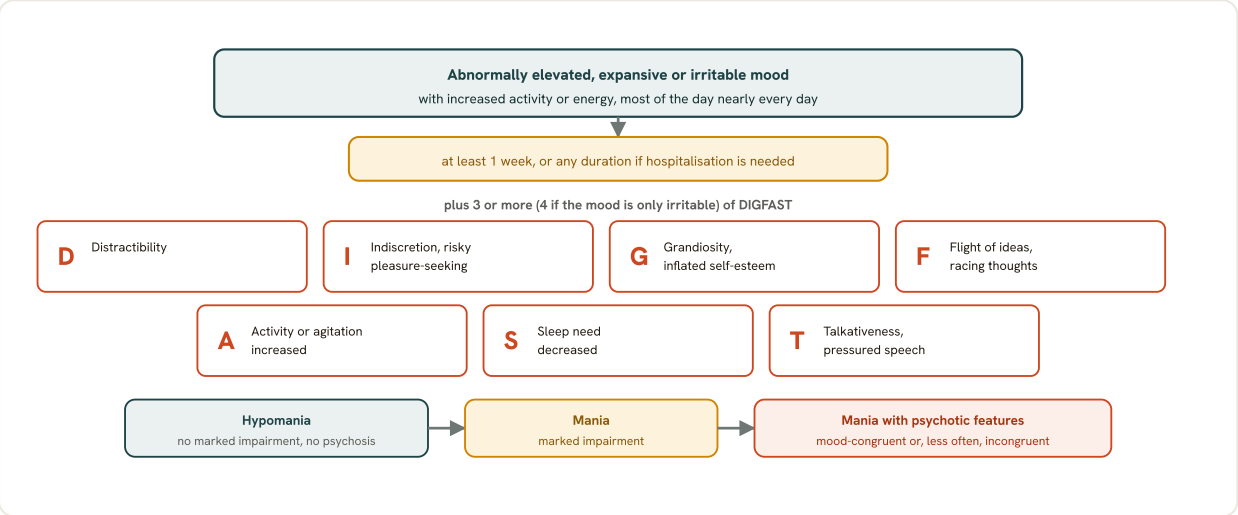


Fig 11.6 The manic episode. A distinct period of abnormally elevated, expansive or irritable mood with increased activity or energy, lasting at least one week (or any duration if hospitalisation is needed), plus three or more of the DIGFAST symptoms (four if the mood is only irritable), causing marked 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.

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

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.

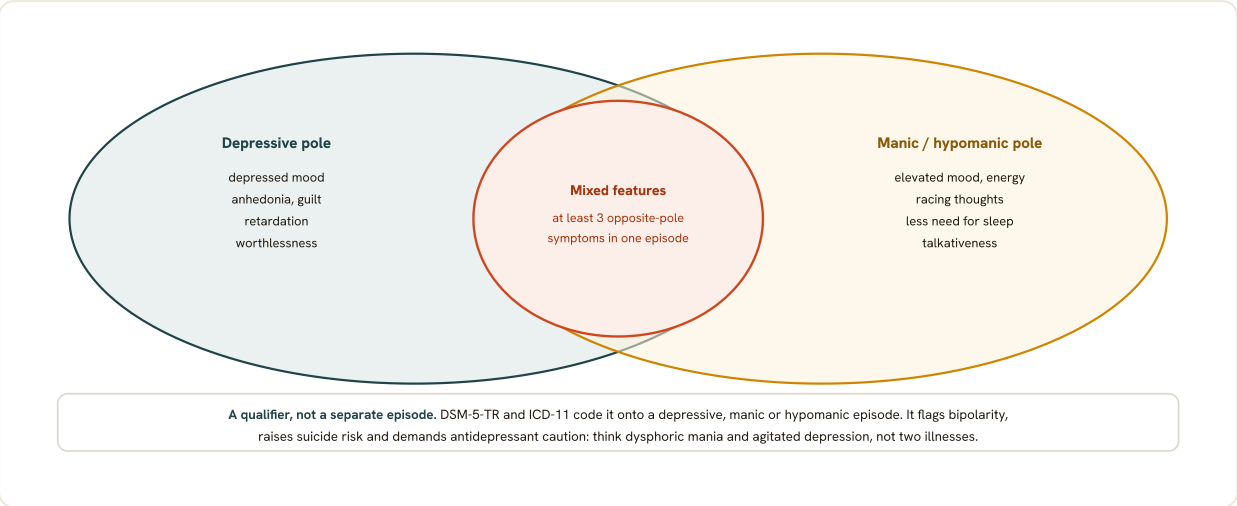


Fig 11.7 Mixed features: opposite-pole symptoms co-occurring within one episode. The DSM-5-TR "with mixed features" specifier needs at least three non-overlapping symptoms of the opposite pole and attaches to a depressive, manic or hypomanic episode rather than standing alone. The overlap is what separates 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 OPPOSITE-POLE SYMPTOMS (DSM-5-TR)	**most days** OF THE EPISODE	**at least 2 wk** ICD-11 MIXED EPISODE	**non-overlapping** 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	at least 2 months	commoner in women
IN TWELVE MONTHS	REMISSION DEMARCATING EPISODES	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.

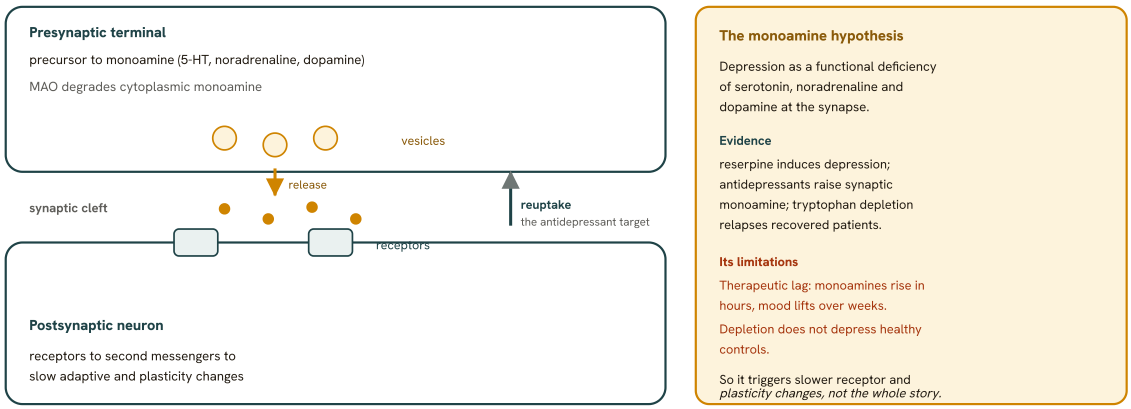


Fig 11.8 The monoamine hypothesis at the synapse, taught with its limits. A monoamine is synthesised, packaged, released into the cleft, and cleared by the reuptake transporter (the target of most antidepressants) and by MAO; the hypothesis holds that depression is a functional deficiency of serotonin, 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.

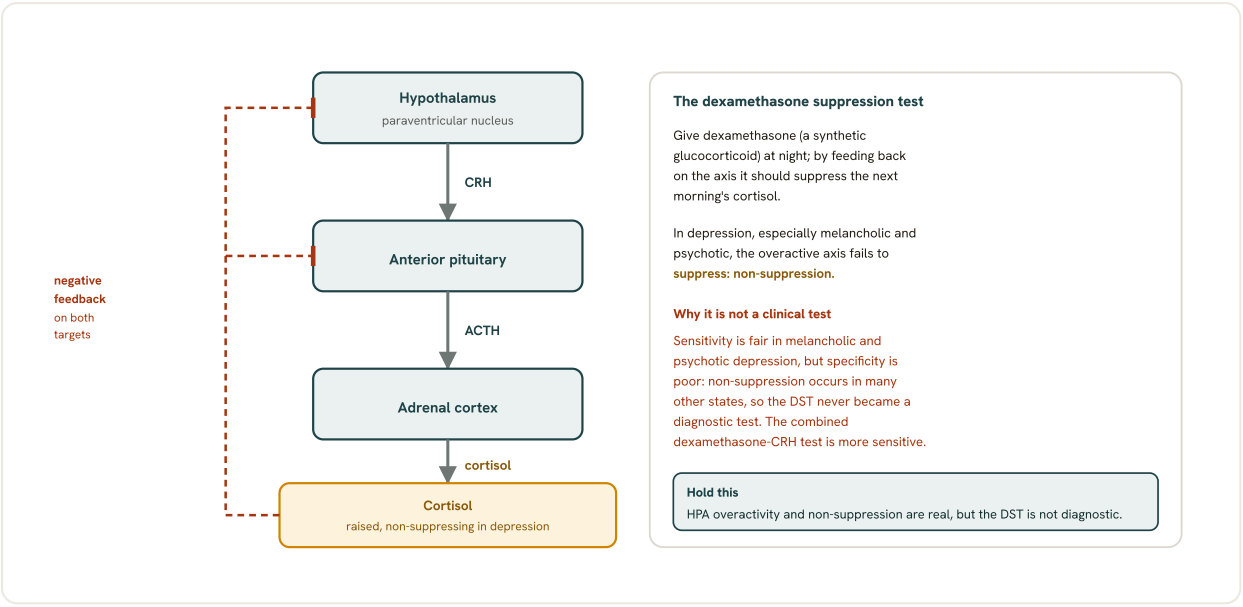


Fig 11.9 The HPA axis and the dexamethasone suppression test. CRH drives ACTH drives cortisol down the spine, and cortisol feeds back negatively on both the pituitary and the hypothalamus to switch the axis off. In depression the axis is overactive and the feedback is blunted, so dexamethasone fails 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.

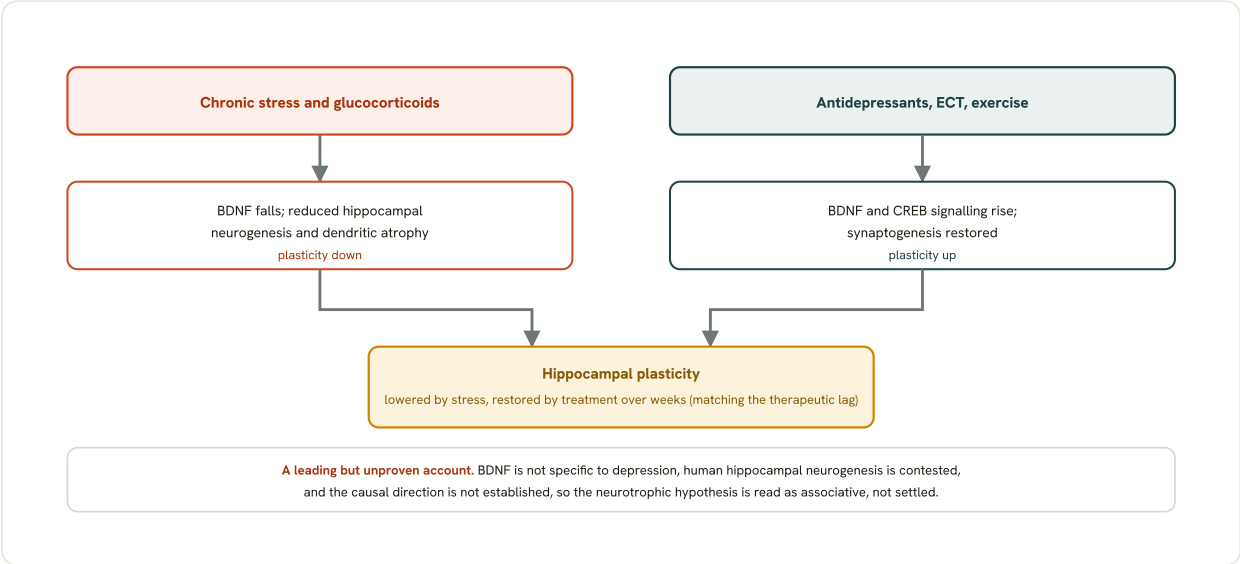


Fig 11.10 The neurotrophic hypothesis. Chronic stress and glucocorticoids lower BDNF and hippocampal neurogenesis, while antidepressants, ECT and exercise raise BDNF and CREB signalling and restore synaptogenesis; the two routes converge on hippocampal plasticity, which is reduced in depression and restored 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.

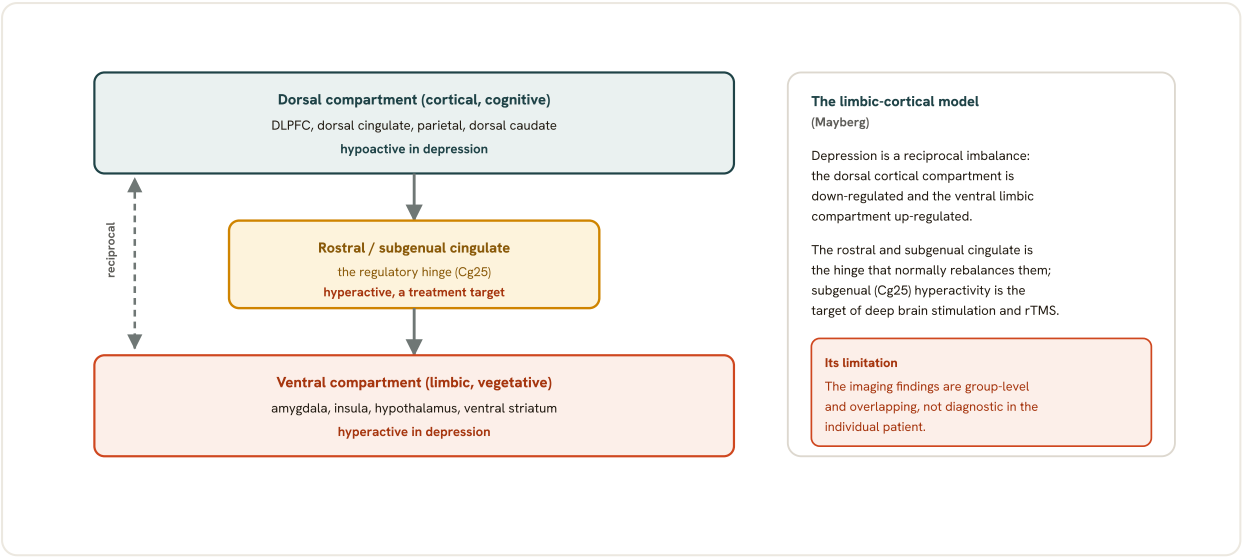


Fig 11.11 A schematic of the limbic-cortical circuit model of depression. The dorsal cortical compartment (cognitive) is down-regulated and the ventral limbic compartment (vegetative) up-regulated, and the two are reciprocally related. The rostral and subgenual cingulate is the hinge that normally rebalances 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.

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.

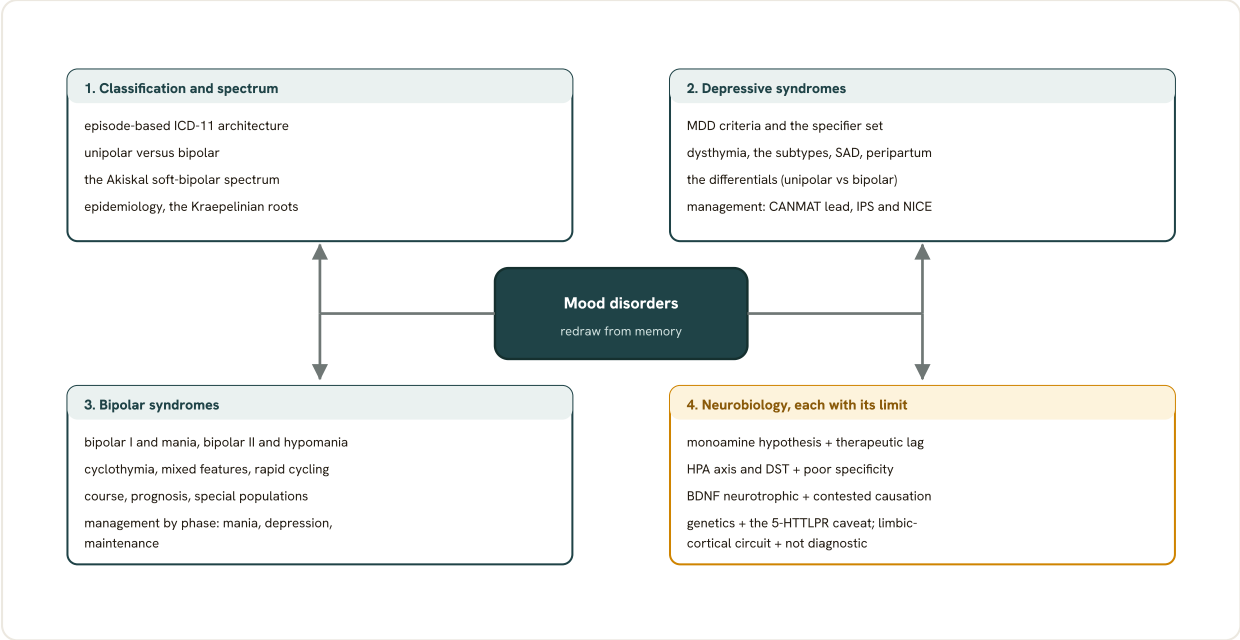


Fig 11.12 The whole-chapter synthesis map, to redraw from memory. Four branches hang off the mood-disorder core: the classification and the Akiskal spectrum; the depressive syndromes and their management; the bipolar syndromes and their phase-based management; and the neurobiology, where every hypothesis 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 11.12).
- **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

- **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

- **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

- **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

- **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.

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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.

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