WEAVE SPRINT · PAPER II

Mood Pharmacotherapy

The drug treatment of mood disorder in one document: the antidepressant classes with their mechanisms, doses, adverse effects and interactions; lithium and the mood stabilisers with their monitoring, toxicity and teratogenicity; and treatment resistance, augmentation and the special populations, every recommendation led by the CANMAT guidelines.

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Concept / rule Key number Trap

PAPER II

Mood disorders: pharmacotherapy

Four sections · one complete notes document

This material closes the mood block, gathering into one document the drug treatment of the depressive and bipolar disorders. The first band is **antidepressant pharmacotherapy**: the classification of the antidepressants and the action of each class at the synapse, the SSRIs, SNRIs, tricyclics, monoamine oxidase inhibitors, mirtazapine, bupropion and the newer multimodal agents with their pharmacology, adverse effects and interactions, serotonin syndrome and the discontinuation syndrome, the rapid-acting glutamatergic agents ketamine and esketamine, and how to choose an antidepressant and manage the phases of an acute depressive episode. The second band is **mood stabilisers and lithium**: lithium in depth, its mechanism, initiation, dosing, monitoring, toxicity and every organ-system effect and interaction and its use in pregnancy, then valproate, carbamazepine, lamotrigine and the antipsychotics used as mood stabilisers, and the guideline-anchored choice of stabiliser across acute mania and maintenance. The third band is **treatment resistance, augmentation and the special populations**: treatment-resistant depression and its staging, the augmentation ladder, depression in the elderly, the suicide-risk and pharmacological angle, ECT and neuromodulation and the psychotherapies in the algorithm, and the dedicated management of bipolar depression, bipolar mixed episodes and bipolar maintenance. The examinable skill is the safe, guideline-anchored choice and monitoring of every mood drug: which agent for which patient and phase, at what dose and serum level, with which adverse effect and interaction watched, and when to escalate.

HOW TO USE THESE NOTES

Read the four bands as one continuous account of how mood disorder is treated with medicines. The **antidepressant** band teaches each class at the synapse and then every agent with its dose range, its signature adverse effect and its key interaction, ending with how to choose and how to run the phases of treatment. The **mood stabiliser** band gives lithium the depth it carries in the examination, its therapeutic window, its monitoring schedule, its toxicity and its organ effects, then valproate, carbamazepine, lamotrigine and the atypicals, and the guideline choice of stabiliser by phase. The **treatment resistance** band teaches the augmentation ladder and the special populations and closes with three dedicated bipolar-management topics: bipolar depression, bipolar mixed episodes and maintenance. Every management recommendation is guideline-anchored, led by the CANMAT guidelines with the Indian Psychiatric Society, BAP and NICE positions stated, on the where-to-treat, target-by-phase, modes-of-treatment spine; every named agent ends with a **Good to remember** box giving the mechanism, the signature adverse effect or interaction, and the one dose or first-line indication. Figures declare one axis and code it in colour: **petrol** marks structure and the neutral case, **coral** marks the trap or the danger, and **marigold** highlights the number to hold. Several boundaries are worth stating up front: the mood-disorder classification, the depressive and bipolar clinical syndromes and the guideline-anchored management plan are taught in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes and are cross-referenced here rather than repeated; the monoamine pathway anatomy, the receptor systems and CYP metabolism live in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the technique of electroconvulsive therapy and of rTMS, VNS and DBS lives in the ECT and neurostimulation notes, and only their place in the algorithm is taught here; the full clinical suicide risk assessment lives in the Somatic-symptom, sexual, impulse-control disorders and suicide notes; the wider emergency and perinatal frames live in the Perinatal/women's mental health and emergency psychiatry notes; and the psychotherapy technique lives in the Psychotherapies, clinical assessment, MSE and nosology notes. This is doctor-facing revision, so the full technical vocabulary is used, brand names lead with the Indian brand, and every dose, serum level, monitoring interval, teratogenicity fact and first-line recommendation is verified against a source or omitted and flagged.

Antidepressant pharmacotherapy

1 . Classifying the antidepressants and the treatment algorithm

This is the opening map of the whole pharmacotherapy block. Two schemas orient everything that follows: a **class map** of the antidepressants and mood stabilisers ordered by what each drug does at the synapse, and a phase-based **treatment algorithm** that tells you which agent, in which phase, on which line. Get both in your head first and every later topic (the SSRIs, lithium and its monitoring, valproate, the mood-stabiliser and antidepressant-selection topics, the emergencies, treatment resistance) becomes a slot to fill, not a list to memorise cold.

The board rewards a resident who reasons in two moves: **first** name the drug by its primary synaptic action, **then** place the patient in a phase and polarity and treat accordingly. Lead with

the CANMAT guidelines (CANMAT 2016 for depression, CANMAT 2018 for bipolar disorder), then state the Indian Psychiatric Society (IPS) position and where the BAP and NICE agree. The mood classification, the depressive and bipolar syndromes, the criteria and the guideline-anchored management PLAN are owned by, and cross-referred to, the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; this block owns the pharmacology, the doses, the monitoring and the algorithm.

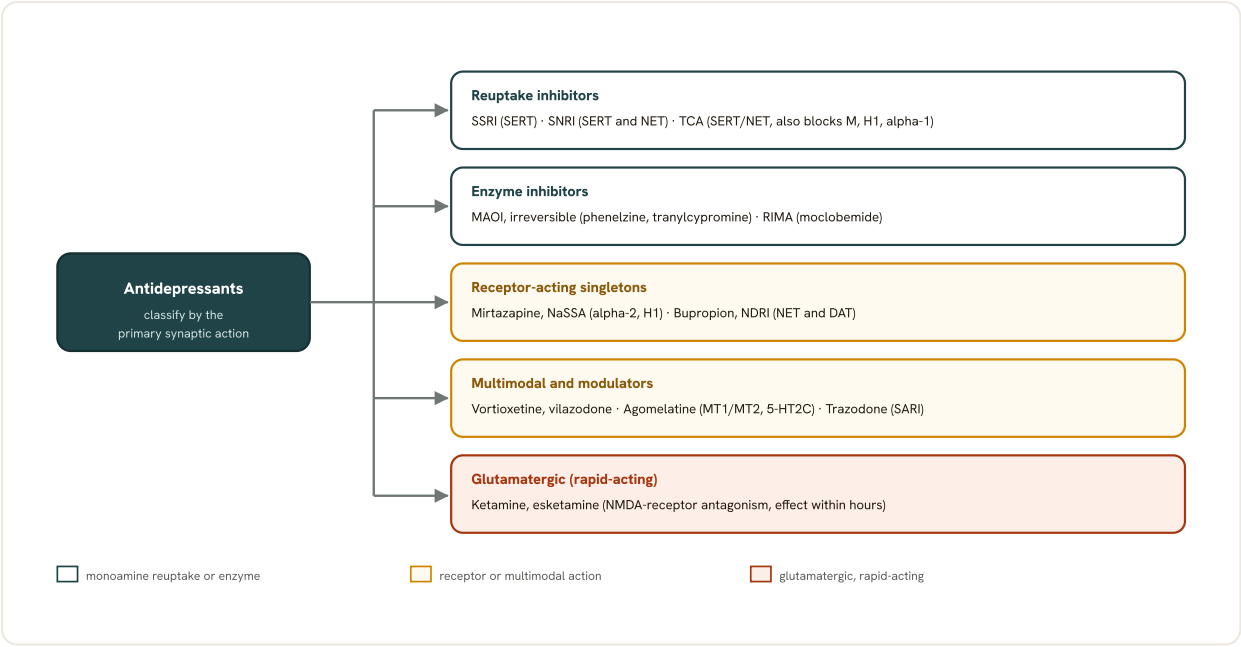

Fig 12.1 The antidepressants classified by their primary synaptic action, which predicts both tolerability and the dangerous interactions. The reuptake inhibitors (SSRI, SNRI, TCA) and the enzyme inhibitors (MAOI, RIMA) act on the monoamine supply; the receptor-acting singletons (mirtazapine, bupropion) and the multimodal and modulator agents (vortioxetine, agomelatine, trazodone) act at specific receptors; and the glutamatergic agents (ketamine, esketamine) act at the NMDA receptor with an effect within hours.

1.1 The organising principle: classify by mechanism, then treat by phase

Two schemas, in order. The **classification of antidepressants** is by **primary synaptic action**: which transporter or receptor the drug primarily hits, and therefore which monoamine it raises and which adverse effects and interactions follow. That single fact predicts most of the tolerability profile and most of the dangerous interactions. The **treatment algorithm** is the second schema: once the drug is classified, the patient is treated by **phase** (acute to remission, then continuation, then maintenance) and by **polarity** (unipolar depression versus bipolar disorder, which are treated with different classes). The monoamine pathway anatomy, the receptor systems and the CYP metabolism that sit underneath the mechanisms are cross-referred to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

RULE **Classify an antidepressant by its synaptic action, then treat by phase.** Mechanism predicts the adverse-effect and interaction set; phase and polarity dictate the agent.

TRAP **Treating every depression the same regardless of phase or polarity.** A bipolar depression treated as a unipolar depression, or a patient stopped at response instead of remission, is the classic examinable error.

1.2 The class map: antidepressants by primary action

The **class map** groups every antidepressant by what it primarily does at the synapse (Stahl 2021; Maudsley 2021). The reuptake-inhibitor families come first, then the receptor-acting families, then the enzyme inhibitors, then the multimodal and glutamatergic agents. The SSRIs (selective serotonin reuptake inhibitors: escitalopram, sertraline, fluoxetine, paroxetine, citalopram, fluvoxamine) block the serotonin transporter (SERT). The SNRIs (serotonin-noradrenaline reuptake inhibitors: venlafaxine, desvenlafaxine, duloxetine) block both SERT and the noradrenaline transporter (NET). The tricyclic antidepressants (amitriptyline, imipramine, clomipramine, nortriptyline) block SERT and NET but additionally antagonise muscarinic, histamine H1 and alpha-1 receptors, which is why they carry the anticholinergic, sedative, orthostatic and cardiotoxic burden and are dangerous in overdose. The monoamine oxidase inhibitors (MAOIs: phenelzine, tranylcypromine as irreversible; moclobemide as the reversible RIMA) inhibit the enzyme that degrades monoamines, raising serotonin, noradrenaline and dopamine, and carry the tyramine (cheese) and serotonergic interaction hazards. The receptor-acting singletons are the NaSSA mirtazapine (a noradrenergic and specific serotonergic antidepressant: alpha-2 autoreceptor and heteroreceptor antagonist plus H1 blockade) and the NDRI bupropion (a noradrenaline-dopamine reuptake inhibitor with no direct serotonergic action). The multimodal and serotonin-modulator agents are vortioxetine (SERT inhibition plus 5-HT1A agonism and 5-HT3/5-HT7 antagonism), agomelatine (melatonin MT1/MT2 receptor agonist plus 5-HT2C antagonist) and trazodone (a serotonin antagonist and reuptake inhibitor, SARI). The glutamatergic agents are ketamine and its S-enantiomer esketamine, NMDA-receptor antagonists that act rapidly and outside the monoamine framework.

CLASS	PROTOTYPE AGENTS	PRIMARY SYNAPTIC ACTION	SIGNATURE TO HOLD
SSRI	escitalopram, sertraline, fluoxetine, paroxetine, citalopram, fluvoxamine	**Selective SERT (serotonin transporter) blockade**	First-line for tolerability and overdose safety
SNRI	venlafaxine, desvenlafaxine, duloxetine	**SERT plus NET (noradrenaline transporter) blockade**	Dose-dependent blood-pressure rise (venlafaxine)
Tricyclic (TCA)	amitriptyline, imipramine, clomipramine, nortriptyline	**SERT/NET blockade plus muscarinic, H1, alpha-1 antagonism**	Anticholinergic load, cardiotoxic, lethal in overdose
MAOI (irreversible)	phenelzine, tranylcypromine	**Irreversible inhibition of monoamine oxidase**	Tyramine (cheese) reaction, serotonergic interactions

CLASS	PROTOTYPE AGENTS	PRIMARY SYNAPTIC ACTION	SIGNATURE TO HOLD
RIMA	moclobemide	**Reversible inhibition of MAO-A**	Far lower tyramine risk than irreversible MAOIs
NaSSA	mirtazapine	**Alpha-2 autoreceptor/heteroreceptor antagonism plus H1 blockade**	Sedation, appetite and weight gain; useful with insomnia
NDRI	bupropion	**Noradrenaline and dopamine reuptake inhibition**	Activating, no sexual dysfunction; lowers seizure threshold
Multimodal (serotonin modulator)	vortioxetine	**SERT inhibition plus 5-HT1A agonism, 5-HT3/5-HT7 antagonism**	Nausea commonest; pro-cognitive claims
Melatonergic	agomelatine	**MT1/MT2 agonist plus 5-HT2C antagonist**	Sleep-promoting; monitor liver function
SARI	trazodone	**5-HT2 antagonism plus weak SERT inhibition**	Sedating; priapism risk; used for insomnia
Glutamatergic	ketamine, esketamine	**NMDA-receptor antagonism**	Rapid action; dissociation and blood-pressure rise

Fig 12.1 in prose: the antidepressant class map keyed to primary synaptic action. The highlighted mechanism cell is the fact that predicts each class's tolerability and its dangerous interactions.

GOOD TO REMEMBER

- **SSRIs:** block SERT selectively; first-line for MDD; hold escitalopram **10 to 20 mg/day** as the type case (CANMAT 2016).
- **SNRIs:** block SERT and NET; venlafaxine raises blood pressure dose-dependently; hold venlafaxine **75 to 225 mg/day** (CANMAT 2016).
- **TCAs:** block SERT/NET but add muscarinic, H1 and alpha-1 antagonism, so anticholinergic, sedating and cardiotoxic; lethal in overdose; second-line (CANMAT 2016).
- **MAOIs:** inhibit monoamine oxidase; signature hazard is the tyramine (cheese) reaction and serotonergic interactions; reserved third-line (CANMAT 2016).
- **Mirtazapine (NaSSA):** alpha-2 antagonist plus H1 blockade; signature is sedation and weight gain; first-line, useful with insomnia; hold **15 to 45 mg/day** (CANMAT 2016).
- **Bupropion (NDRI):** noradrenaline-dopamine reuptake inhibitor; activating, spares sexual function, lowers seizure threshold; first-line; hold **150 to 300 mg/day** (CANMAT 2016).
- **Vortioxetine (multimodal):** SERT inhibition plus receptor modulation; nausea commonest; first-line; hold **10 to 20 mg/day** (CANMAT 2016).
- **Agomelatine (melatonergic):** MT1/MT2 agonist plus 5-HT2C antagonist; sleep-promoting; monitor LFTs; first-line; hold **25 to 50 mg/day** (CANMAT 2016).
- **Trazodone (SARI):** 5-HT2 antagonist with weak reuptake inhibition; sedating, priapism risk; second-line, common as a hypnotic (CANMAT 2016).
- **Ketamine/esketamine (glutamatergic):** NMDA antagonists; rapid antidepressant and anti-suicidal effect; monitor blood pressure and dissociation; adjunct in treatment resistance (CANMAT 2016).

PEARL

The whole tolerability story of the tricyclics is off-target receptor blockade, not the reuptake inhibition. Muscarinic antagonism gives the dry mouth, constipation and urinary hesitancy; H1 gives the sedation and weight gain; alpha-1 gives the postural drop; and sodium-channel blockade gives the overdose cardiotoxicity. The SSRIs are "clean" precisely because they do none of this.

1.3 The mood stabilisers alongside the class map

The class map does not stop at the antidepressants. The bipolar arm of this block is built on the **mood stabilisers**: lithium (the archetype, with anti-manic, prophylactic and specific anti-suicide effect), the anticonvulsants valproate (sodium valproate and divalproex), carbamazepine (and its keto-analogue oxcarbazepine) and lamotrigine (the depression-predominant stabiliser), and the atypical antipsychotics used as mood stabilisers (quetiapine, olanzapine, aripiprazole, risperidone, asenapine, cariprazine, lurasidone). Each is a slot expanded later: lithium initiation, monitoring and toxicity, the valproate topic and its teratogenicity, the lamotrigine titration and the stabiliser-selection topic all belong downstream. The deep antipsychotic pharmacology, including the receptor profiles and the extrapyramidal and metabolic adverse effects, is cross-referred to the Schizophrenia: management, antipsychotics and adverse effects notes.

GOOD TO REMEMBER

- **Lithium:** the archetypal mood stabiliser; first-line for acute mania and maintenance with specific anti-suicide evidence; hold maintenance level **0.6 to 1.0 mmol/L** (CANMAT 2018).
- **Valproate/divalproex:** broad-spectrum anticonvulsant stabiliser; first-line for acute mania; signature hazard is teratogenicity (neural tube defects), so avoid in women of childbearing potential; hold serum **50 to 100 microg/mL** (CANMAT 2018).
- **Carbamazepine:** anticonvulsant stabiliser; signature is enzyme induction, hyponatraemia and the HLA-B*1502 Stevens-Johnson risk in at-risk Asian ancestry; second-line (CANMAT 2018).
- **Lamotrigine:** the depression-predominant stabiliser; first-line for bipolar depression and maintenance; signature hazard is the rash, so titrate slowly; target a minimum of **200 mg/day** starting at 25 mg (CANMAT 2018).
- **Atypical antipsychotics as stabilisers:** quetiapine, olanzapine, aripiprazole, risperidone, asenapine, cariprazine, lurasidone; first-line across mania, bipolar depression and maintenance; signature is metabolic burden (CANMAT 2018).

1.4 The treatment algorithm: the LOCUS-FOCUS-MODUS spine

Every management plan in this block runs on one spine. **LOCUS** is *where*: outpatient (or the day care centre) is the default, and admission is reserved for high suicide risk, psychotic features, severe self-neglect, or the need for inpatient-level treatment such as ECT. **FOCUS** is *the target by phase*: what you are trying to achieve right now. **MODUS** is *the modes of treatment*: which pharmacological and psychological modes each guideline recommends first. This is not a mnemonic for its own sake; it is the order in which a board answer is constructed. Decide the locus, name the phase, then list the guideline-first modes for that phase. The full clinical suicide risk assessment and safety planning that set the admission threshold are cross-referred to the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

RULE **LOCUS then FOCUS then MODUS orders every plan.** Where to treat, which phase you are targeting, then which mode is first-line for that phase.

1.5 FOCUS for depression: acute, continuation, maintenance

The unipolar depression skeleton is three phases (CANMAT 2016; BAP 2015; Gautam et al. 2017). The **acute** phase runs from the outset to **remission** (not merely response): start one first-line second-generation antidepressant, review every **1 to 2 weeks**, and judge the trajectory by **2 to 4 weeks**, optimising the dose or switching if there is no improvement. The **continuation** phase then holds the same agent at the **acute treatment dose** for **6 to 9 months** after remission, to lock in the remission and prevent relapse. The **maintenance** phase extends treatment to **2 years or longer** for recurrent or high-risk illness to prevent recurrence, with CBT or MBCT as the psychological relapse-prevention modes. The individual phase-by-phase management plan, the augmentation and the psychotherapy detail are owned by the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; here it is the orienting skeleton only.

1 to 2 wk	2 to 4 wk	6 to 9 mo	2 years+
ACUTE REVIEW INTERVAL	JUDGE ACUTE RESPONSE TRAJECTORY	CONTINUATION AFTER REMISSION	MAINTENANCE IF RECURRENT

1.6 FOCUS for bipolar disorder: mania, depression, maintenance

The bipolar skeleton is a different triad because the classes are different (CANMAT 2018; Grover and Avasthi 2017). **Acute mania** is treated with lithium, quetiapine, divalproex, aripiprazole, asenapine, paliperidone, risperidone or cariprazine as first-line monotherapy, or an atypical antipsychotic plus lithium or divalproex in severe presentations; any antidepressant is discontinued. **Bipolar depression** is treated with quetiapine, lurasidone (with or without lithium/divalproex), lithium, lamotrigine or the olanzapine-fluoxetine combination as first-line, and is *not* treated with an antidepressant alone. **Bipolar maintenance** continues the agent that worked acutely, with lithium, quetiapine, divalproex, lamotrigine, asenapine or aripiprazole as first-line monotherapy and a maintenance lithium level of **0.6 to 1.0 mEq/L**. Each limb is expanded later in the block; here it is the skeleton that sits beside the depression skeleton.

TRAP **Giving an antidepressant alone in a bipolar depression.** It risks a manic switch and rapid cycling; the first-line agents are quetiapine, lurasidone, lithium, lamotrigine or the olanzapine-fluoxetine combination (CANMAT 2018).

1.7 The Indian Psychiatric Society, BAP and NICE positions

The Indian Psychiatric Society Clinical Practice Guidelines are the Indian reference and the guideline most likely named in Indian postgraduate examinations. For depression, the **IPS guidelines** (Gautam et al. 2017) name the SSRIs as first-line on tolerability and overdose safety, with TCAs, mirtazapine, bupropion and venlafaxine as further options, and continue treatment after remission with a maintenance phase for recurrent illness. For bipolar disorder, the IPS guidelines (Grover and Avasthi 2017) direct that antidepressants are not used as monotherapy in bipolar depression, prefer bupropion and avoid paroxetine if an antidepressant is added, and name lithium and valproate as the best-evidenced maintenance agents. The BAP and NICE converge on the same spine: SSRIs and other newer agents are first-line for depression because they are better tolerated and safer in overdose (BAP 2015), and NICE names lithium as the first-line long-term treatment for bipolar disorder (NICE 2014). Where the IPS position on a specific point could not be confirmed against the parsed library it is flagged rather than invented.

INDIA

Every drug in this block is available in India; this chapter names no brand, and the Indian brand for each agent, Indian brand first, is given in the individual drug topics that follow (for example escitalopram, sertraline, lithium carbonate, sodium valproate, lamotrigine, quetiapine). The Indian Psychiatric Society Clinical Practice Guidelines are the guideline to cite first in Indian postgraduate examinations: Gautam et al. for depression and Grover and Avasthi for bipolar disorder. Lithium remains a mainstream first-line mood stabiliser in Indian practice, and ECT is widely available and heavily used for severe, psychotic, suicidal or treatment-resistant mood illness across Indian teaching hospitals.

1.8 The master mnemonic: chaining the chapter

One master **mnemonic** chains the four movements of this block so nothing is dropped: the antidepressant classes, then lithium and the mood stabilisers, then the emergencies, then

treatment resistance. Hold it as **"A SNoM LiVeS, then CALM the STORM, then climb the LADDER"**, unpacked below. It is a scaffold, not the content: each capitalised beat is a downstream topic.

MNEMONIC

A-SNoM-Li-VeS then CALM the STORM then the LADDER

The four movements of the pharmacotherapy block. **Antidepressant classes** (A): SSRI, SNRI, NaSSA/NDRI, MAOI, Multimodal (A SNoM). **Mood stabilisers**: Lithium, Valproate, lamotrigine and the Stabiliser antipsychotics (LiVeS). **Emergencies**: serotonin syndrome and lithium toxicity (CALM the STORM). **Treatment resistance**: the switch-augment-combine-neuromodulate ladder (the LADDER). Classify first (A SNoM LiVeS), then know what goes wrong (CALM the STORM), then know the next step when first-line fails (the LADDER).

MOVEMENT	WHAT IT HOLDS	WHERE IT IS EXPANDED
Antidepressant classes	SSRI, SNRI, TCA, MAOI, NaSSA, NDRI, multimodal, SARI, glutamatergic	**The SSRI, SNRI, TCA/MAOI and newer-agent topics in this block**
Lithium and mood stabilisers	Lithium, valproate, carbamazepine, lamotrigine, atypicals	**Lithium initiation/monitoring/toxicity, valproate, lamotrigine, stabiliser-selection topics**
Emergencies	Serotonin syndrome, lithium toxicity	**The emergencies topics in this block; wider acute management cross-referred to the Perinatal/women's mental health and emergency psychiatry notes**
Treatment resistance	Switch, augment, combine, neuromodulate	**The treatment-resistant-depression ladder topic**

The master mnemonic mapped to the four downstream movements of the block; each highlighted cell names where that movement is taught in full.

GOOD TO REMEMBER

- **Classify by mechanism:** name the antidepressant by its primary synaptic action (SERT, NET, receptor, enzyme, NMDA) before you prescribe.
- **The phases are acute, continuation, maintenance:** aim remission, then hold at the acute dose, then extend for recurrence.
- **LOCUS-FOCUS-MODUS orders every plan:** decide where, name the phase, list the guideline-first modes for that phase.
- **Polarity matters:** unipolar depression and bipolar disorder use different classes; do not give an antidepressant alone in bipolar depression.
- **Guideline order:** lead with CANMAT, then state the Indian Psychiatric Society, BAP and NICE positions.

WORKED EXAMPLE

A 30-year-old man presents with a moderate depressive episode, no psychosis, no active suicidal plan and no history of mania. Working the two schemas: the class map says a first-line second-generation antidepressant (an SSRI such as escitalopram), classified as a SERT blocker; the algorithm says LOCUS outpatient, FOCUS the acute phase aiming at remission, MODUS one first-line agent with measurement-based review at 2 weeks and a trajectory judgement by 2 to 4 weeks. On reaching remission by month 3, the continuation phase holds the same agent at the same dose for 6 to 9 months. Had the same man reported a past manic episode, polarity would flip the plan entirely: the class map moves to the mood stabilisers and the bipolar-depression first-line agents, and an antidepressant alone would be a trap.

HOLD THIS

Classify the antidepressant by its primary synaptic action, then treat by phase (acute to remission, continuation 6 to 9 months at the acute dose, maintenance 2 years or longer if recurrent) and by polarity (unipolar and bipolar use different classes), on the LOCUS-FOCUS-MODUS spine, leading with CANMAT.

2 . Selective serotonin reuptake inhibitors

The **selective serotonin reuptake inhibitor** class is the first-line antidepressant group and the single most-prescribed drug family in psychiatry, so the board expects the mechanism, the individual agents with their doses, and the whole adverse-effect set at your fingertips. The organising truth the examiner rewards: the members of the **ssri** class are broadly equal in antidepressant efficacy and differ mainly in **half-life**, **cytochrome interactions** and **adverse-effect emphasis**, not in how well they lift mood (Maudsley 2021; Stahl 2021). This topic teaches the pharmacology; the guideline-anchored choice of which antidepressant, and the discontinuation and serotonin-syndrome detail, are cross-referred where relevant.

Learn each agent by its one distinguishing feature (the long half-life of **fluoxetine**, the QTc ceiling of **escitalopram**, the discontinuation burden of **paroxetine**), then hang the shared class adverse effects on top. The dosing anchors are verified against Stahl's Prescriber's Guide and the Maudsley (Stahl 2021; Maudsley 2021); the monoamine-pathway anatomy and cytochrome metabolism underneath all of this belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

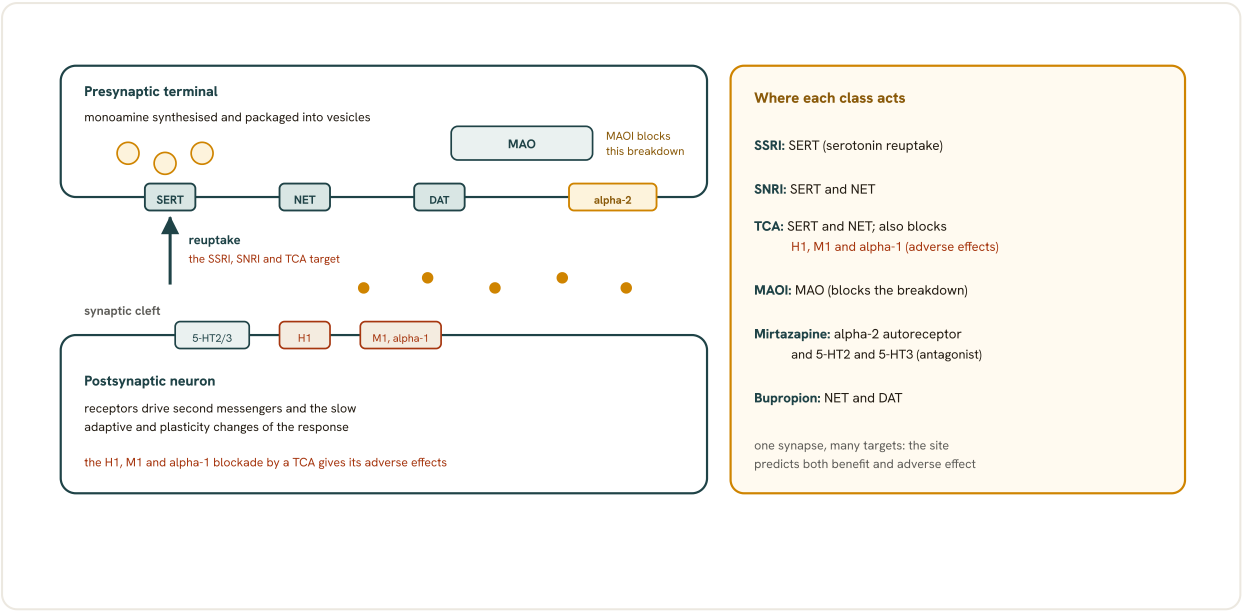

Fig 12.2 The monoamine synapse and where each antidepressant class acts. The reuptake transporters (SERT, NET, DAT) and the enzyme MAO clear the monoamine, and the post-synaptic and autoreceptors shape the signal. The SSRIs block SERT; the SNRIs block SERT and NET; the TCAs block both and, off-target, H1, M1 and alpha-1 (their adverse effects); the MAOIs block MAO; mirtazapine blocks the alpha-2 autoreceptor and 5-HT2/5-HT3; and bupropion blocks NET and DAT. The site of action predicts both the benefit and the adverse-effect profile.

2.1 Mechanism: SERT blockade, then receptor adaptation

The acute action. Every SSRI blocks the presynaptic serotonin transporter (**SERT**, the SLC6A4 protein), the pump that clears serotonin from the synapse back into the neuron. Blocking SERT raises **synaptic serotonin**, which is the immediate pharmacological effect and happens within hours of the first dose (Stahl 2021). Yet the antidepressant benefit does not appear for weeks, and that gap is the key teaching point.

The therapeutic lag. The initial rise in serotonin first stimulates somatodendritic 5-HT1A autoreceptors at the cell body, which shut down neuronal firing and blunt the expected increase in serotonin in the projection fields. Only with continued dosing do these autoreceptors **desensitise and downregulate**, after which firing resumes, serotonin release in the forebrain rises, and downstream postsynaptic receptor adaptation delivers the mood effect. This slow receptor adaptation, not the transporter block itself, is why the clinical response takes about 2 to 4 weeks to build (Stahl 2021; Companion 2010).

RULE **SERT block is immediate; the antidepressant effect is not.** The therapeutic lag reflects 5-HT1A autoreceptor desensitisation, so give an adequate trial before judging efficacy.

2.2 The class as a whole: what "selective" and "equal efficacy" mean

Selective. The SSRIs are highly potent and selective inhibitors of SERT with little direct action on noradrenaline or dopamine transporters and, unlike the tricyclics, little affinity for muscarinic, histaminergic or alpha-adrenergic receptors, which is why they are far safer in overdose and better tolerated (Companion 2010). Sertraline is the partial exception, with a mild dopamine reuptake effect at the top of its range.

Equal efficacy, different profiles. Head-to-head, no SSRI is convincingly more effective than another for major depression; the choice is driven by half-life, cytochrome interactions, and the adverse-effect emphasis of each drug (Maudsley 2021). That single sentence answers most "which SSRI and why" viva questions.

2.3 The individual agents: doses and distinguishing features

Six agents matter. The table gives the verified adult dose range with the unit in the header; the prose gives the one feature that makes each one examinable. All start at or near the minimum effective dose and are given once daily (fluvoxamine often divided).

SSRI (INDIAN BRAND)	DOSE (MG/DAY)	HALF-LIFE	DISTINGUISHING FEATURE	KEY CYP EFFECT
Fluoxetine (Fludac)	**20 to 80**	Parent 2 to 3 days; norfluoxetine ~2 weeks	Longest half-life, activating, self-tapering on stopping	Inhibits CYP2D6 and CYP3A4
Sertraline (Serta, Daxid)	50 to 200	~26 hours	**Broadest first choice; mild dopamine effect; prominent GI upset/diarrhoea**	Weak CYP2D6 inhibitor
Escitalopram (Nexito, S-Citadep)	10 to 20	27 to 32 hours	**Cleanest, fewest interactions; dose-dependent QTc**	Minimal CYP effect
Citalopram	20 to 40	~33 hours	Racemate of escitalopram; QTc cap at 40 (20 in the elderly / 2C19 inhibition)	Weak CYP2D6 inhibitor
Paroxetine (Pexep)	20 to 50	~21 hours (short)	**Anticholinergic, weight gain, worst discontinuation, avoid in pregnancy**	Potent CYP2D6 inhibitor
Fluvoxamine	100 to 300	~13 to 22 hours	OCD workhorse; sedating; no active metabolite	Potent CYP1A2 inhibitor

The six SSRIs with verified adult dose ranges (Stahl 2021), half-lives and the one feature each is tested on; the highlighted cell is the board discriminator for that drug. Doses are for adult depression.

Fluoxetine (Fludac). The prototype. Its very long half-life (parent 2 to 3 days, active metabolite norfluoxetine about 2 weeks) means it effectively self-tapers and rarely causes a discontinuation syndrome, but also means a 5-week washout before an MAOI. It is the most **activating** SSRI and inhibits both CYP2D6 and CYP3A4 (Stahl 2021).

Sertraline (Serta or Daxid). The pragmatic broadest first choice with the widest evidence base and a mild dopamine-reuptake effect at higher doses; its signature adverse effect is

gastrointestinal, especially diarrhoea. It is only a weak CYP inhibitor, which helps in the medically complex or polypharmacy patient (Maudsley 2021).

Escitalopram (Nexito or S-Citadep) and citalopram. Escitalopram is the S-enantiomer of citalopram and the **cleanest** SSRI, with the fewest cytochrome interactions; 10 mg of escitalopram is roughly comparable to 20 mg of citalopram (Stahl 2021). Both carry a **dose-dependent QTc** prolongation: citalopram must not exceed **40 mg/day** (and 20 mg in the elderly or with a CYP2C19 inhibitor), and escitalopram is capped at **20 mg/day**.

Paroxetine (Pexep). The most troublesome of the group: a short half-life with no active metabolite, so it has the **worst discontinuation** syndrome; the most **anticholinergic** SSRI (dry mouth, constipation); the most weight gain; a potent CYP2D6 inhibitor; and the one SSRI specifically to **avoid in pregnancy** (see 2.7).

Fluvoxamine. Positioned mainly for OCD, sedating rather than activating, with no active metabolite. Its defining pharmacological hazard is potent **CYP1A2 inhibition**, which raises levels of theophylline, clozapine, caffeine and duloxetine (Stahl 2021).

GOOD TO REMEMBER

- **Fluoxetine (Fludac):** longest half-life (norfluoxetine ~2 weeks), activating, CYP2D6/3A4 inhibitor; dose **20 to 80 mg/day**.
- **Sertraline (Serta or Daxid):** broadest first choice, mild dopamine effect, GI/diarrhoea; dose **50 to 200 mg/day**.
- **Escitalopram (Nexito or S-Citadep):** cleanest, fewest interactions, dose-dependent QTc; dose **10 to 20 mg/day** (max 20).
- **Citalopram:** escitalopram's racemate; QTc cap at **40 mg/day** (20 in elderly); dose **20 to 40 mg/day**.
- **Paroxetine (Pexep):** short half-life, anticholinergic, weight gain, worst discontinuation, avoid in pregnancy; dose **20 to 50 mg/day**.
- **Fluvoxamine:** OCD agent, strong CYP1A2 inhibitor, sedating; dose **100 to 300 mg/day**.

2.4 The class adverse-effect set: GI, sexual, activation

Gastrointestinal. Nausea, loose stools and dyspepsia are the commonest early adverse effects, driven by gut 5-HT3 stimulation; they are usually dose-related and settle over the first 1 to 2 weeks. Sertraline is the most likely to cause diarrhoea (Maudsley 2021).

Sexual dysfunction. **sexual dysfunction** (use "sexual dysfunction") is very common with all SSRIs (reduced desire, delayed orgasm or anorgasmia, and erectile or ejaculatory difficulty) and is the leading cause of covert non-adherence, so ask about it directly rather than waiting for the patient to volunteer it (Maudsley 2021). Management options include dose reduction, switching to a lower-risk agent (bupropion, mirtazapine or agomelatine), a drug holiday, or adding sildenafil/tadalafil. Do not dismiss it: an unasked, untreated sexual side effect is a classic reason a patient silently stops an effective antidepressant.

Early activation and anxiety. A jittery, agitated worsening of anxiety and insomnia can occur in the first days, most with the activating fluoxetine; in anxiety disorders start at half the usual dose

and titrate up. Emergent agitation, especially in a young person, also raises the question of an unmasked bipolar state (Maudsley 2021).

TRAP **Dismissing or never asking about sexual dysfunction.** It is very common, patient-limiting, and the commonest silent cause of SSRI non-adherence; ask directly and act.

2.5 Hyponatraemia, bleeding and QTc: the systemic risks

Hyponatraemia and SIADH. All SSRIs can cause hyponatraemia through the syndrome of inappropriate antidiuretic hormone secretion, and the risk is greatest in the **elderly**, in women, in low body weight, and with co-prescribed diuretics; it is a first-month risk (Maudsley 2021; Stahl 2021). In an older patient who becomes confused, drowsy, unsteady or has a seizure after starting or increasing an SSRI, check the sodium before anything else.

Bleeding. By depleting platelet serotonin, SSRIs impair platelet aggregation and raise the risk of gastrointestinal and other bleeding, and this risk is amplified when combined with **NSAIDs** or antiplatelet or anticoagulant drugs; co-prescribe gastroprotection where an NSAID or antiplatelet cannot be avoided (Maudsley 2021).

QTc. Citalopram and escitalopram cause a dose-dependent QTc prolongation, which is the reason for the hard dose ceilings above; caution with other QT-prolonging drugs, hypokalaemia and pre-existing cardiac disease.

TRAP **Missing SSRI-induced hyponatraemia in an older patient.** New confusion, falls, unsteadiness or a seizure weeks into an SSRI is hyponatraemia until the sodium proves otherwise.

2 to 4 wk	40	20
THERAPEUTIC LAG TO RESPONSE	CITALOPRAM QTC CEILING (MG/DAY)	ESCITALOPRAM MAXIMUM (MG/DAY)

2.6 The paediatric suicidality signal and serotonin syndrome

Paediatric suicidality. A small but real increase in suicidal ideation and behaviour (not completed suicide) is seen with antidepressants in children, adolescents and young adults up to about age 25, prompting a boxed warning and close monitoring in the early weeks; the same reanalyses show a reduction in suicidality with antidepressants in adults over 65 (Stahl 2021). The message is monitoring in the young, not avoidance: untreated depression is itself a suicide risk. The full clinical suicide risk assessment and safety planning are owned by the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

Serotonin syndrome. Combining an SSRI with another serotonergic drug, above all an MAOI (including moclobemide), tramadol, triptans, linezolid or another serotonergic antidepressant, can precipitate serotonin syndrome, the triad of neuromuscular excitation (clonus, hyperreflexia, tremor), autonomic instability and altered mental state. An adequate washout is mandatory when switching to or from an MAOI, and the long half-life of fluoxetine means a 5-week gap. The acute recognition and emergency management of serotonin syndrome are cross-referred to the Perinatal/women's mental health and emergency psychiatry notes.

RULE **Never co-prescribe an SSRI with an MAOI.** Leave 14 days after an MAOI, and 5 weeks after fluoxetine before starting one, to avoid serotonin syndrome.

2.7 CYP interactions and the discontinuation caveat

Cytochrome interactions in brief. The clinically important inhibitors are the ones to memorise: fluoxetine and paroxetine are potent CYP2D6 inhibitors (fluoxetine also inhibits CYP3A4), and fluvoxamine is a potent CYP1A2 inhibitor. Practical consequences: paroxetine reduces the efficacy of tamoxifen (a CYP2D6-activated pro-drug); fluoxetine raises clozapine and TCA levels; fluvoxamine markedly raises theophylline, clozapine and caffeine levels. Sertraline, escitalopram and citalopram are comparatively clean, which is why escitalopram or sertraline is preferred in the medically complex patient (Maudsley 2021; Stahl 2021).

Discontinuation caveat. Stopping an SSRI abruptly, especially a short-half-life agent, produces a discontinuation syndrome (flu-like symptoms, insomnia, nausea, imbalance, sensory "electric-shock" disturbances and hyperarousal). Paroxetine is the worst offender and fluoxetine essentially exempt because it self-tapers. Always taper; the full discontinuation-and-withdrawal detail is cross-referred to the Perinatal/women's mental health and emergency psychiatry notes.

INDIA

SSRIs are the most-prescribed antidepressants in Indian practice and all six are cheap and freely available as generics and branded generics. Lead with the Indian brand: escitalopram is sold as Nexito or S-Citadep, sertraline as Serta or Daxid, fluoxetine as Fludac, and paroxetine as Pexep; citalopram and fluvoxamine are marketed generically and by brand. Escitalopram and sertraline are the workhorse first-line agents in Indian outpatient departments, and monthly cost is low (a month of a generic SSRI typically costs a small fraction of a single private consultation), which matters for adherence in a largely out-of-pocket health system.

WORKED EXAMPLE

A 72-year-old woman on a thiazide for hypertension is started on an SSRI for a moderate depressive episode. Ten days later she is brought in confused, unsteady and drowsy. Rather than escalating the antidepressant or reaching for an antipsychotic, the first action is a serum sodium, which is 122 mmol/L: SSRI-induced hyponatraemia from SIADH, compounded by the diuretic and her age. The SSRI is stopped, sodium corrected cautiously, and a lower-risk strategy planned. Missing the sodium here is the classic examined error.

PEARL

Match the SSRI to the patient by its non-efficacy features: the anxious or agitated patient may do better away from activating fluoxetine; the medically complex, polypharmacy patient suits clean escitalopram or sertraline; the patient likely to miss doses should avoid short-half-life paroxetine because of its discontinuation burden. The efficacy is broadly the same; the fit is not.

MNEMONIC

FINISH

SSRI discontinuation syndrome, worst with paroxetine: **F**lu-like symptoms, **I**nsomnia, **N**ausea, **I**mbalance, **S**ensory disturbances (the "electric shocks"), **H**yperarousal. Taper slowly; fluoxetine self-tapers.

HOLD THIS

SSRIs are first-line and equally effective, differing in half-life, CYP interactions and adverse-effect emphasis: fluoxetine long and activating, paroxetine short with the worst discontinuation and avoided in pregnancy, escitalopram cleanest with a QTc ceiling, fluvoxamine a CYP1A2 inhibitor for OCD; watch for sexual dysfunction, hyponatraemia in the elderly, NSAID-associated bleeding, and never combine with an MAOI.

3 · Serotonin-noradrenaline reuptake inhibitors

Why this matters. The **serotonin-noradrenaline reuptake inhibitor** (SNRI) class is the most heavily examined second-generation antidepressant group after the SSRIs, and it is where a resident must marry a clean synaptic mechanism to a small set of dose-dependent adverse effects. Every SNRI blocks both the serotonin transporter (SERT) and the noradrenaline transporter (NET), but the noradrenergic action is not free at every dose: with venlafaxine it emerges only as the dose is raised, which is exactly why the blood-pressure rise, the sweating and the urinary effects track dose. The class also carries the single most feared antidepressant discontinuation problem, the venlafaxine withdrawal syndrome.

The examinable skill is threefold: to state the dual SERT and NET mechanism and its dose-dependence, to name and dose each agent (venlafaxine, desvenlafaxine, duloxetine, milnacipran and levomilnacipran) with its signature adverse effect, and to place the class in the algorithm, a common second step after an SSRI, or a first-line choice where depression is comorbid with neuropathic pain. The monoamine-transporter pharmacology and CYP metabolism that underpin this class are developed in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

3.1 The mechanism: dual SERT and NET blockade with a noradrenergic action that emerges at higher dose

The class name says the mechanism: an SNRI inhibits reuptake at both the serotonin transporter and the noradrenaline transporter, combining two therapeutic actions in one molecule (Stahl 2021; Kaplan & Sadock 2024). What distinguishes the newer SNRIs from the older dual-acting tricyclics is **selectivity**: they have essentially no affinity for muscarinic, histaminergic or alpha-adrenergic receptors, which is why they are far better tolerated than clomipramine or amitriptyline while sharing the dual-reuptake logic (Kaplan & Sadock 2024). The crucial teaching point is that the two actions are not equipotent at every dose. For venlafaxine the affinity for SERT is much greater than for NET, so at the lowest therapeutic dose the drug behaves as a de-facto SSRI, and NET is only reliably engaged as the dose climbs; Stahl frames this as serotonergic actions present at low doses with noradrenergic actions "progressively enhanced as dose

increases" (Stahl 2021). This ascending dose-response is the conceptual spine of the whole topic: the noradrenergic benefits and the noradrenergic adverse effects both arrive together, at higher dose.

RULE **An SNRI is an SSRI at low dose and a dual agent higher up.** The noradrenergic action, and every noradrenergic adverse effect, appears as you push the dose, so dose determines the pharmacology.

3.2 Venlafaxine: the dose-dependent noradrenergic effect and the ascending dose-response

Venlafaxine (Venlor) is a bicyclic phenylethylamine, the prototype SNRI, approved for major depressive disorder, generalised anxiety disorder, social anxiety disorder and panic disorder (Kaplan & Sadock 2024). Its pharmacology is textbook dose-dependence: it acts as a serotonergic agent at the minimum effective dose of **75 mg/day**, whereas the noradrenaline transporter is consistently engaged only at a dose of about **225 mg/day** (Kaplan & Sadock 2024). CANMAT lists venlafaxine as a first-line SNRI for MDD at **75 to 225 mg/day** (CANMAT 2016). The immediate-release form has a short elimination half-life of roughly **4 hours** (its active metabolite O-desmethylvenlafaxine about **10 hours**), and this short half-life is what drives the discontinuation problem covered below (Kaplan & Sadock 2024). The extended-release capsule allows once-daily dosing but does not lengthen the elimination half-life, so it does not abolish the withdrawal risk (Kaplan & Sadock 2024).

WORKED EXAMPLE

A patient on venlafaxine 75 mg/day for depression has partial response with no side effects. Because 75 mg is essentially a serotonergic dose, uptitration towards 150 to 225 mg/day recruits the noradrenergic action and can improve response, but from about 150 mg upward you must begin checking blood pressure, because the noradrenergic effect that helps also raises blood pressure.

3.3 Venlafaxine: the dose-dependent blood-pressure rise and the monitoring rule

The signature venlafaxine adverse effect is a **dose-dependent rise in blood pressure**, a direct consequence of dose-dependent noradrenergic reuptake blockade. With the immediate-release formulation, sustained hypertension was dose-related, rising from about **3 to 7 percent** at doses of 100 to 300 mg/day and to about **13 percent** at doses greater than 300 mg/day (Kaplan & Sadock 2024). Capping the extended-release dose largely attenuated the signal, but the prescribing rule stands: when higher doses are used, monitoring of blood pressure is recommended (Kaplan & Sadock 2024). The Maudsley makes the class point plainly, that the SNRIs venlafaxine and duloxetine are associated with dose-dependent increases in blood pressure (Maudsley 2021). This is the load-bearing SNRI prescribing principle: blood pressure is checked, and checked again, as the dose is raised.

3 to 7	13	75 to 225
SUSTAINED HYPERTENSION AT 100 TO 300 MG/DAY (PERCENT)	SUSTAINED HYPERTENSION ABOVE 300 MG/DAY (PERCENT)	FIRST-LINE VENLAFAXINE RANGE (MG/DAY)

RULE **Venlafaxine's noradrenergic effect and blood-pressure rise are dose-dependent, so monitor blood pressure at higher doses.** Check a baseline and recheck as you titrate past the low serotonergic range.

3.4 Venlafaxine: the short half-life and the marked discontinuation syndrome

Venlafaxine is one of the antidepressants most commonly associated with a discontinuation syndrome, a direct consequence of its short half-life (Kaplan & Sadock 2024). On rapid taper or abrupt cessation, and even after a few missed doses, patients develop dizziness, nausea, insomnia, nervousness, sweating, anorexia, diarrhoea, somnolence and sensory disturbances (the "electric shock" or "brain zap" paraesthesiae) (Kaplan & Sadock 2024). Because the extended-release formulation does not change the elimination half-life, switching to it does not reduce the discontinuation potential (Kaplan & Sadock 2024). The Maudsley notes that antidepressants with noradrenergic effects tend to have more severe withdrawal, and names venlafaxine, desvenlafaxine, duloxetine and paroxetine as the agents most often implicated (Maudsley 2021). Management is prevention: warn the patient not to stop abruptly, and taper slowly, reducing the daily dose by no more than about **75 mg each week** when longer-term treatment must be stopped; a few bridging doses of fluoxetine can smooth the final step (Kaplan & Sadock 2024).

TRAP **Stopping venlafaxine abruptly precipitates a severe discontinuation syndrome.** The short half-life means even missed doses can trigger it; never stop it suddenly, taper by no more than about 75 mg per week.

GOOD TO REMEMBER

- **Venlafaxine (Venlor):** dual SERT and NET reuptake inhibitor, noradrenergic action emerges with dose; signature effect is a dose-dependent blood-pressure rise (monitor at higher doses) plus a marked discontinuation syndrome from its short half-life; hold 75 to 225 mg/day, serotonergic at 75, NET engaged near 225.

3.5 Desvenlafaxine: the active metabolite, less CYP-dependent

Desvenlafaxine is O-desmethylvenlafaxine, the principal active metabolite of venlafaxine, formed from the parent drug by CYP2D6 (Stahl 2021; Kaplan & Sadock 2024). Because it is already the downstream metabolite, its systemic exposure is **less dependent on CYP2D6 conversion** than venlafaxine's, so its plasma levels are more predictable across the genetic polymorphisms of that enzyme (Stahl 2021). It has relatively greater noradrenaline reuptake inhibition than venlafaxine but remains more potent at SERT (Stahl 2021). The minimum therapeutic dose is **50 mg/day**, and controlled trials showed no greater efficacy at higher doses; CANMAT lists it as a first-line SNRI for MDD at **50 to 100 mg/day** (Kaplan & Sadock 2024; CANMAT 2016). Note the Maudsley caveat that desvenlafaxine was not marketed in the UK at the time of writing, so it appears in guidelines as an option rather than a mainstream UK agent (Maudsley 2021).

GOOD TO REMEMBER

- **Desvenlafaxine:** the active O-desmethyl metabolite of venlafaxine, less CYP2D6-dependent so more predictable levels; relatively more noradrenergic than venlafaxine but still SERT-predominant; hold a minimum effective dose of 50 mg/day (first-line range 50 to 100 mg/day).

3.6 Duloxetine: the neuropathic-pain and stress-incontinence indications

Duloxetine (Duzela) inhibits both SERT and NET, and because it has lower affinity for NET than for SERT, doses higher than **60 mg/day** are needed to reliably obtain a central noradrenergic effect (Stahl 2021; Kaplan & Sadock 2024). CANMAT lists duloxetine as a first-line SNRI for MDD at **60 mg/day** (CANMAT 2016). Its distinguishing feature is a set of pain and urological indications that flow from noradrenergic action on descending spinal pathways and on urethral sphincter tone: it is specifically used for **diabetic and other neuropathic pain**, for fibromyalgia, and for **stress urinary incontinence** in women because it increases urethral tone (Tripathi 2019; Kaplan & Sadock 2024). This makes duloxetine the natural first-line antidepressant when depression coexists with a chronic pain syndrome. Its blood-pressure effect is smaller than venlafaxine's and, curiously, does not appear to be dose-dependent, with only about a 1 percent greater risk of sustained hypertension than placebo (Kaplan & Sadock 2024).

INDIA

Duloxetine is widely stocked in India under several brands (Duzela among them); the internationally recognised innovator brand is Cymbalta. When comorbid neuropathic pain drives the choice, duloxetine is often the pragmatic first antidepressant on an Indian formulary because it treats both targets with one drug.

3.7 Duloxetine: the hepatotoxicity caution and key interactions

The specific safety caution for duloxetine is **hepatotoxicity**: the Maudsley references a drug-induced liver injury case series, and the drug should be avoided in patients with significant hepatic impairment or substantial alcohol use, with liver function monitored if there is concern (Maudsley 2021). Metabolically, duloxetine is a CYP1A2 and CYP2D6 substrate: its levels are about 30 percent lower in smokers (CYP1A2 induction) and rise about four-fold with potent CYP1A2 inhibitors such as fluvoxamine and some fluoroquinolone antibiotics, so co-prescription with fluvoxamine is a notable interaction to avoid (Kaplan & Sadock 2024). As with all serotonergic agents, a lethal interaction with monoamine oxidase inhibitors is expected, and the MAOI washout rules must be followed; the acute serotonin-syndrome frame that this interaction can trigger is developed in the Perinatal/women's mental health and emergency psychiatry notes.

TRAP **Co-prescribing duloxetine with fluvoxamine multiplies its level roughly four-fold.** Fluvoxamine is a potent CYP1A2 inhibitor; the combination, and heavy alcohol use, both stack onto duloxetine's hepatotoxicity risk.

GOOD TO REMEMBER

- **Duloxetine (Duzela):** dual SERT and NET inhibitor, doses above 60 mg needed for a central noradrenergic effect; signature niche is neuropathic pain, fibromyalgia and stress urinary incontinence, with a hepatotoxicity caution (avoid in hepatic impairment or heavy alcohol use); hold a first-line dose of 60 mg/day.

3.8 Milnacipran and levomilnacipran in brief

Milnacipran is a dual reuptake inhibitor that, unlike venlafaxine, is preferentially noradrenergic, roughly twice as potent at NET as at SERT; it behaves as a preferential NE uptake inhibitor at its minimum therapeutic dose of **50 mg twice daily** and recruits more serotonergic action as the dose rises to its maximal recommended **200 mg/day** for fibromyalgia (Kaplan & Sadock 2024). In many countries it is licensed for major depressive disorder, but in the United States it is approved only for fibromyalgia (Kaplan & Sadock 2024). Consistent with its noradrenergic bias, its notable adverse effects, at rates higher than an SSRI, are dizziness, sweating and urinary hesitancy (Kaplan & Sadock 2024). Levomilnacipran is the more active enantiomer, developed as a separate once-daily antidepressant for MDD; like the others it must never be given close to an MAOI (Kaplan & Sadock 2024).

GOOD TO REMEMBER

- **Milnacipran:** the preferentially noradrenergic SNRI (about twice as potent at NET as SERT), signature effects sweating and urinary hesitancy; hold a minimum therapeutic dose of 50 mg twice daily (maximum 200 mg/day, licensed mainly for fibromyalgia).
- **Levomilnacipran:** the more active enantiomer of milnacipran, marketed as a once-daily SNRI antidepressant for MDD; never combine with an MAOI.

3.9 The class adverse-effect profile: the noradrenergic signature

Beyond the shared serotonergic effects (nausea, which is more frequent than with SSRIs, sexual dysfunction, headache), the examinable SNRI signature is the **noradrenergic** cluster, all traceable to NET blockade: **sweating**, a rise in **blood pressure**, increased pulse, and **urinary** effects (hesitancy). With venlafaxine these are dose-dependent, tracking the emergence of noradrenergic action at higher dose; milnacipran, being preferentially noradrenergic, shows the sweating and urinary signal even at usual dose (Kaplan & Sadock 2024). Layered on top is the discontinuation liability, most marked for venlafaxine because of its short half-life. Holding these together, the class is well tolerated but demands two things of the prescriber that SSRIs do not: blood-pressure monitoring as the dose rises, and a deliberate, slow taper on stopping.

PEARL

Every noradrenergic SNRI adverse effect, sweating, raised blood pressure, urinary hesitancy, is the same pharmacology (NET blockade) seen from a different organ. If you remember "sweat, pressure, pee" you have reconstructed the class side-effect profile from first principles.

3.10 Adverse-effect comparison across the agents

AGENT (BRAND)	USUAL DOSE (MG/DAY)	NE VS 5-HT BALANCE	SIGNATURE ADVERSE EFFECT / CAUTION
Venlafaxine (Venlor)	75 to 225	SERT > NET; NET recruited with dose	**Dose-dependent blood-pressure rise; marked discontinuation syndrome**
Desvenlafaxine	50 to 100	More NET than venlafaxine, still SERT-predominant	Less CYP2D6-dependent, more predictable levels
Duloxetine (Duzela)	60 (up to 120)	SERT > NET; NET needs >60 mg	**Hepatotoxicity caution; neuropathic pain and stress incontinence indications**
Milnacipran	100 (50 twice daily), max 200	NET > SERT (preferentially noradrenergic)	Sweating, urinary hesitancy; mainly fibromyalgia
Levomilnacipran	40 to 120	Noradrenergic-leaning enantiomer	Once-daily; MAOI contraindication

SNRI agents compared on dose, transporter balance and the single adverse effect or caution to hold for each; blood-pressure monitoring and slow taper apply across the class.

3.11 The place in therapy: a common second step after an SSRI, or first-line with comorbid pain

In the guideline algorithm the SNRIs sit as core options for major depressive disorder. CANMAT names venlafaxine (75 to 225 mg/day), duloxetine (60 mg/day) and desvenlafaxine (50 to 100 mg/day) as **first-line** SNRI agents for MDD, individualising the choice to the patient (CANMAT 2016). The commonest practical use is as a **second step after an SSRI**: when a first-line SSRI fails on efficacy grounds, a switch to an SNRI is a standard next move, and CANMAT directs that for a non-improver at 2 to 4 weeks you increase the dose if tolerated and switch to another agent if tolerability is the problem (CANMAT 2016). The BAP similarly reserves maximised-efficacy agents including venlafaxine at 150 mg or more for more severely ill patients, and NICE positions SNRIs among the alternatives after an initial SSRI (Malhi 2015 for the BAP position on severity; NICE 2014). The other clear first-line indication is **comorbid pain**: duloxetine is the natural first choice when depression coexists with neuropathic pain, fibromyalgia or stress urinary incontinence. For the Indian Psychiatric Society position, kb-search did not return a confirmable IPS depression recommendation on SNRI sequencing in the parsed library, so the specific IPS line could not be confirmed and is flagged rather than invented; the guideline-anchored management plan for depression as a whole is developed in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

RULE **An SNRI is a standard second step after a failed SSRI, and first-line when pain is comorbid.** Venlafaxine, duloxetine and desvenlafaxine are all CANMAT first-line SNRIs; duloxetine also treats the pain.

COMMON TRAP

Do not treat a bipolar depression with an SNRI as monotherapy. As with any antidepressant, using it alone in bipolar depression risks a switch into mania or mixed states; the SNRI place in therapy described here is for unipolar depression, and the bipolar-depression algorithm belongs in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

HOLD THIS

Every SNRI blocks SERT and NET, but venlafaxine's noradrenergic action, and its blood-pressure rise, are dose-dependent (SSRI-like at 75 mg, NET engaged near 225 mg), so monitor blood pressure as you titrate and never stop it abruptly (short half-life, severe discontinuation syndrome).

MNEMONIC

"VDD-ML": Venlafaxine, Desvenlafaxine, Duloxetine, Milnacipran, Levomilnacipran

The five SNRIs in rough order of exam weight. Venlafaxine carries blood pressure and discontinuation; Desvenlafaxine is its less-CYP-dependent metabolite; Duloxetine owns pain and stress incontinence with a liver caution; Milnacipran and Levomilnacipran are the noradrenergic-leaning, fibromyalgia-associated tail.

4 . Tricyclic antidepressants

The **tricyclic antidepressants** (the **TCAs**) are the oldest effective antidepressant class, and although second-generation agents have displaced them from first line, they remain firmly on the exam because their pharmacology is the teaching template for the whole antidepressant syllabus: a wanted reuptake action bundled with three unwanted receptor blockades that generate the entire adverse-effect picture, and a cardiotoxicity that makes them lethal in overdose. On a guideline reading they are a **second-line** option for major depression (CANMAT 2016) and have specific evidence in treatment-resistant depression and, for clomipramine, in obsessive-compulsive disorder.

Why the class still matters. A resident must be able to say, in one breath, why a TCA works (reuptake blockade), why it is unpleasant (muscarinic, H1 and alpha-1 blockade), and why it kills (quinidine-like sodium-channel blockade in the myocardium). The receptor systems behind these actions are laid out in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the guideline-anchored place of the class within the depression algorithm is in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

4.1 Mechanism: reuptake blockade plus three off-target blockades

The wanted action. TCAs block the presynaptic serotonin transporter (SERT) and the noradrenaline transporter (NET), raising synaptic monoamine availability, exactly the shared final pathway of the SSRIs and SNRIs (Stahl 2021). **The unwanted actions.** Unlike the selective

agents, TCAs simultaneously block three off-target receptors, and this promiscuity, not the reuptake action, drives almost every adverse effect: **muscarinic (antimuscarinic)** blockade gives the anticholinergic set, **histamine H1** blockade gives sedation and weight gain, and **alpha-1 adrenergic** blockade gives orthostatic hypotension (Stahl 2021, Kaplan and Sadock 2024). A fourth, separate action, blockade of fast cardiac sodium channels, is what makes overdose dangerous and is covered in 4.6.

Muscarinic (M1) blockade
dry mouth, constipation, blurred vision, urinary hesitancy, tachycardia, cognitive slowing, delirium in the elderly

Histamine H1 blockade
sedation, drowsiness and appetite-driven weight gain

Alpha-1 adrenergic blockade
orthostatic (postural) hypotension, dizziness and reflex tachycardia

Fast sodium-channel blockade
the quinidine-like membrane-stabilising effect on the myocardium, dormant at therapeutic dose but lethal in overdose

4.2 Tertiary versus secondary amines

The structural distinction that predicts tolerability. **Tertiary amine** TCAs (amitriptyline, imipramine, clomipramine, doxepin, trimipramine) are more potent at all the off-target receptors and are therefore more anticholinergic, more sedating and more hypotensive. Their demethylated **secondary amine** metabolites and drugs (nortriptyline from amitriptyline, desipramine from imipramine) are relatively more noradrenergic and, crucially, **less anticholinergic and better tolerated** (Kaplan and Sadock 2024). Nortriptyline in particular has the least orthostatic hypotension of the class and desipramine is the least anticholinergic, which is why the secondary amines are preferred in the elderly.

RULE **Secondary before tertiary in the frail.** If a TCA is unavoidable in an older or medically compromised patient, choose a secondary amine (nortriptyline, desipramine): same reuptake efficacy, lighter anticholinergic and orthostatic load.

AGENT (INDIAN BRAND)	AMINE CLASS	SIGNATURE FEATURE	DOSE (MG/DAY)
Amitriptyline (Tryptomer)	tertiary	**most sedating and cardiotoxic; also pain and migraine prophylaxis**	75 to 200
Imipramine (Depsonil)	tertiary	the original TCA; childhood enuresis	75 to 200
Clomipramine (Anafranil)	tertiary	**most serotonergic; OCD**	up to 250
Nortriptyline	secondary	**best-tolerated; therapeutic window 50 to 150 ng/mL**	75 to 150
Desipramine	secondary	least anticholinergic	100 to 200

Tertiary amines are more sedating, anticholinergic and hypotensive; secondary amines are better tolerated and preferred in the elderly.

4.3 Amitriptyline: the sedating prototype

The workhorse tertiary amine. Amitriptyline (Tryptomer) is strongly serotonergic and noradrenergic but also the most anticholinergic, sedating and cardiotoxic, and it is one of the leading single-drug causes of death by overdose (Kaplan and Sadock 2024). Its sedation and analgesic action make it a standard low-dose agent for **chronic pain** and **migraine prophylaxis**, well below antidepressant doses. Antidepressant dosing runs up through the usual antidepressant range of **75 to 200 mg/day**, and up to 300 mg/day only under specialist supervision (Companion 2010), taken at night to exploit the sedation.

4.4 Imipramine and clomipramine

Imipramine, the original and the enuresis drug. Imipramine (Depsonil) was the first tricyclic; beyond depression it retains a niche use in childhood nocturnal **enuresis**, where the antidepressants (unlike anxiolytics) reduce bed-wetting (Shorter Oxford 2018). **Clomipramine, the serotonergic one.** Clomipramine (Anafranil) is the **most serotonergic** TCA and is the tricyclic with first-line-strength efficacy in obsessive-compulsive disorder (Lopez-Ibor, 1967; Shorter Oxford 2018): conventional TCAs are ineffective in OCD, clomipramine is the exception. Its OCD dosing climbs to a maximum around **250 mg/day** (Maudsley 2021). Because it is the most serotonergic, clomipramine carries the highest serotonin-syndrome risk of the class if combined with an MAOI or another serotonergic drug.

COMMON TRAP

Reaching for a "plain" TCA (amitriptyline, imipramine) for obsessive-compulsive disorder. Only **clomipramine**, the most serotonergic tricyclic, works in OCD; the others are essentially inactive against obsessions and compulsions.

4.5 Nortriptyline: best-tolerated, with a therapeutic window

The monitorable secondary amine. Nortriptyline is the best-tolerated TCA (least orthostatic hypotension, relatively low anticholinergic burden) and is the one TCA with a genuine

therapeutic window: efficacy tracks a plasma level of roughly **50 to 150 ng/mL**, and levels above the window are associated with loss of response and rising toxicity, so plasma-level monitoring is meaningfully used to guide dosing (Kaplan and Sadock 2024, Maudsley 2021). The average dose needed to reach about 100 ng/mL is near **75 mg/day** but varies widely, which is exactly why the level, not just the dose, is checked.

WORKED EXAMPLE

A 70-year-old with recurrent depression needs a TCA after two SSRIs failed. You choose nortriptyline (a secondary amine, least orthostatic), get a baseline ECG, start low, titrate every few days, and draw a plasma level after 5 to 7 days on a steady dose, aiming for the **50 to 150 ng/mL** window rather than pushing the milligram dose blind.

4.6 The adverse-effect set and the cardiotoxicity

The everyday adverse effects follow directly from the three off-target blockades in 4.1: anticholinergic effects (dry mouth, constipation, blurred vision, urinary retention, precipitation of narrow-angle glaucoma, delirium in the elderly), sedation, weight gain, and orthostatic hypotension, which is in fact the single most common reason for stopping a TCA (Kaplan and Sadock 2024). **The cardiotoxicity** is separate and more dangerous. TCAs have a **quinidine-like** (type 1A antiarrhythmic) membrane-stabilising action: by blocking fast cardiac sodium channels they slow intraventricular conduction, which shows on the ECG as **QRS widening** and QT prolongation and, at higher exposure, as ventricular arrhythmia and heart block (Kaplan and Sadock 2024). A pre-existing conduction delay, or a QTc of 450 msec or greater, is a contraindication, and an ECG should precede TCA use in the elderly or the cardiac patient.

50 to 150	450	75 to 200
NORTRIPTYLINE THERAPEUTIC WINDOW (NG/ML)	QTC CONTRAINDICATION THRESHOLD (MSEC)	CLASS ANTIDEPRESSANT RANGE (MG/DAY)

4.7 Key interactions

The two that matter for the exam. The most dangerous is the **TCA plus MAOI** combination: adding a large dose of a tricyclic to a patient already on a monoamine oxidase inhibitor can precipitate a serotonin syndrome or a fatal hypertensive reaction, so an adequate washout is mandatory (Kaplan and Sadock 2024). The second is **pharmacokinetic**: TCAs are cleared by cytochrome P450, and CYP2D6 inhibitors, notably fluoxetine, paroxetine, duloxetine and bupropion, raise TCA plasma levels (fluoxetine roughly triples desipramine levels), pushing an otherwise safe dose toward cardiotoxic territory. Enzyme inducers such as carbamazepine do the reverse and can make a therapeutic level unattainable. The CYP machinery is detailed in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

TRAP **Co-prescribing a 2D6 inhibitor with a TCA and not rechecking the level.** Adding fluoxetine or paroxetine to a stable TCA can several-fold raise the tricyclic level and tip a well-tolerated dose into QRS-widening toxicity.

4.8 Overdose: the reason TCAs are feared

A small multiple of the daily dose can be lethal. Because the target population is depressed and at risk of self-harm, overdose lethality is the defining safety problem of the class: a tricyclic overdose of about **10 times the daily dose** can be fatal, and death is most often from cardiac toxicity, with seizures and respiratory depression also occurring (Kaplan and Sadock 2024). The mortality risk with TCAs in overdose is many-fold higher than with SSRIs. The **toxidrome** combines the anticholinergic picture (hot, dry, dilated, delirious, tachycardic, ileus, retention) with central nervous system depression and **seizures**, and the cardiac picture of a **wide QRS**, ventricular arrhythmia and **hypotension**.

The management headline. Secure the airway, get an urgent **ECG**, and give intravenous **sodium bicarbonate** for QRS widening (and for significant arrhythmia or hypotension): serum alkalinisation and a sodium load counteract the quinidine-like sodium-channel block. The rest is supportive, activated charcoal if early, benzodiazepines for seizures, fluids and pressors for hypotension. The full acute-emergency detail, including the wider poisoning and serotonin-syndrome frame, is in the Perinatal/women's mental health and emergency psychiatry notes.

HOLD THIS

A TCA overdose of about ten times the daily dose can be fatal, kills mainly through quinidine-like cardiotoxicity (wide QRS, arrhythmia, hypotension) plus seizures, and the antidote to the widened QRS is intravenous sodium bicarbonate.

4.9 Where the TCAs sit in the guidelines

Second-line, weighed against overdose risk. CANMAT (CANMAT 2016) places TCAs (amitriptyline, clomipramine and others) as a **second-line** monotherapy for major depression, behind the SSRIs and SNRIs, precisely because the newer agents are safer in overdose and better tolerated. The BAP (Cleare, 2015) makes the same point at guideline level, choose antidepressants that are better tolerated and safer in overdose first, and reserves TCAs and MAOIs for when first-line treatment has failed, while noting that TCAs have evidence for **superior efficacy in treatment-resistant depression** where serum levels can guide dosing. The place of the class in the wider stepped algorithm is set out in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

INDIA

TCAs remain widely and cheaply available in India: amitriptyline as Tryptomer, imipramine as Depsonil, clomipramine as Anafranil. Low cost keeps them in real-world use, which makes the overdose-lethality counselling in 4.8 and the prescribing rule below all the more important where supply and follow-up may be limited.

RULE **Weigh suicide risk before you prescribe.** TCAs are effective but dangerous in overdose (cardiotoxic), so assess suicide risk first and prefer a safer agent, or dispense small quantities, in anyone at risk.

TRAP **Handing an actively suicidal patient a large quantity of a TCA.** A month's supply of amitriptyline is a lethal stockpile; this is the classic, avoidable prescribing error of the class.

MNEMONIC

TCA overdose: the 3 Cs plus Seize

Convulsions (seizures), **C**oma (CNS depression), **C**ardiotoxicity (wide QRS, arrhythmia, hypotension), on a background of anticholinergic delirium. QRS widening is answered by sodium bicarbonate.

GOOD TO REMEMBER

- **TCA class:** SERT and NET reuptake blockade drives efficacy; muscarinic, H1 and alpha-1 blockade drives the adverse effects; second-line for depression, dangerous in overdose.
- **Tertiary vs secondary amine:** secondary amines (nortriptyline, desipramine) are less anticholinergic and better tolerated; prefer them in the elderly.
- **Amitriptyline (Tryptomer):** sedating, most anticholinergic and cardiotoxic tertiary amine; also used for chronic pain and migraine prophylaxis; antidepressant range 75 to 200 mg/day.
- **Imipramine (Depsonil):** the original TCA; niche use in childhood nocturnal enuresis.
- **Clomipramine (Anafranil):** the most serotonergic TCA; first-line-strength for OCD, up to about 250 mg/day; highest serotonin-syndrome risk with MAOIs.
- **Nortriptyline:** best-tolerated (least orthostatic); therapeutic window 50 to 150 ng/mL, so plasma-level monitoring guides dosing.
- **Cardiotoxicity:** quinidine-like sodium-channel block, QRS widening, arrhythmia; ECG before use, avoid if QTc 450 msec or more.
- **Overdose:** about 10 times the daily dose can be fatal; discriminator is a wide QRS; first management step is ECG plus intravenous sodium bicarbonate.

5 . Monoamine oxidase inhibitors

The **monoamine oxidase inhibitors** (the **MAOIs**) were the first effective antidepressants, and although they have been pushed to a late line by their diet and interaction hazards, they remain firmly on the exam for two reasons: the **tyramine (cheese) reaction** and the **serotonergic interaction** are the most examinable drug-safety stories in the whole antidepressant syllabus, and the class retains a real place in atypical and treatment-resistant depression. A resident must be able to say, in one breath, why they work (they block monoamine breakdown), why the diet matters (dietary tyramine is normally destroyed by gut MAO-A), and why they must never be co-prescribed with a serotonergic drug without a washout.

Why the class still matters. The monoamine oxidase enzyme and the monoamine pathways it acts on are laid out in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the guideline-anchored place of the class within the depression algorithm is in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes. Here the teaching is the pharmacology: the mechanism, the agents, the tyramine reaction, the drug interactions and the mandatory washout intervals.

5.1 Mechanism: irreversible non-selective inhibition of MAO

The target. Monoamine oxidase is the mitochondrial enzyme that oxidatively deaminates the monoamines. It exists as two isoforms: **MAO-A** preferentially metabolises serotonin, noradrenaline and dietary tyramine, and **MAO-B** preferentially metabolises phenylethylamine, while both isoforms handle dopamine and tyramine (Stahl 2021, Companion 2010). **The action.** The classical agents produce **irreversible non-selective inhibition of MAO-A and MAO-B**, so monoamine breakdown is blocked and synaptic serotonin, noradrenaline and dopamine all rise, which is the antidepressant action. Because the inhibition is irreversible, the effect persists until new enzyme is synthesised, which takes about two weeks and is precisely why the washout intervals in 5.6 are so long (Kaplan and Sadock 2024).

RULE **Irreversible means think in weeks, not half-lives.** Enzyme activity returns only as new MAO is made (about two weeks), so the drug's danger outlasts its plasma clearance.

5.2 The agents: irreversible, reversible and transdermal

The irreversible non-selective agents. Phenelzine, tranylcypromine and isocarboxazid are the classical irreversible MAOIs. Phenelzine and isocarboxazid are hydrazines (with a small hepatotoxicity risk); tranylcypromine is a non-hydrazine with an amphetamine-like structure and can be activating (Kaplan and Sadock 2024). **The reversible agent.** Moclobemide is a **reversible inhibitor of MAO-A** (a RIMA), and this is its defining safety advantage: because tyramine can competitively displace it from the enzyme, moclobemide is much safer for the tyramine reaction and does not require adherence to a low-tyramine diet at normal doses (Shorter Oxford 2018). **The transdermal agent.** Transdermal selegiline (a patch) delivers drug systemically for antidepressant effect while, at the lowest patch strength, largely sparing gut MAO-A, so the lowest dose does not require dietary restriction; the higher patch strengths do (Kaplan and Sadock 2024).

AGENT	TYPE	SIGNATURE POINT	DOSE (MG/DAY)
Phenelzine	irreversible non-selective	**hydrazine; most weight gain of the class**	45 to 90
Tranylcypromine	irreversible non-selective	**amphetamine-like, activating**	20 to 60
Isocarboxazid	irreversible non-selective	hydrazine; least used	20 to 60
Moclobemide	**reversible MAO-A (RIMA)**	much safer for tyramine; no strict diet	300 to 600
Selegiline (transdermal)	patch	lowest strength spares gut MAO-A, no diet	see monograph

Phenelzine 45 to 90 and tranylcypromine 20 to 60 mg/day per CANMAT (2016); moclobemide 300 to 600 mg/day per CANMAT (2016).

GOOD TO REMEMBER

- **Phenelzine:** irreversible non-selective MAOI; signature is the tyramine (cheese) reaction and most weight gain of the class; hold the dose **45 to 90 mg/day** and that it is a third-line antidepressant.
- **Tranylcypromine:** irreversible non-selective MAOI, amphetamine-like and activating; signature is the hypertensive tyramine reaction; hold the dose **20 to 60 mg/day**.
- **Isocarboxazid:** irreversible non-selective hydrazine MAOI; signature is the same tyramine and serotonergic hazard; hold that it is third-line and least used.
- **Moclobemide:** reversible inhibitor of MAO-A (a RIMA); signature is that it is much safer for the tyramine reaction and needs no strict diet; hold the dose **300 to 600 mg/day** as a second-line agent (CANMAT 2016).
- **Transdermal selegiline:** patch delivery; signature is that the lowest strength spares gut MAO-A and needs no diet, higher strengths do; hold this as its whole reason for existing.

5.3 The tyramine reaction: the cheese reaction and hypertensive crisis

The mechanism. Dietary **tyramine** is a sympathomimetic amine normally broken down by gut and hepatic MAO-A before it reaches the circulation. On an irreversible MAOI that first-pass breakdown is abolished, so ingested tyramine passes into the circulation and drives a surge of noradrenaline release from sympathetic nerve terminals, producing a **hypertensive crisis** (Kaplan and Sadock 2024). This is the historical **cheese reaction**, first traced by Blackwell at the Maudsley to certain cheeses. **The clinical picture.** A tyramine crisis presents with a severe throbbing occipital headache, palpitations, nausea, vomiting, sweating and a dangerously raised blood pressure, and can progress to arrhythmia, stroke and intracranial haemorrhage (Kaplan and Sadock 2024).

WORKED EXAMPLE

A patient stable on phenelzine eats a mature cheddar and salami platter with a glass of red wine, and within the hour develops a pounding occipital headache, sweating and a blood pressure of 210/130. This is a tyramine-driven hypertensive crisis. The management headline is to treat it as a hypertensive emergency with a rapid-acting agent to lower the pressure, for example intravenous phentolamine, with the wider acute management set out in the Perinatal/women's mental health and emergency psychiatry notes.

The foods to avoid. The high-tyramine foods a patient on an irreversible MAOI must avoid include aged cheeses, aged and cured or fermented meats, improperly stored or spoiled meat, poultry or fish, broad (fava) bean pods, Marmite and other yeast extracts, sauerkraut, soy sauce and soybean condiments, and tap or draught beer (Kaplan and Sadock 2024). Fresh foods and moderate amounts of most everyday items are safe; it is the aged, cured, fermented and spoiled that concentrate tyramine.

MNEMONIC

AGED foods bite the MAOI patient

Aged cheese, Aged and cured meats, Alcohol (tap beer, some wines); Gone-off (spoiled) meat, poultry or fish; broad bEans (fava pods) and yeast extract; Draught beer and soy or fermented (sauerkraut) condiments. The unifying theme is anything Aged, fermented, cured or spoiled, because that is where tyramine accumulates.

5.4 The serotonergic interaction and serotonin syndrome

The most dangerous drug combination. Combining an MAOI with a serotonergic drug can precipitate a potentially fatal serotonin syndrome: the MAOI blocks serotonin breakdown while the second drug raises serotonin further, and the two together can produce runaway serotonergic activity (Stahl 2021, Kaplan and Sadock 2024). The offending drugs are the **SSRIs, SNRIs and clomipramine and other TCAs**, and among analgesics the classic culprits are **tramadol** and **pethidine (meperidine)**, both of which have serotonergic activity and are absolutely contraindicated with an MAOI (Kaplan and Sadock 2024). The clinical triad of serotonin syndrome is neuromuscular excitation (clonus, hyperreflexia, tremor, rigidity), autonomic instability (fever, tachycardia, sweating, diarrhoea) and altered mental state (agitation, confusion), detailed in the Perinatal/women's mental health and emergency psychiatry notes.

The sympathomimetic interaction. Separately, combining an MAOI with a **sympathomimetic** drug, amphetamines, methylphenidate, cocaine, and the sympathomimetic amines in some cold and cough remedies (pseudoephedrine, phenylephrine), produces the same noradrenaline-surge **hypertensive crisis** as the tyramine reaction, by the same final mechanism of unopposed pressor amine (Stahl 2021).

GOOD TO REMEMBER

- **Serotonin syndrome (the discriminator):** the triad is neuromuscular (clonus, hyperreflexia, rigidity), autonomic (fever, tachycardia, sweating) and mental-state (agitation, confusion) change; clonus and hyperreflexia are the features that distinguish it from neuroleptic malignant syndrome. First step: stop all serotonergic drugs and give supportive care.
- **The forbidden co-prescriptions:** never give an MAOI with an SSRI, SNRI, clomipramine, tramadol or pethidine (serotonin syndrome), nor with a sympathomimetic (hypertensive crisis).

5.5 The washout periods when switching

Why washout is non-negotiable. Because irreversible MAO inhibition lasts until new enzyme is made, an adequate **washout** must be observed in both directions when switching between an MAOI and a serotonergic drug, or a serotonin syndrome or hypertensive reaction can result even after the drug itself has cleared (Kaplan and Sadock 2024). **The intervals.** Allow at least **two weeks** after stopping an irreversible MAOI before starting a serotonergic drug (to let new enzyme regenerate), and at least **one week** (about five half-lives) after stopping most SSRIs and SNRIs before starting an MAOI, or two weeks after a tricyclic. The important exception is **fluoxetine**: because of its very long-acting active metabolite norfluoxetine, allow a longer

washout of about **five weeks** after stopping fluoxetine before starting an MAOI (Maudsley 2021, Kaplan and Sadock 2024).

2	1	5
OFF AN MAOI BEFORE A SEROTONERGIC DRUG (WEEKS)	OFF MOST SSRIS/SNRIS BEFORE AN MAOI (WEEKS)	OFF FLUOXETINE BEFORE AN MAOI (WEEKS)

RULE **Never combine an MAOI with a serotonergic drug, and observe the washout both ways.** At least two weeks off an MAOI before a serotonergic drug, and about five weeks off fluoxetine before an MAOI.

TRAP **Starting an SSRI too soon after an MAOI, or missing dietary tyramine counselling.** The commonest lethal errors are ignoring the washout when switching and failing to counsel the patient on the tyramine-rich foods to avoid.

5.6 Where the MAOIs sit in the guidelines

A later-line option. The MAOIs are reserved for **atypical depression** and **treatment-resistant depression** once better-tolerated, safer agents have failed. CANMAT (CANMAT 2016) places the irreversible agents, phenelzine **45 to 90 mg/day** and tranylcypromine **20 to 60 mg/day**, as **third-line** antidepressants, and moclobemide **300 to 600 mg/day**, the reversible MAO-A inhibitor, as a **second-line** option (CANMAT 2016). The BAP (Cleare, 2015) makes the same point at guideline level, reserve older TCAs and MAOIs for when first-line treatment has failed, and initiate an MAOI only with expertise in treating mood disorders. For the Indian Psychiatric Society position, the IPS depression guidance (Gautam et al., 2017) prioritises SSRIs and other second-generation agents first line and does not foreground the MAOIs; the specific IPS line-position for MAOIs could not be confirmed and is therefore not stated here. In pregnancy the MAOIs are to be avoided (CANMAT 2016). The place of the class in the wider stepped algorithm is set out in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

INDIA

The irreversible MAOIs (phenelzine, tranylcypromine) are little used in routine Indian practice and are not widely stocked, which is itself protective against the diet and interaction hazards. Where an MAOI is considered, it belongs in specialist hands for atypical or treatment-resistant depression, with explicit tyramine counselling and a documented washout when switching from or to a serotonergic drug.

HOLD THIS

Irreversible non-selective MAOIs (phenelzine, tranylcypromine, isocarboxazid) block tyramine breakdown, so aged, cured and fermented foods cause a hypertensive crisis, and a serotonergic drug causes serotonin syndrome; allow at least two weeks off an MAOI before a serotonergic drug and about five weeks off fluoxetine before an MAOI.

6 . Mirtazapine and bupropion

Two atypical antidepressants that a resident reaches for when an **SSRI is the wrong fit**. Each is a CANMAT Level-1 first-line agent for major depression, yet each is prescribed for its side-effect signature as much as its efficacy: mirtazapine (the **nassa**) is sedating and appetite-boosting, so it suits the depressed patient who cannot sleep and will not eat; bupropion (the **ndri**) is activating and pro-sexual, so it suits the fatigued, apathetic patient and the one whose SSRI killed libido. The mirror-image profiles are the exam point. The one hard caveat is bupropion's dose-dependent lowering of the **seizure threshold**.

Framing. This pair sits next to the SSRI and SNRI monographs; for how they slot into the guideline-anchored selection algorithm see the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes. For the receptor systems and CYP metabolism they act on, see the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. Verify every dose and the seizure caveat: a wrong one is a prescribing error.

6.1 Mirtazapine: the NaSSA mechanism

Noradrenergic and specific serotonergic antidepressant. Mirtazapine (brand Mirtaz; generic mirtazapine) is a nassa that works without any reuptake blockade (Stahl 2021). It antagonises the **alpha-2 adrenergic autoreceptor** on noradrenergic neurons, removing the noradrenaline brake and so raising noradrenaline release; and it antagonises the **alpha-2 heteroreceptor** sitting on serotonin neurons, which disinhibits and raises serotonin release. On top of this dual monoamine boost it blocks **5-HT2A, 5-HT2C and 5-HT3** serotonin receptors and the **H1 histamine** receptor (Stahl 2021, Maudsley 2021). The receptor set explains the whole clinical picture below.

RULE **Reroute, don't block.** Mirtazapine raises noradrenaline and serotonin by antagonising alpha-2 auto- and heteroreceptors, not by inhibiting a reuptake pump, so it carries none of the SSRI serotonergic-tone side effects.

6.2 Mirtazapine: dose and the paradox of low doses

15 to 45 mg at night. Start **15 mg** in the evening, titrate every 1 to 2 weeks to a usual maximum of **45 mg/day** (Stahl 2021, CANMAT 2016). The counter-intuitive teaching point: **sedation and the antihistamine load are worse at the LOWER dose**. At 7.5 to 15 mg the H1 blockade dominates; as the dose climbs, the rising noradrenergic drive partly offsets the histaminergic sedation, so sedation may not worsen and can even ease (Stahl 2021). Breaking a 15 mg tablet to give 7.5 mg can therefore increase, not reduce, drowsiness.

PEARL

If a patient complains mirtazapine is too sedating at 15 mg, the fix is often to go UP, not down: 30 mg is frequently less sedating than 15 mg because added noradrenergic tone counters the H1 effect (Stahl 2021).

6.3 Mirtazapine: the adverse-effect profile that is the selling point

Sedation and appetite gain, with clean serotonergic tolerability. The signature effects are **sedation** (H1 antagonism) and **increased appetite and weight gain** (H1 plus 5-HT2C antagonism), both of which are the reason to choose it in a depressed patient with insomnia and poor appetite (Stahl 2021, Maudsley 2021). Because it does not raise synaptic serotonin by reuptake blockade and it antagonises 5-HT2 and 5-HT3, it has **minimal sexual dysfunction** (5-HT2 sparing) and **minimal GI upset or nausea** (5-HT3 blockade, the same mechanism as ondansetron). Rare but examinable: dizziness, abnormal dreams, dry mouth, and a rare risk of low white cell count, so flu-like symptoms warrant a blood count (Stahl 2021).

RECEPTOR ACTION	CLINICAL CONSEQUENCE
Alpha-2 auto- and heteroreceptor antagonism	**antidepressant effect (raises noradrenaline and serotonin)**
H1 histamine block	**sedation and weight gain (both worse at low dose)**
5-HT2C block	appetite and weight gain
5-HT2A block	minimal sexual dysfunction; may aid sleep
5-HT3 block	minimal nausea and GI upset (anti-emetic)

Each mirtazapine side effect maps to a specific receptor it blocks (Stahl 2021).

15 to 45 MIRTAZAPINE DOSE (MG/DAY)	**20 to 40** MIRTAZAPINE HALF-LIFE (HOURS)

6.4 Mirtazapine: where it fits, and the interaction to hold

First-line for depression with insomnia and weight loss; a favoured add-on. CANMAT lists mirtazapine 15 to 45 mg/day as a Level-1 first-line antidepressant for major depression, singling out the patient with sleep disturbance (CANMAT 2016). It is a metabolised substrate of CYP2D6, 3A4 and 1A2 with no significant pharmacokinetic interactions of its own (Stahl 2021), which makes it an easy combination partner: added to an SNRI it forms the dual-action combination Stahl nicknames "California rocket fuel", and CANMAT rates mirtazapine or mianserin 30 to 60 mg/day added to an antidepressant as a second-line adjunct (CANMAT 2016). The one dangerous interaction to hold: like all monoaminergic antidepressants it can precipitate serotonin syndrome with an MAOI, so allow a 14-day washout after stopping an MAOI (Stahl 2021). For the acute management of serotonin syndrome see the Perinatal/women's mental health and emergency psychiatry notes.

GOOD TO REMEMBER

- **Mirtazapine (Mirtaz), mechanism:** NaSSA, alpha-2 auto- and heteroreceptor antagonist raising noradrenaline and serotonin, plus 5-HT2/5-HT3 and H1 block, no reuptake inhibition.
- **Mirtazapine, signature effect:** sedation and weight gain (worse at LOWER dose), with minimal sexual dysfunction and minimal nausea.
- **Mirtazapine, one to hold:** 15 to 45 mg/day at night, CANMAT first-line for depression with insomnia and poor appetite; 14-day washout with MAOIs (serotonin syndrome).

6.5 Bupropion: the NDRI mechanism

Norepinephrine-dopamine reuptake inhibitor. Bupropion (brand Bupron; generic bupropion, formerly amfebutamone) is an ndri that blocks the noradrenaline transporter and the dopamine transporter, raising noradrenaline and dopamine neurotransmission (Stahl 2021). Because the prefrontal cortex largely lacks dopamine transporters and clears dopamine via the noradrenaline pump, blocking that pump also lifts prefrontal dopamine. It has essentially **no direct serotonergic action**, which is why its side-effect profile is the mirror image of the SSRIs: it is **activating**, not sedating. It is also a CYP2D6 inhibitor, a fact that matters for interactions (Stahl 2021).

MNEMONIC

DA-NO-BUP

bupropion boosts DA and NA and has NO serotonin action, hence NO weight gain, NO sexual dysfunction, and NO sedation; but it does lower the seizure threshold.

6.6 Bupropion: dose and formulations

Three formulations, one first-line depression range. CANMAT lists bupropion **150 to 300 mg/day** as a Level-1 first-line NDRI for major depression (CANMAT 2016). The formulation determines the dosing schedule and the single-dose ceiling, which exists precisely to cap the seizure risk (Stahl 2021):

FORMULATION	RANGE (MG/DAY)	SCHEDULE	MAX SINGLE DOSE (MG)
Immediate-release (IR)	225 to 450	3 divided doses	**150**
Sustained-release (SR)	200 to 450	2 divided doses	**200**
Extended-release (XL)	150 to 450	once daily	450

Splitting the dose and capping the single dose limits the peak concentration that drives seizures (Stahl 2021).

6.7 Bupropion: the indications, including smoking cessation

Depression, SSRI-adjunct, and nicotine dependence. Beyond monotherapy for major depression, bupropion is the antidepressant of choice as an **adjunct for SSRI-induced sexual dysfunction** and for residual **fatigue, cognitive slowing and apathy** ("SSRI poop-out"), because it adds dopaminergic and noradrenergic drive without serotonergic burden (Stahl 2021). It is separately licensed for **smoking cessation** (as sustained-release bupropion, marketed for that indication as Zyban): begin it 1 to 2 weeks before the quit date, titrating to 150 mg twice daily, and it reduces craving (Stahl 2021).

RULE **Match the deficit to the drug.** Mirtazapine helps depression with insomnia and weight loss; bupropion helps depression with fatigue and sexual dysfunction. Choose by the residual-symptom profile.

6.8 Bupropion: low sexual dysfunction, low weight gain

The tolerability edge. Because it lacks serotonergic action, bupropion causes **little or no sexual dysfunction** and **little or no weight gain** (indeed it is weight-neutral to weight-reducing), and it is less likely to induce hypomania than some antidepressants (Stahl 2021). This is why it is the go-to switch or add-on for the SSRI-treated patient troubled by anorgasmia, low libido or antidepressant-associated weight gain. The trade-off is activation: insomnia, agitation, dry mouth, tremor and, at the extreme, the seizure risk that dominates its contraindications.

6.9 Bupropion: the seizure threshold caveat and contraindications

Dose-dependent lowering of the seizure threshold. The one caveat every examiner wants: bupropion lowers the **seizure threshold** in a **dose-dependent** way (Stahl 2021, Maudsley 2021). It is therefore **contraindicated in a current or past seizure disorder**; in a **current or past eating disorder** (anorexia or bulimia, where electrolyte disturbance and low body weight amplify the risk, the historical signal coming from high-dose immediate-release use in low-weight anorexia); and in a patient **abruptly discontinuing alcohol, sedatives or an anticonvulsant**, since withdrawal itself lowers the threshold (Stahl 2021). Also avoid with an MAOI and within 14 days of stopping one (hypertensive risk), and use caution combining with nicotine replacement (hypertension) (Stahl 2021).

TRAP **The forbidden prescription.** Prescribing bupropion to a patient with a seizure disorder or an eating disorder, or during alcohol/sedative withdrawal, is the classic error: each independently lowers the seizure threshold that bupropion also lowers.

COMMON TRAP

"Low sexual dysfunction" makes bupropion tempting for the SSRI patient with a bulimia history, but the eating-disorder contraindication is absolute. Screen for a current or past eating disorder before any bupropion prescription.

INDIA

Bupropion (Bupron) and mirtazapine (Mirtaz) are both widely available in India. The Indian Psychiatric Society guidance on bipolar disorder notes that where an antidepressant must be used, bupropion is preferred over paroxetine (IPS guidelines); the Indian Psychiatric Society depression CPG (Gautam et al.) endorses second-generation antidepressants including these agents as first-line, though a mirtazapine- or bupropion-specific first-line row for depression could not be confirmed from the guideline database and is stated here at class level only.

GOOD TO REMEMBER

- **Bupropion (Bupron), mechanism:** NDRI, blocks noradrenaline and dopamine reuptake, activating, no serotonergic action, a CYP2D6 inhibitor.
- **Bupropion, signature caveat:** dose-dependent lowering of the seizure threshold, contraindicated in seizure disorders, eating disorders and abrupt alcohol/sedative withdrawal.
- **Bupropion, one to hold:** 150 to 300 mg/day, CANMAT first-line for depression and adjunct for SSRI-induced sexual dysfunction and fatigue; licensed (SR) for smoking cessation, started 1 to 2 weeks before the quit date.

HOLD THIS

Mirtazapine (NaSSA, alpha-2 antagonist) sedates and grows appetite with clean sexual and GI tolerability, best for depression with insomnia and weight loss; bupropion (NDRI) activates with no sexual dysfunction or weight gain, best for fatigue and SSRI-induced sexual dysfunction and for smoking cessation, but its dose-dependent lowering of the seizure threshold forbids it in seizure and eating disorders.

7 . Newer and multimodal antidepressants

A compact fold covering the agents that sit outside the SSRI, SNRI, TCA and MAOI classes yet keep appearing in exams because each carries one signature receptor mechanism and one signature caveat. The theme is **receptor engineering beyond simple reuptake**: two **multimodal** agents that add direct receptor actions to serotonin reuptake block, one melatonergic agent that resets the body clock, one sedating serotonin modulator repurposed for sleep, and one frankly atypical drug with a glutamate-and-opioid mechanism. Learn each as mechanism plus the one adverse effect the examiner is hunting for.

Framing. These are the "others" beside the SSRI and SNRI monographs; for how each slots into the guideline-anchored selection algorithm see the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes. For the serotonin receptor subtypes and CYP metabolism these agents act on, see the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. Two facts are CRITICAL and verified below: agomelatine needs scheduled liver function monitoring, and trazodone causes priapism.

7.1 Vortioxetine and vilazodone: the multimodal serotonin modulators

An SSRI backbone plus direct receptor actions. Both are serotonin modulator antidepressants that block the serotonin transporter (SERT), the same pump the SSRIs act on, but add clinically meaningful action at specific 5-HT receptor subtypes (Stahl 2021, K&S 2024). Vortioxetine (generic vortioxetine) is the fuller **multimodal** agent: SERT reuptake inhibitor, full agonist at 5-HT1A, partial agonist at 5-HT1B, and antagonist at 5-HT3, 5-HT7 and 5-HT1D (K&S 2024). Vilazodone (generic vilazodone) is narrower: an SSRI combined with 5-HT1A partial agonism, the same 5-HT1A property that makes buspirone anxiolytic, which is why Stahl files it as a SPARI (serotonin partial agonist reuptake inhibitor) (Stahl 2021). The added receptor actions are what differentiate the tolerability and, for vortioxetine, the cognitive signal.

RULE **Reuptake plus receptor.** A multimodal serotonin modulator does two things at once, block SERT and directly hit a named 5-HT receptor; the direct receptor action is what sets its side-effect profile apart from a plain SSRI.

7.2 Vortioxetine: dose, the pro-cognitive signal, and dose-dependent nausea

10 to 20 mg once daily, a first-line multimodal agent. CANMAT lists vortioxetine **10 to 20 mg/day** as a Level-1 first-line antidepressant for major depression (CANMAT 2016). PET occupancy of SERT reaches about 80% only at the 20 mg dose, so 10 to 20 mg is the effective band (K&S 2024). Its distinctive claims: a **pro-cognitive signal**, an improvement in processing speed, attention and executive function that trials suggest is partly independent of the antidepressant effect (attributed to its 5-HT7 and 5-HT3 antagonism and 5-HT1A agonism); a comparatively **lower rate of sexual dysfunction** than SSRIs; and a favourable cardiac profile with no meaningful effect on QT (Maudsley 2021, K&S 2024). The dominant adverse effect is **dose-dependent nausea**, driven by its serotonergic load, usually early and transient. It is a CYP2D6 substrate with a long **66-hour** half-life, so a strong 2D6 inhibitor roughly doubles levels and calls for a dose reduction, and a 14-day gap is needed before starting an MAOI (Stahl 2021, K&S 2024).

WORKED EXAMPLE

A depressed accountant with prominent complaints of "brain fog", slowed thinking and SSRI-related anorgasmia is a rational fit for vortioxetine 10 mg/day, uptitrated to 20 mg: the pro-cognitive signal targets the cognitive complaint and the lower sexual-dysfunction rate addresses the anorgasmia. Warn about early nausea and take it after food if needed (Stahl 2021, K&S 2024).

7.3 Vilazodone: dose, titration and the GI trade-off

20 to 40 mg once daily, titrated slowly with food. CANMAT places vilazodone **20 to 40 mg/day** as a second-line antidepressant, started at 10 mg and titrated up over about 2 weeks, taken **with food** to ensure absorption (CANMAT 2016, K&S 2024). The 5-HT1A partial agonism gives a relatively lower rate of sexual dysfunction and weight gain than pure reuptake blockers, but the price is **gastrointestinal**: diarrhoea and nausea are the commonest adverse effects, which is exactly why the slow titration and food rule exist, to blunt the GI burden (K&S 2024). It has no clinically significant effect on cardiac conduction. Head-to-head network meta-analyses find no clear efficacy advantage of vilazodone or vortioxetine over older antidepressants, which keeps vilazodone in the second line (Maudsley 2021).

10 to 20	20 to 40	66
VORTIOXETINE (MG/DAY)	VILAZODONE (MG/DAY)	VORTIOXETINE HALF-LIFE (HOURS)

GOOD TO REMEMBER

- **Vortioxetine, mechanism:** multimodal serotonin modulator, SERT reuptake inhibitor plus 5-HT1A agonist and 5-HT3/5-HT7 antagonist; a pro-cognitive signal.
- **Vortioxetine, signature effect and one to hold:** dose-dependent nausea and lower sexual dysfunction; CANMAT first-line 10 to 20 mg/day, CYP2D6 substrate, 66-hour half-life.
- **Vilazodone, mechanism:** an SSRI plus 5-HT1A partial agonism (SPARI); lower sexual dysfunction, but GI diarrhoea and nausea.
- **Vilazodone, one to hold:** CANMAT second-line 20 to 40 mg/day, titrate from 10 mg over 2 weeks and take with food.

7.4 Agomelatine: the melatonergic agonist that resets the body clock, and its liver caveat

An MT1/MT2 agonist and 5-HT2C antagonist. Agomelatine (generic agomelatine) is the uniquely **melatonergic** antidepressant: it is an agonist at the melatonin receptors **MT1** (mt1) and **MT2** (mt2), using the older M1/M2 nomenclature in some texts, and an antagonist at the serotonin **5-HT2C** (5-ht2c) receptor (K&S 2024, Stahl 2021). The MT1/MT2 agonism resynchronises circadian rhythm, restoring sleep architecture, while the 5-HT2C antagonism disinhibits frontocortical noradrenaline and dopamine, giving the antidepressant effect. CANMAT lists agomelatine **25 to 50 mg/day** at bedtime as a first-line agent, singled out for depression **with sleep disturbance**, and it has a low rate of sexual dysfunction, weight gain and discontinuation symptoms (CANMAT 2016). The defining caveat is **hepatotoxicity**: dose-related transaminase rises, and rare hepatitis and hepatic failure, mostly in the first months (Maudsley 2021).

The one monitoring rule. Agomelatine mandates **liver function monitoring**: check LFTs at baseline and again at 3, 6, 12 and 24 weeks after starting, and at every dose increase, then as clinically indicated; **stop the drug if transaminases rise above 3 times the upper limit of normal**; and it is **contraindicated in hepatic impairment** including cirrhosis and active liver disease (Maudsley 2021). It is a CYP1A2 substrate, so a strong 1A2 inhibitor such as fluvoxamine or ciprofloxacin markedly raises levels and is contraindicated.

25 to 50	0, 3, 6, 12, 24	3x ULN
AGOMELATINE (MG/DAY)	LFT WEEKS AFTER STARTING	TRANSAMINASE STOP THRESHOLD

RULE **Agomelatine needs baseline and follow-up liver function tests.** LFTs at baseline, then 3, 6, 12 and 24 weeks and at each dose increase; stop if transaminases exceed 3 times the upper limit of normal.

TRAP **Forgetting the LFTs.** Starting agomelatine without baseline liver function monitoring, or omitting the follow-up bloods, is the classic error; the same trap in reverse is missing high-dose trazodone priapism below.

GOOD TO REMEMBER

- **Agomelatine, mechanism:** melatonergic MT1 and MT2 agonist plus 5-HT2C antagonist that resynchronises circadian rhythm; CANMAT first-line 25 to 50 mg/day, especially with sleep disturbance.
- **Agomelatine, signature caveat and one to hold:** hepatotoxicity, so liver function monitoring at baseline and 3, 6, 12, 24 weeks; stop if transaminases exceed 3x ULN; contraindicated in hepatic impairment.

7.5 Trazodone: the sedating SARI, and the priapism caveat

A serotonin antagonist/reuptake inhibitor used low-dose for sleep. Trazodone (generic trazodone) is a SARI serotonin modulator: a potent 5-HT2A antagonist with weak serotonin reuptake inhibition and, crucially, **alpha-1 adrenergic** and H1 histamine antagonism (K&S 2024). At full antidepressant doses CANMAT rates it a second-line agent at **150 to 300 mg/day**, but in practice it is used far more often at **low dose (25 to 100 mg at night) for insomnia**, where the H1 and 5-HT2A block deliver sedation without the dependence of a benzodiazepine (CANMAT 2016, K&S 2024). The signature caveat is priapism: the alpha-1 antagonism that also causes its orthostatic hypotension can produce prolonged, painful erection, a urological emergency requiring immediate attention (K&S 2024). It is a CYP3A4 substrate, so a strong 3A4 inhibitor raises levels.

TRAP **The priapism warning omitted.** Prescribing trazodone, even low-dose for sleep, without counselling a male patient that a prolonged or painful erection is a medical emergency needing urgent care is the classic trazodone error.

PEARL

Trazodone's alpha-1 antagonism is the common thread: it explains the orthostatic hypotension AND the priapism. The mnemonic is that trazodone can "drop the pressure and raise the wrong thing" (K&S 2024).

GOOD TO REMEMBER

- **Trazodone, mechanism:** SARI serotonin modulator, 5-HT2A antagonist with weak SERT block plus alpha-1 and H1 antagonism; sedating, hence widely used low-dose (25 to 100 mg) for insomnia.
- **Trazodone, signature caveat and one to hold:** priapism (alpha-1 antagonism), a urological emergency; antidepressant dose 150 to 300 mg/day, CANMAT second-line.

7.6 Tianeptine: the glutamatergic, opioid-modulating atypical antidepressant

A mechanism unlike any other antidepressant. Tianeptine (generic tianeptine) is a genuinely atypical antidepressant whose action is **glutamatergic** rather than classically monoaminergic: it potentiates AMPA-receptor function and promotes synaptic plasticity, reversing stress-induced hippocampal remodelling, and (paradoxically for an antidepressant) it enhances rather than blocks serotonin reuptake (New Oxford 2020). More recently it has been shown to act as a **mu-opioid receptor agonist**, which is now thought to underlie much of its acute effect (New Oxford 2020). It is dosed at **25 to 50 mg/day** and is not marketed in many countries, including the UK

and USA (Maudsley 2021). The examinable concern that flows directly from the opioid mechanism is **abuse potential**: at supratherapeutic doses tianeptine behaves as an opioid, and misuse and dependence have been reported.

RULE **Glutamate and opioid, not just monoamine.** Tianeptine's antidepressant action rests on AMPA/glutamatergic modulation plus mu-opioid agonism; that opioid action is exactly why it carries abuse potential.

GOOD TO REMEMBER

- **Tianeptine, mechanism:** atypical glutamatergic antidepressant, AMPA-receptor potentiator that promotes synaptic plasticity and enhances serotonin reuptake, plus mu-opioid receptor agonism.
- **Tianeptine, signature concern and one to hold:** abuse potential from its opioid action; dose 25 to 50 mg/day; not marketed in many countries.

INDIA

Among these agents, agomelatine and vortioxetine are marketed in India; low-dose trazodone is in routine use for insomnia. A specific Indian brand for vortioxetine (sometimes cited as Vortioxa) could not be confirmed from the parsed reference library, so the generic name is used here rather than an unverified brand. The Indian Psychiatric Society depression CPG (Gautam et al.) endorses newer second-generation antidepressants as first-line at class level, but an IPS agent-specific first-line row for these particular molecules could not be confirmed from the guideline database and is stated at class level only.

COMMON TRAP

Treating this whole group as interchangeable SSRIs. They are not: agomelatine demands scheduled LFTs, trazodone risks priapism, and tianeptine has genuine abuse liability. Each carries a caveat an SSRI does not.

HOLD THIS

Vortioxetine (multimodal, SERT plus 5-HT1A agonism and 5-HT3/5-HT7 antagonism, pro-cognitive, dose-dependent nausea, 10 to 20 mg/day first-line) and vilazodone (SSRI plus 5-HT1A partial agonism, GI-heavy, 20 to 40 mg/day) are the multimodal serotonin modulators; agomelatine (melatonergic MT1/MT2 agonist and 5-HT2C antagonist, 25 to 50 mg/day) resets the body clock but needs liver function monitoring at baseline and 3, 6, 12, 24 weeks with a stop at transaminases above 3x ULN; trazodone (sedating SARI) is used low-dose for insomnia and can cause priapism; tianeptine is a glutamatergic, mu-opioid-agonist atypical with abuse potential.

8 . Serotonin syndrome and the NMS differential

Of all the complications an antidepressant can cause, **serotonin syndrome** is the one the exam asks about most reliably, because it is the drug-safety story that ties the whole antidepressant syllabus together: it is what happens when serotonergic drive is pushed too hard, usually by a combination of agents, and the single most dangerous combination, an MAOI plus a serotonergic drug, is exactly the interaction taught in the monoamine oxidase inhibitor topic. A resident must

be able to recite the triad, name the diagnostic criteria (the **hunter criteria**), give the first management step, and, above all, separate it cleanly from **neuroleptic malignant syndrome**, its dopamine-blocker mimic.

Why the differential is the whole point. Serotonin syndrome and neuroleptic malignant syndrome are both hyperthermic, rigid, autonomically unstable, altered-consciousness emergencies, and they are constantly confused. The examiner rewards the candidate who can name the one discriminator that tells them apart. The pharmacology of the serotonergic and dopaminergic pathways is in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the wider acute management of both syndromes (cooling, sedation, restraint, the medical emergency frame) is set out in the Perinatal/women's mental health and emergency psychiatry notes. Here the teaching is recognition, criteria, first management and the differential.

Discriminator	Serotonin syndrome serotonergic excess	Neuroleptic malignant syndrome dopamine blockade
Onset speed	over hours, rapid	over days, slower
Trigger drug	a serotonergic drug or combination SSRI plus MAOI, tramadol, linezolid	a dopamine blocker (antipsychotic), or abrupt dopamine-agonist withdrawal
Neuromuscular the pivot	clonus, hyperreflexia, tremor, myoclonus	lead-pipe rigidity, bradyreflexia
Bowel sounds	hyperactive	normal or reduced
Pupils	dilated (mydriasis)	normal
Course	resolves within about a day if stopped	evolves over days, slow recovery
Specific drug	cyproheptadine	dantrolene, bromocriptine
First step	stop the serotonergic agent	stop the antipsychotic

Fig 12.5 Serotonin syndrome versus neuroleptic malignant syndrome. The pivot is the neuromuscular sign: clonus and hyperreflexia point to serotonin syndrome, lead-pipe rigidity with hyporeflexia to NMS. Serotonin syndrome comes on over hours from a serotonergic combination, resolves fast once the drug is stopped and responds to cyproheptadine; NMS comes on over days from a dopamine blocker, evolves slowly and is treated with dantrolene or bromocriptine.

8.1 Pathophysiology: serotonergic excess, usually from a combination

The mechanism. Serotonin syndrome is a state of excessive serotonergic activity at central and peripheral serotonin receptors, chiefly the postsynaptic 5-HT2A and 5-HT1A receptors, produced by drugs that raise synaptic serotonin (Shorter Oxford 2018, Stahl 2021). It is extremely rare with a single agent at a recommended dose and is almost always the product of a **combination** of serotonergic drugs, or of an overdose (Kaplan and Sadock 2024). **The most dangerous combination.** The classic and most lethal pairing is an **MAOI plus a serotonergic drug**: the MAOI blocks serotonin breakdown while the second agent, an SSRI, an SNRI, clomipramine, tramadol or pethidine, drives serotonin higher, and together they produce runaway 5-HT toxicity (Shorter Oxford 2018, Stahl 2021). Other precipitants added to an SSRI

include a second serotonergic antidepressant, lithium, tryptophan, triptans, linezolid, methylene blue and the recreational drug ecstasy.

RULE **Serotonin syndrome is usually a combination, and MAOI-plus-serotonergic is the deadliest.** A single serotonergic drug at a normal dose rarely does it; two together, above all an MAOI, is the danger.

8.2 The clinical triad: neuromuscular, autonomic, mental-state

The three-part picture. Serotonin syndrome presents as a triad, and holding the triad is the fastest route to recognition (Shorter Oxford 2018, Stahl 2021). The first arm is **neuromuscular excitation**: clonus (spontaneous, inducible and ocular clonus, the single most characteristic sign), hyperreflexia, myoclonus, tremor and rigidity, and the neuromuscular findings are typically more prominent in the lower limbs. The second arm is **autonomic instability**: hyperthermia, tachycardia, diaphoresis, **mydriasis** (dilated pupils) and hyperactive bowel sounds with diarrhoea. The third arm is **altered mental state**: agitation, restlessness, anxiety and, in severe cases, confusion progressing to coma. Onset is **rapid, over hours** of the offending exposure.

clonus	hours	3
MOST CHARACTERISTIC NEUROMUSCULAR SIGN	TYPICAL ONSET AFTER THE TRIGGER	ARMS OF THE TRIAD (NEUROMUSCULAR, AUTONOMIC, MENTAL)

MNEMONIC

The three A's plus the clonus

Think Agitation (mental state), Autonomic instability (hyperthermia, tachycardia, diaphoresis, mydriasis, hyperactive bowel sounds) and Augmented neuromuscular activity (clonus, hyperreflexia, tremor, rigidity). The one sign that clinches it and that NMS does not share is clonus with hyperreflexia.

8.3 Diagnostic criteria: the hunter criteria and the older Sternbach criteria

The Hunter criteria. The hunter criteria (the Hunter Serotonin Toxicity Criteria, Dunkley et al. 2003) are the more specific and now-preferred diagnostic rule. In a patient who has taken a serotonergic agent, the diagnosis is made if any one of the following is present: spontaneous clonus; inducible clonus plus agitation or diaphoresis; ocular clonus plus agitation or diaphoresis; tremor plus hyperreflexia; or hypertonia plus a temperature above 38 degrees Celsius plus ocular or inducible clonus (Kaplan and Sadock 2024). The recurring anchors, clonus, agitation, diaphoresis, tremor and hyperreflexia, are why clonus and hyperreflexia are the exam discriminators. **The older Sternbach criteria.** The **Sternbach criteria** (Sternbach 1991) are the original, broader rule: a recent addition or dose increase of a serotonergic agent plus at least three of a list of features (agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhoea, incoordination, fever, mental-state change), with other causes and a recent neuroleptic excluded. Sternbach is more sensitive but less specific than Hunter.

TRAP **Treating serotonin syndrome as a diagnosis of exclusion only.** It is a clinical diagnosis anchored on clonus in a patient on a serotonergic drug; there is no confirmatory blood test, so waiting for one wastes time.

8.4 Management: stop the drug, support, benzodiazepines, cyproheptadine

The first and most important step. Stop all serotonergic agents immediately; if a 5-HT syndrome develops, all serotonergic medication should be withdrawn at once (Shorter Oxford 2018). **Supportive care.** Give supportive care with intravenous fluids, continuous monitoring and active **cooling** for hyperthermia, which is the feature that kills; the wider acute emergency frame, aggressive cooling, sedation and the management of severe hyperthermia, is set out in the Perinatal/women's mental health and emergency psychiatry notes. **Benzodiazepines.** Use a benzodiazepine (for example lorazepam or diazepam) to control agitation, tremor and the neuromuscular hyperactivity and to reduce the hyperadrenergic state. **The specific antidote.** In moderate-to-severe cases give cyproheptadine, a 5-HT2A antagonist, as the serotonin-antagonist antidote (Maudsley 2021, Kaplan and Sadock 2024); it is given orally, a common regimen being an initial 12 mg then 2 mg every two hours if symptoms continue, to a ceiling around 32 mg in 24 hours. Most cases resolve within about 24 hours of stopping the trigger and starting supportive care.

WORKED EXAMPLE

A patient on phenelzine is inadvertently started on tramadol for back pain and within hours becomes agitated and sweaty, with a temperature of 39 degrees Celsius, dilated pupils, a tachycardia of 130, brisk reflexes and sustained ankle clonus. This is serotonin syndrome from an MAOI-serotonergic combination. Stop both drugs at once, cool the patient and give intravenous fluids, sedate with a benzodiazepine, and give cyproheptadine as the serotonin antagonist. The Hunter criteria are met by the spontaneous clonus alone.

GOOD TO REMEMBER

- **Serotonin syndrome (the feature):** serotonergic excess, usually a combination and most dangerously an MAOI plus a serotonergic drug; the triad is neuromuscular excitation (clonus, hyperreflexia, tremor, rigidity), autonomic instability (hyperthermia, tachycardia, diaphoresis, mydriasis, hyperactive bowel sounds) and altered mental state (agitation); onset is rapid over hours.
- **Hunter criteria (the discriminator):** in a patient on a serotonergic agent, diagnose on clonus (spontaneous, inducible or ocular) with agitation or diaphoresis, or tremor plus hyperreflexia; clonus and hyperreflexia are the signs that separate it from NMS.
- **Cyproheptadine (the first management after stopping the drug):** a 5-HT2A antagonist used as the serotonin-antagonist antidote in moderate-to-severe cases; the management sequence is stop the serotonergic agents, support and cool, benzodiazepine for agitation, then cyproheptadine.

8.5 The differential from neuroleptic malignant syndrome

Why they are confused. Serotonin syndrome and neuroleptic malignant syndrome share hyperthermia, muscular rigidity, autonomic instability and altered consciousness, and 5-HT neurotoxicity is occasionally confused with NMS at the bedside (Shorter Oxford 2018, Maudsley

2021). What separates them is the **trigger, the neuromuscular sign and the tempo**. Serotonin syndrome follows a serotonergic drug, comes on **rapidly over hours**, and is defined by **clonus** and **hyperreflexia** with hyperactive bowel sounds and mydriasis. Neuroleptic malignant syndrome follows a **dopamine-blocker** (an antipsychotic or another dopamine antagonist such as metoclopramide), comes on **slowly over days**, and is defined by **lead-pipe rigidity** with **hyporeflexia**, normal-to-sluggish bowel sounds, and a marked rise in creatine kinase, often above 1000 units per litre (Maudsley 2021). The one discriminator to carry into the exam is **clonus and hyperreflexia (serotonin syndrome) versus lead-pipe rigidity and hyporeflexia (NMS).**

FEATURE	SEROTONIN SYNDROME	NEUROLEPTIC MALIGNANT SYNDROME
Trigger	a serotonergic drug (SSRI, SNRI, MAOI combination, tramadol)	a dopamine-blocker (antipsychotic, metoclopramide)
Onset / tempo	rapid, over hours	slow, over days
Neuromuscular sign (the discriminator)	**clonus and hyperreflexia**	**lead-pipe rigidity and hyporeflexia**
Pupils	mydriasis	normal
Bowel sounds	hyperactive, diarrhoea	normal or reduced
Creatine kinase	usually mild rise	marked rise, often above 1000 units per litre
Resolution	fast, often within about 24 hours of stopping the drug	slow, over days to weeks
Specific agent	cyproheptadine (5-HT2A antagonist)	bromocriptine and dantrolene

The serotonin-syndrome versus NMS grid: clonus and hyperreflexia against lead-pipe rigidity is the one discriminator (Shorter Oxford 2018, Maudsley 2021).

RULE **Clonus and hyperreflexia point to serotonin syndrome; lead-pipe rigidity points to NMS.** A serotonergic trigger over hours with brisk clonus is serotonin syndrome; a dopamine-blocker over days with lead-pipe rigidity and a high CK is NMS.

TRAP **Missing serotonin syndrome after an MAOI-serotonergic combination, or confusing it with NMS.** The commonest errors are failing to recognise 5-HT toxicity when an MAOI meets a serotonergic drug, and mislabelling clonus-with-hyperreflexia as NMS.

INDIA

Tramadol and pethidine are widely and casually co-prescribed for pain in Indian practice, so the highest-risk everyday scenario is a patient on an antidepressant (or, worse, an MAOI) who is given tramadol for a musculoskeletal complaint. Cyproheptadine is freely available in India as an oral antihistamine (commonly stocked as Ciplactin or Practin), which makes the antidote easy to obtain when moderate-to-severe serotonin syndrome is recognised.

GOOD TO REMEMBER

- **The one discriminator:** clonus and hyperreflexia mean serotonin syndrome; lead-pipe rigidity and hyporeflexia mean neuroleptic malignant syndrome.
- **Serotonin syndrome:** serotonergic trigger, rapid onset over hours, clonus, hyperreflexia, mydriasis, hyperactive bowel sounds, usually mild CK rise; first step stop the drug, then support/cool, benzodiazepine, cyproheptadine.
- **Neuroleptic malignant syndrome:** dopamine-blocker trigger, slow onset over days, lead-pipe rigidity, hyporeflexia, marked CK rise (often above 1000 units per litre); stop the antipsychotic, support, benzodiazepine, then bromocriptine and dantrolene.

HOLD THIS

Clonus and hyperreflexia after a serotonergic drug (rapid, over hours) is serotonin syndrome; lead-pipe rigidity and hyporeflexia after a dopamine-blocker (slow, over days) with a high CK is neuroleptic malignant syndrome, and the first step in serotonin syndrome is to stop the serotonergic agents and give cyproheptadine.

9 . Antidepressant discontinuation syndrome

When an antidepressant taken continuously for at least a few weeks is stopped or reduced, a recognisable cluster of somatic and psychological symptoms can emerge within a few days. This is **antidepressant discontinuation syndrome**, and the examiner tests three things: that you can name the cluster (the **finish** mnemonic), that you can predict who is at risk (the short-half-life agents), and that you can tell it apart from a true relapse of depression. Getting the last point wrong is the classic clinical error, because the fix for discontinuation is a slower taper and reassurance, whereas the fix for relapse is restarting treatment.

The framing that scores. Discontinuation symptoms are a pharmacological withdrawal phenomenon from an abrupt fall in synaptic serotonin availability, not a sign of addiction or drug dependence: there is no craving, no compulsive use and no dose escalation, and the syndrome is self-limiting. The organising fact is that onset, severity and duration all track the **half-life** of the agent, so paroxetine and venlafaxine are the worst offenders and fluoxetine the least (Maudsley 2021; Kaplan 2024). The receptor and cytochrome background sits in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the perinatal analogue is cross-referred to the Perinatal/women's mental health and emergency psychiatry notes.

9.1 The syndrome and the FINISH cluster

The setup. The patient has usually been on the antidepressant for a month or more, and symptoms begin within a few days of stopping, halving the dose, or even missing doses in a poor adherer (Kaplan 2024). The symptoms are typically mild and **self-limiting over one to two weeks**, though for some patients and some agents they last longer.

The cluster. The high-yield handle is **finish** (use "finish"): **F**lu-like symptoms (lethargy, myalgia, sweating), **I**nsomnia (often with vivid dreams), **N**ausea, **I**mbalance (dizziness, lightheadedness, vertigo), **S**ensory disturbances (paraesthesiae and the classic **electric-shock** or "brain-zap"

sensations), and **H**yperarousal (anxiety, irritability, agitation). The sensory "brain zaps", brief intracranial electric-shock feelings often triggered by eye movement, are close to pathognomonic and rarely feature in a depressive relapse (Maudsley 2021; Kaplan 2024).

MNEMONIC

FINISH

Flu-like, Insomnia, Nausea, Imbalance, Sensory disturbances (the electric-shock "brain zaps"), Hyperarousal/anxiety. The six-symptom cluster of antidepressant discontinuation syndrome, coming on within days of stopping and settling over one to two weeks.

RULE **Taper antidepressants slowly, especially the short-half-life agents.** A gradual reduction over weeks, or a switch to fluoxetine to taper, prevents most discontinuation symptoms.

9.2 Risk factors: half-life drives everything

The agent. Onset and severity correlate inversely with half-life. Paroxetine (Pexep) and venlafaxine (Venlor) are the worst because both have short half-lives with no meaningful active metabolite, and paroxetine adds a high serotonin-transporter affinity and anticholinergic rebound; short-half-life agents produce symptoms within a day or two of stopping (Maudsley 2021). Fluoxetine (Fludac) is the least likely to cause a discontinuation syndrome because its parent drug (2 to 3 days) and its active metabolite norfluoxetine (about 2 weeks) mean the drug effectively **self-tapers**; when symptoms do occur they may be delayed by 2 to 6 weeks (Maudsley 2021).

The other two levers. A **longer duration** of treatment and, above all, **abrupt cessation** raise the risk; a higher dose and a rapid taper method compound it (Maudsley 2021). Discontinuation is reported to some degree with every antidepressant class, including SNRIs, TCAs and MAOIs, not just the SSRIs.

AGENT (INDIAN BRAND)	HALF-LIFE	DISCONTINUATION RISK
Paroxetine (Pexep)	Short (~21 h), no active metabolite	**Worst: fast onset, prominent brain-zaps**
Venlafaxine (Venlor)	Short (~5 h; ODV ~11 h)	**Worst: notoriously severe, dizziness prominent**
Most other SSRIs/SNRIs	Intermediate	Moderate, dose- and taper-dependent
Fluoxetine (Fludac)	Long (norfluoxetine ~2 wk)	**Least: self-tapers; onset may be delayed**

Discontinuation risk tracks half-life inversely: shortest-half-life agents (paroxetine, venlafaxine) are the worst, the long-half-life fluoxetine the least (Maudsley 2021; Kaplan 2024).

9.3 Distinguishing discontinuation from relapse, and management

The discriminator. Two features separate **discontinuation** (use "discontinuation") from a depressive relapse. First, **timing**: discontinuation symptoms appear fast, within a few days of

stopping or reducing, and resolve over one to two weeks, whereas a genuine relapse builds gradually over weeks and does not remit on its own. Second, the **somatic and sensory quality**: the flu-like malaise, imbalance and electric-shock paraesthesiae of discontinuation are not part of a depressive syndrome, and a fast, dramatic improvement within hours of a single reinstated dose points firmly to discontinuation rather than relapse (Maudsley 2021; Kaplan 2024).

Management. The core intervention is a slow **taper** (use "taper") over weeks (in practice, weeks to months for a short-half-life agent, with hyperbolic small reductions near the bottom of the dose range), plus reassurance that the symptoms are self-limiting and are not a sign of addiction. If symptoms are already troublesome, reinstate the original antidepressant (or switch to fluoxetine and taper from there, exploiting its long half-life) until stable, then reduce more gradually. Reassurance and forewarning at the outset prevent much of the distress (Kaplan 2024).

TRAP **Mistaking discontinuation symptoms for a depressive relapse.** Restarting or escalating on the wrong call keeps the patient on a drug they were coming off; use timing and the somatic/sensory quality to tell them apart.

9.4 The perinatal analogue: neonatal adaptation syndrome

A related phenomenon follows late-pregnancy antidepressant exposure. The neonate, having been exposed transplacentally, can show a self-limiting **neonatal adaptation syndrome** after delivery, with jitteriness, irritability, feeding and respiratory difficulty and, occasionally, tremor, that mirrors an adult discontinuation picture and settles within days. The examiner's point is that abrupt withdrawal of the antidepressant before delivery is usually the wrong response, because it exposes the mother to relapse and postpartum depression; the fuller perinatal handling belongs to the Perinatal/women's mental health and emergency psychiatry notes.

1 to 2 wk	1 to 2 days	2 to 6 wk
TYPICAL DURATION, SELF-LIMITING	ONSET WITH SHORT-HALF-LIFE AGENTS	DELAYED ONSET WITH FLUOXETINE

HOLD THIS

Discontinuation symptoms come on within days, are captured by FINISH (with the "brain-zap" as the near-pathognomonic clue), are worst with paroxetine and venlafaxine and least with fluoxetine, and are treated by a slower taper and reassurance, not by treating a relapse.

GOOD TO REMEMBER

- **The cluster (FINISH):** Flu-like, Insomnia, Nausea, Imbalance, Sensory (electric-shock "brain zaps"), Hyperarousal, within days of stopping, self-limiting over **1 to 2 weeks**.
- **The discriminator:** fast onset plus somatic/sensory quality (brain-zaps, imbalance) mark discontinuation; a slow-building, purely mood picture marks relapse.
- **Worst agents:** paroxetine (Pexep) and venlafaxine (Venlor), short half-lives; fluoxetine (Fludac) least because it self-tapers.
- **First step:** taper slowly (or switch to fluoxetine to taper) and reassure; reinstate the agent if symptoms are severe. It is not addiction.

10 . Ketamine and esketamine

This is the glutamatergic corner of the antidepressant map, and it is a high-yield one because it breaks two things every resident is taught about depression. The first is the **monoamine model**: ketamine and esketamine do not touch the serotonin, noradrenaline or dopamine pumps as their primary act; they antagonise the glutamate NMDA (nmda) receptor. The second is the **therapeutic lag**: where a monoamine antidepressant is said to take weeks, these **rapid-acting** agents lift depressive symptoms and suicidal ideation within hours (K&S 2024, Maudsley 2021). That combination, a novel target and a rapid onset, is exactly what examiners probe, alongside the safety scaffolding the rapidity forces on you.

Framing. Treat this topic as two agents on one mechanism: racemic ketamine (intravenous, off-label) and esketamine, the S-enantiomer (intranasal, brand Spravato, licensed). For the receptor systems and the wider glutamate story, see the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; for where these agents sit in the treatment-resistant depression ladder and the CANMAT algorithm, see the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; for the acute-suicidality assessment that flanks the licensed indication, see the Somatic-symptom, sexual, impulse-control disorders and suicide notes. Two facts are CRITICAL and verified below: the licensed indication is add-on esketamine for treatment-resistant depression (and for major depression with acute suicidal ideation), and it must be given under observation for dissociation and blood pressure.

10.1 The mechanism: NMDA antagonism, an AMPA burst and synaptogenesis

Block the brake, trigger a glutamate surge, grow synapses. Ketamine is a non-competitive (uncompetitive) antagonist at the NMDA receptor (K&S 2024, Maudsley 2021). The current model is a disinhibition cascade: NMDA blockade falls preferentially on GABAergic inhibitory interneurons, which normally suppress glutamate output; taking that brake off produces an acute cortical **glutamate surge** onto the pyramidal neuron (K&S 2024, Maudsley 2021). That surge activates postsynaptic **AMPA** (ampa) receptors, and the AMPA-throughput step drives brain-derived neurotrophic factor (BDNF) release, TrkB and mTOR activation, and downstream **synaptogenesis** and synaptic potentiation (K&S 2024). Because the antidepressant effect is carried by rapid neuroplasticity rather than by slow receptor down-regulation, it appears within hours, which is the direct **glutamatergic** reframing of depression: a disorder of impaired synaptic plasticity that a glutamate modulator can rapidly reverse.

RULE **NMDA off, AMPA on.** Ketamine works by antagonising NMDA receptors on inhibitory interneurons, which disinhibits a glutamate surge onto AMPA receptors and drives synaptogenesis; that plasticity, not monoamine reuptake block, is why the effect is rapid.

TRAP **Calling it a monoamine drug.** Ketamine has weak serotonergic, dopaminergic and opioid actions, but its rapid antidepressant effect is glutamatergic; framing it as "just another reuptake inhibitor" misses both the mechanism and the therapeutic-lag contrast the examiner wants.

10.2 The two agents: racemic ketamine and the S-enantiomer esketamine

Same target, different enantiomer, different regulatory status. Ketamine is a racemic mixture of two mirror-image enantiomers, (S)-ketamine and (R)-ketamine (arketamine); the S-enantiomer, esketamine, binds the NMDA receptor with roughly four times the affinity of the R-enantiomer (K&S 2024). Racemic ketamine is given **intravenously** and remains an **off-label** treatment for depression, drawing on its long licence as a dissociative anaesthetic (K&S 2024, Maudsley 2021). Esketamine was developed as an **intranasal** spray (brand Spravato) and is the licensed molecule (K&S 2024). A point of contrast worth holding: because esketamine is the more potent NMDA binder, it was the enantiomer taken to licence, yet head-to-head evidence suggests intravenous racemate is possibly at least as effective as intranasal esketamine (Maudsley 2021).

Ketamine (racemic)

50:50 S and R enantiomer mixture; intravenous, off-label for depression, anaesthetic licence.

Esketamine

the S-enantiomer, four-fold higher NMDA affinity; intranasal, brand Spravato, the licensed antidepressant.

Arketamine

the R-enantiomer; lower NMDA affinity, still investigational for depression.

10.3 The licensed indication and the treatment-resistant depression context

Add-on esketamine for treatment-resistant depression, and for major depression with acute suicidal ideation. Intranasal esketamine (Spravato) is licensed as an add-on to an oral antidepressant for **treatment-resistant depression**, defined by failure of at least two adequate antidepressant trials in the current episode, and separately for **major depression with acute suicidal ideation or behaviour** (K&S 2024, Maudsley 2021). It is not a monotherapy: the licence is as an add-on to an SSRI or SNRI. Racemic ketamine itself carries no depression licence and is used off-label (K&S 2024). At guideline level, CANMAT places **add-on intranasal esketamine** as a second-line adjunct for patients failing at least two adequate antidepressant trials, and **add-on intravenous racemic ketamine** as a second-line adjunct for a rapid antidepressant effect including rapid reduction of suicidal ideation, both with blood-pressure and dissociation monitoring (CANMAT 2023). Non-esketamine racemic ketamine by oral, intramuscular or intranasal route is reserved third-line given variable protocols (CANMAT 2023).

The other guidelines. The **Indian Psychiatric Society** depression guideline (Gautam et al.) endorses second-generation antidepressants first-line and reserves novel and specialist strategies for later steps; a specific IPS guidelines agent-level first-line row for esketamine could not be confirmed from the parsed reference library and is therefore not stated. The BAP TRD framework favours augmenting with quetiapine, aripiprazole or lithium first-line for treatment-resistant depression rather than naming esketamine as a first step (BAP). NICE recognises nasal esketamine as a licensed treatment for treatment-resistant major depression but, as of the parsed edition, had not approved it for routine NHS use in the UK, while it is used elsewhere (Maudsley 2021).

2	within hours	2
FAILED ANTIDEPRESSANT TRIALS DEFINING TRD	ONSET OF ANTIDEPRESSANT EFFECT	POST-DOSE OBSERVATION (HOURS)

10.4 The dosing schedule and why the benefit needs maintenance

Induction twice weekly, then step down; the effect is transient and must be scheduled. The intranasal esketamine dose is either **56 mg** or **84 mg** (K&S 2024). In the **induction phase** (weeks 1 to 4) dosing is **twice weekly**, starting at 56 mg after the first administration, titratable up to 84 mg as indicated. In the **maintenance phase** the schedule reduces to **once weekly for 4 weeks**, then continues once weekly or steps down to once every 2 weeks (K&S 2024). Intravenous racemic ketamine in the antidepressant setting is **0.5 mg/kg** infused over **40 minutes**, up to twice weekly, and not exceeding 6 weeks (K&S 2024, Maudsley 2021).

Why a schedule at all. A single ketamine infusion produces a rapid response that peaks around 24 hours but is short-lived: improvement typically lasts about 3 days and symptoms return toward baseline by around 7 days (K&S 2024). That transience is the whole reason for a repeated-dose induction and then a maintenance schedule; the drug is a bridge whose effect decays, not a one-off cure. This is the pharmacological basis of the topic RULE below.

WORKED EXAMPLE

A patient with treatment-resistant depression, already on an adequately dosed SSRI after two prior failed trials, is started on intranasal esketamine 56 mg twice weekly for the 4-week induction, titrated to 84 mg for tolerability, then moved to weekly and later fortnightly dosing while the oral antidepressant continues. Each session is given in the clinic with 2 hours of post-dose observation. The rapid lift in weeks 1 to 2 is real, but the oral antidepressant and the maintenance schedule are what hold it (K&S 2024).

10.5 Adverse effects: dissociation, blood pressure, sedation and abuse potential

The neuropsychiatric signature is dissociation. The hallmark adverse effect of ketamine and esketamine is dissociation and perceptual change: perceptual disturbances, vivid or abnormal sensory experiences, derealisation and depersonalisation, reported by over 70 percent of patients with intravenous ketamine (K&S 2024). These are experienced at the time of administration, are transient, and typically resolve within about 2 hours (K&S 2024). Related short-term effects include sedation, dizziness, confusion, memory disturbance and, particularly in those with a schizophrenia history, **psychotomimetic** (nondissociative psychotic) symptoms. The commonest intranasal esketamine adverse events are dissociation, dizziness, nausea, sedation, vertigo and increased blood pressure (K&S 2024).

The cardiovascular effect is a transient blood-pressure rise. At antidepressant doses both agents cause **transient hypertension and tachycardia** (K&S 2024). Rarely, hypotension, bradycardia, arrhythmias and cardiac decompensation are reported. Both are **contraindicated in uncontrolled significant hypertension**, and esketamine additionally in aneurysmal vascular disease, arteriovenous malformation and intracerebral haemorrhage (K&S 2024). Gastrointestinal nausea and vomiting are common enough to warrant antiemetic readiness.

Abuse potential and other cautions. Ketamine is a Schedule III controlled substance with recognised recreational misuse (the high-dose "K-hole"), and repeated use can produce tolerance and dependence (K&S 2024). Long-term chronic use is associated with a ketamine-induced **cystitis** (dysuria, frequency, haematuria, reduced bladder capacity), which is why longer-term ketamine or esketamine use attracts periodic urinalysis for cystitis (K&S 2024, CANMAT 2023). Esketamine carries a boxed warning for sedation, dissociation, abuse and misuse potential, availability only through the REMS programme, and increased suicidal thoughts in young people. Concomitant benzodiazepines or lamotrigine may attenuate the antidepressant response, and combining ketamine with opioids or other CNS depressants risks profound sedation and respiratory depression (K&S 2024).

TRAP **Giving it to a hypertensive patient unmonitored.** Both agents raise blood pressure transiently and are contraindicated in uncontrolled significant hypertension; administering without a baseline check and post-dose monitoring, or in a psychotic-prone patient without weighing the psychotomimetic risk, is the classic error.

10.6 The monitoring: in-clinic administration and the REMS-style observation

Because it dissociates and raises blood pressure, it is given under observation. The rapidity and the dissociative and cardiovascular effects force a supervised model. In the United States esketamine is dispensed and administered only in a certified, medically supervised setting under a **risk evaluation and mitigation strategy** (REMS), with the patient monitored for at least **2 hours** post-administration (K&S 2024). Practically this means the drug is self-sprayed under direct observation of a healthcare provider, with blood pressure checked before and after, and the patient not driving on the day of dosing or until the following morning (K&S 2024). For intravenous racemic ketamine, the Maudsley advises a pretreatment physical examination with baseline blood pressure and a pretreatment ECG, blood-pressure monitoring before and after the infusion, and observation during and for at least 1 hour after the infusion by a clinician trained in life support (Maudsley 2021). This is the REMS-style monitoring an examiner expects you to name.

PEARL

The monitoring headline maps to the two dangerous effects: observe for **dissociation** (neuropsychiatric) and for the **blood-pressure rise** (cardiovascular). Both are transient and settle within about 2 hours, which is exactly why the observation window is 2 hours for intranasal esketamine (K&S 2024).

RULE **Esketamine works within hours for treatment-resistant depression but must be given under observation for dissociation and blood pressure.** In-clinic administration, blood pressure before and after, and at least 2 hours of post-dose observation.

10.7 India, availability and cost

INDIA

Racemic ketamine is widely available in India as an injectable anaesthetic and is a controlled drug; its use for depression is off-label and confined to specialist and academic settings. Intranasal esketamine (Spravato) is a high-cost, cold-chain, REMS-gated product, and a specific Indian brand or routine Indian availability could not be confirmed from the parsed reference library, so no Indian brand is asserted here and the international brand Spravato is named only as the licensed innovator product. For Indian postgraduate answers, the practical position is that these are rapid-acting glutamatergic agents used in tertiary and research centres rather than routine practice, that the guideline to cite first is the Indian Psychiatric Society depression guideline (Gautam et al.), and that where a rapid response to severe or suicidal depression is needed in Indian teaching hospitals, ECT remains the widely available and heavily used option (see the ECT and neurostimulation notes).

MNEMONIC

"RAPID KETAMINE": Receptor NMDA, AMPA burst, Plasticity, In-clinic, Dissociation and blood pressure, Keeps needing repeats.

Receptor target is NMDA; the effect runs through an AMPA burst driving synaptic Plasticity; it is given In-clinic under observation; watch Dissociation and the blood-pressure rise; and because the benefit is transient it Keeps needing repeats on a maintenance schedule.

HOLD THIS

Esketamine (S-ketamine, intranasal, Spravato) is an NMDA antagonist licensed as an add-on to an oral antidepressant for treatment-resistant depression and for major depression with acute suicidal ideation; it works within hours, dose is 56 or 84 mg twice weekly at induction then stepped down, and it must be given in-clinic with blood-pressure checks and at least 2 hours of post-dose observation for dissociation.

GOOD TO REMEMBER

- **Ketamine, mechanism:** non-competitive NMDA-receptor antagonist producing a glutamate surge onto AMPA receptors and rapid synaptogenesis; a glutamatergic, not monoamine, antidepressant.
- **Ketamine, signature effect and one to hold:** dissociation and a transient blood-pressure rise, with abuse potential and chronic-use cystitis; racemic, intravenous, off-label, 0.5 mg/kg over 40 minutes, up to twice weekly.
- **Esketamine, mechanism:** the S-enantiomer with four-fold higher NMDA affinity, intranasal spray (brand Spravato).
- **Esketamine, indication and one to hold:** licensed add-on to an oral antidepressant for treatment-resistant depression and for major depression with acute suicidal ideation; 56 or 84 mg, twice weekly induction then stepped down, given under REMS-style observation with at least 2 hours of post-dose monitoring for dissociation and blood pressure.
- **The transience rule:** the response is rapid but short-lived (peaks about 24 hours, fades by about 7 days after a single dose), so it is a bridge needing a maintenance schedule and an ongoing oral antidepressant, not a cure.

11 . Choosing an antidepressant

Once the diagnosis of a depressive episode is settled and pharmacotherapy is indicated, the next decision the examiner tests is not *whether* to prescribe but *which* agent, and the reasoning behind it. **Choosing an antidepressant** is a selection topic, and the single organising principle the board rewards is that the first-line antidepressants are broadly equal in antidepressant efficacy, so the choice is driven not by presumed potency but by the adverse-effect profile, the **comorbidity**, past response, drug interactions, safety in overdose and cost (Kaplan & Sadock 2024; Maudsley 2021). This topic teaches **antidepressant selection** in clinical practice as a guideline-anchored algorithm; the pharmacology of each agent lives in its own topic and the deep treatment-resistance ladder is the treatment-resistance topic.

Ground the algorithm in the guidelines. Lead with **CANMAT**: the Canadian Network for Mood and Anxiety Treatments recommends a second-generation antidepressant as the first-line pharmacological treatment for major depression, individualising the choice to patient and medication factors under measurement-based monitoring (CANMAT 2016). Then state the **Indian Psychiatric Society** position, and what NICE and the BAP recommend. Every dose, interval and first-line recommendation below is verified against the CANMAT and IPS guideline rows and the Maudsley (CANMAT 2016; IPS 2017; Maudsley 2021).

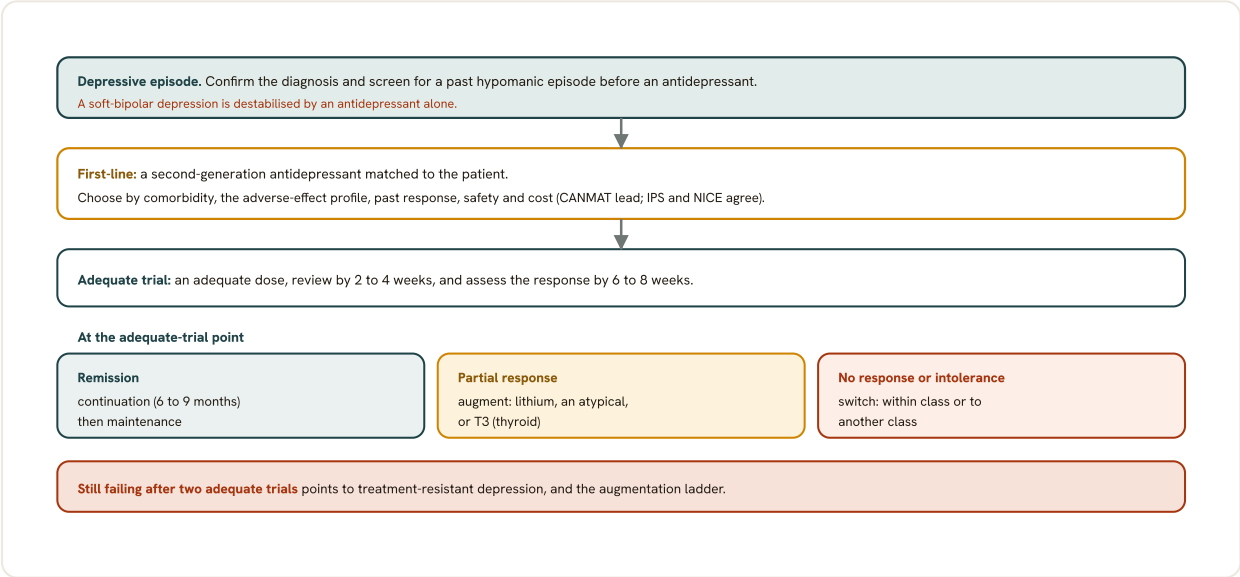

Fig 12.3 Choosing and sequencing an antidepressant. After confirming the diagnosis and screening for past hypomania, choose a second-generation antidepressant matched to the patient (the first-line agents are broadly equal in efficacy, so comorbidity and the adverse-effect profile drive the choice). Run an adequate trial, then act on the response: continue a remission, augment a partial response, switch a non-response. Two failed adequate trials define treatment resistance.

11.1 The governing principle: equal efficacy, so choose by profile

Efficacy is broadly equal. Head-to-head, no first-line antidepressant is convincingly more effective than another for the average patient with major depression, so the whole art of **choosing an antidepressant** is matching the drug to the individual patient rather than ranking drugs by strength (Kaplan & Sadock 2024; Maudsley 2021). A handful of agents (escitalopram, sertraline, venlafaxine, mirtazapine) carry a modest efficacy edge in network meta-analyses and

are worth preferring where maximising response is paramount, but this edge is small and never overrides tolerability.

So the choice is driven by six things. The adverse-effect and tolerability profile; the **comorbidity** (a coexisting condition the drug can help or harm); the patient's past response and any family response; drug interactions with existing medication; safety in overdose; and cost and availability (Kaplan & Sadock 2024; Maudsley 2021). Hold these six as the answer to almost any "which antidepressant and why" viva.

RULE **Choose the antidepressant by the adverse-effect and comorbidity match, not by presumed potency.** First-line agents are broadly equal in efficacy; the fit to the patient is what differs.

11.2 The CANMAT first-line list (lead guideline)

Second-generation antidepressants, first-line. CANMAT names the following as Level-1 first-line agents for major depression, all broadly equal and chosen by profile (CANMAT 2016): the SSRIs, the SNRIs, mirtazapine, bupropion, vortioxetine and agomelatine. The tricyclics and irreversible MAOIs are held back to second and third line because of their adverse-effect burden and danger in overdose.

CANMAT FIRST-LINE AGENT (INDIAN BRAND)	CLASS	DOSE (MG/DAY)	PROFILE NOTE THAT DRIVES SELECTION
Escitalopram (Nexito, S-Citadep)	SSRI	**10 to 20**	Cleanest, fewest interactions; dose-dependent QTc ceiling
Sertraline (Serta, Daxid)	SSRI	50 to 200	Broadest first choice; safe in pregnancy and post-MI
Fluoxetine (Fludac)	SSRI	20 to 60	Long half-life, activating, self-tapering
Paroxetine (Pexep)	SSRI	20 to 50	Anticholinergic, worst discontinuation; avoid in pregnancy
Venlafaxine (Venlor)	SNRI	**75 to 225**	Efficacy edge; monitor blood pressure at higher dose
Duloxetine (Duzela)	SNRI	60	First choice when depression coexists with neuropathic pain
Mirtazapine (Mirtaz)	NaSSA	15 to 45	Sedating, promotes appetite; for insomnia and weight loss
Bupropion (Bupron)	NDRI	150 to 300	No sexual dysfunction, no weight gain, activating; lowers seizure threshold

CANMAT FIRST-LINE AGENT (INDIAN BRAND)	CLASS	DOSE (MG/DAY)	PROFILE NOTE THAT DRIVES SELECTION
Vortioxetine (Vortioxa)	Multimodal	10 to 20	Low sexual dysfunction; possible pro-cognitive benefit
Agomelatine	Melatonergic	25 to 50	For sleep disturbance; monitor liver function tests

The CANMAT 2016 Level-1 first-line antidepressants with verified adult dose ranges and the one profile feature that drives selection; the Indian brand leads the generic. The highlighted cells are the two workhorse first steps.

GOOD TO REMEMBER

- **Escitalopram (Nexito or S-Citadep):** SSRI, cleanest and fewest interactions, dose-dependent QTc; first-line, **10 to 20 mg/day**.
- **Sertraline (Serta or Daxid):** SSRI, broadest first choice, safe post-MI and in pregnancy; first-line, **50 to 200 mg/day**.
- **Venlafaxine (Venlor):** SNRI, efficacy edge, dose-dependent hypertension; first-line, **75 to 225 mg/day**.
- **Duloxetine (Duzela):** SNRI, dual antidepressant and analgesic action; first-line when pain is comorbid, **60 mg/day**.
- **Mirtazapine (Mirtaz):** NaSSA, sedating and appetite-promoting; first-line for insomnia with weight loss, **15 to 45 mg/day**.
- **Bupropion (Bupron):** NDRI, no sexual dysfunction, activating, lowers seizure threshold; first-line, **150 to 300 mg/day**.

11.3 The Indian Psychiatric Society position

SSRIs first. The **indian psychiatric society** Clinical Practice Guidelines for depression (Gautam et al.) make the SSRIs the first-line antidepressant for major depression given their favourable side-effect and safety profile, with the TCAs, mirtazapine, bupropion and venlafaxine as the other preferred options (IPS 2017). For moderate to severe depression the **ips guidelines** name escitalopram 10 to 20 mg, sertraline 50 to 200 mg or fluoxetine 20 to 60 mg as the initial choice, matching the CANMAT list at guideline level.

The IPS reassessment and next-step rule. The IPS advises reviewing pharmacotherapy response at 4 to 6 weeks; if at least a moderate improvement is not seen, reappraise and adjust, by optimising the dose to the maximum tolerated, switching within class (one SSRI to another), or switching across class to an SNRI such as venlafaxine 75 to 225 mg or duloxetine 60 mg (IPS 2017). After acute-phase response the same dose is continued for a total of 6 to 9 months from initiation to prevent relapse. This IPS position is verified against the guideline rows; where a finer IPS specific cannot be confirmed it is flagged under gaps rather than invented.

INDIA

The IPS first-line choice mirrors CANMAT but is calibrated to Indian practice and cost: escitalopram (Nexito or S-Citadep) and sertraline (Serta or Daxid) are the outpatient workhorses because they are cheap generics, well tolerated, and safe in the medically complex and largely out-of-pocket patient. A month of a generic SSRI costs a small fraction of a single private consultation, which matters for adherence. The TCAs remain in wide use in India for comorbid pain and for cost, but their overdose danger keeps them off first line.

11.4 What NICE and the BAP recommend

NICE. When an antidepressant is used, NICE holds that the SSRIs are generally well tolerated, have a good safety profile and should be the first choice for most people; it warns that the TCAs are dangerous in overdose, with lofepramine having the best safety profile of the class (NICE 2022). NICE does not routinely offer an antidepressant first-line for less severe depression, preferring the least intrusive option such as guided self-help, and reviews symptoms and side effects usually within 2 weeks of starting (within 1 week in those aged 18 to 25 or where there is particular suicide concern).

BAP. The British Association for Psychopharmacology likewise directs, in the absence of special factors, to choose antidepressants that are better tolerated and safer in overdose, so the SSRIs and other newer antidepressants are the first-line choices, reserving older TCAs and MAOIs for when first-line treatment has failed (BAP 2015). Where maximising efficacy is paramount in a more severely ill patient, the BAP lists clomipramine, venlafaxine at 150 mg or more, escitalopram 20 mg, sertraline, amitriptyline or mirtazapine in preference to other agents (BAP 2015).

RULE **Every major guideline puts second-generation antidepressants (led by the SSRIs) first.** CANMAT, the IPS, NICE and the BAP all cite tolerability and overdose safety as the reason.

11.5 Practical matching: fit the agent to the comorbidity

The examinable skill is turning "equal efficacy" into a concrete choice by reading the patient. Match a favourable adverse effect or a coexisting condition to the drug that helps it, and avoid the drug that would harm it.

CLINICAL SITUATION	PREFERRED AGENT	WHY (THE PROFILE MATCH)
Comorbid chronic or neuropathic pain	**An SNRI (duloxetine) or a TCA (amitriptyline)**	Dual serotonin-noradrenaline action treats depression and pain with one drug
Insomnia and weight loss	**Mirtazapine**	H1-antihistamine sedation aids sleep; appetite stimulation restores weight
Fatigue or sexual dysfunction	**Bupropion**	Activating dopaminergic agent; no sexual dysfunction, no weight gain

CLINICAL SITUATION	PREFERRED AGENT	WHY (THE PROFILE MATCH)
Cardiac disease or overdose-risk patient	Avoid a TCA; use an SSRI (sertraline)	TCAs are cardiotoxic and lethal in overdose; SSRIs are safe post-MI
The elderly	An SSRI, watch hyponatraemia	Avoid TCA anticholinergic and orthostatic load; SSRIs risk SIADH/hyponatraemia
A woman planning pregnancy	Sertraline	Lowest infant exposure in breastfeeding; avoid paroxetine

The high-yield comorbidity-and-adverse-effect matches for antidepressant selection (Maudsley 2021; CANMAT 2016; IPS 2017). Read the situation, pick the agent whose profile fits, and avoid the agent whose profile harms.

Turn a side effect into an advantage. The sedating, weight-gaining mirtazapine is a liability in an obese sleeper but an asset in the thin, anorexic insomniac; the activating bupropion is wrong for the anxious patient but ideal for the fatigued patient with SSRI-induced sexual dysfunction. This inversion (one drug's adverse effect is another patient's indication) is the crux of the topic.

WORKED EXAMPLE

A 58-year-old man with diabetic peripheral neuropathy presents with a moderate depressive episode, poor sleep and low appetite. Rather than a default SSRI, duloxetine (Duzela) 60 mg is the pragmatic choice: one drug treats both the depression and the neuropathic pain, sparing a second prescription. Had the dominant problem instead been early insomnia with marked weight loss and no pain, mirtazapine (Mirtaz) 15 to 45 mg would be the better fit, using its sedation and appetite stimulation as therapeutic, not merely tolerated, effects.

PEARL

Ask two questions before writing the prescription: "what else does this patient have that a drug could help?" and "what must I not make worse?" The first points you to duloxetine for pain, mirtazapine for insomnia and weight loss, or bupropion for fatigue; the second steers you away from a TCA in cardiac or overdose risk and away from paroxetine in a woman planning pregnancy.

11.6 Safety in overdose and interactions as tie-breakers

Safety in overdose. Because depressed patients are at risk of self-harm, the toxicity of the drug in overdose is a genuine selection factor. The SSRIs and other second-generation agents are far safer in overdose than the tricyclic antidepressants, whose overdose is cardiotoxic (QRS widening, arrhythmia), proconvulsant and frequently fatal; this is a principal reason the guidelines put SSRIs first and hold TCAs back (NICE 2022; BAP 2015). Where a TCA is unavoidable, lofepramine is the least dangerous in overdose (NICE 2022).

Interactions. Existing medication narrows the field. In a polypharmacy or medically complex patient, prefer the clean agents (escitalopram, sertraline) over the potent cytochrome inhibitors (fluoxetine, paroxetine and fluvoxamine); never co-prescribe with an MAOI. The receptor and CYP metabolism that underlie these interactions belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

TRAP **Reaching for a TCA in a patient with cardiac disease or overdose risk.** TCAs are cardiotoxic and lethal in overdose; an SSRI is the safer first-line choice.

11.7 The reassessment rule: review by 2 to 4 weeks

Review early. Having chosen the agent, the guidelines converge on reviewing the patient by 2 to 4 weeks. The BAP directs an initial review every 1 to 2 weeks after starting, noting that a lack of significant improvement by 2 to 4 weeks substantially reduces the chance of eventual sustained response (BAP 2015). CANMAT frames the same window as measurement-based care: for non-improvers at 2 to 4 weeks, increase the dose if tolerated, and switch if tolerability is the problem, with early improvement defined as roughly a 20 to 30 percent reduction on a depression rating scale (CANMAT 2016).

Then step up or switch. If there is no early improvement trajectory, act: optimise the dose to the maximum tolerated, then switch (within or across class, the outcome is similar) after an adequate trial. The BAP assesses response formally at 4 weeks and again at 6 to 8 weeks, switching or moving to a next-step treatment if there is no trajectory by 4 weeks (BAP 2015). The full next-step and augmentation ladder for the patient who fails an adequate trial is the treatment-resistance topic.

TRAP **Switching too early, or persisting past 4 weeks with no trajectory.** Give an adequate trial before declaring failure, but do not sit on a non-responder beyond 4 weeks hoping it will turn.

2 to 4 wk	4 wk	6 to 9 mo
FIRST REVIEW AFTER STARTING	ACT IF NO IMPROVEMENT TRAJECTORY	CONTINUATION AFTER REMISSION

GOOD TO REMEMBER

- **The selection principle:** first-line antidepressants are equal in efficacy, so choose by adverse effects, comorbidity, past response, interactions, overdose safety and cost.
- **CANMAT first-line:** the SSRIs, SNRIs, mirtazapine, bupropion, vortioxetine and agomelatine, individualised to the patient (CANMAT 2016).
- **Comorbidity match:** pain to an SNRI or TCA, insomnia with weight loss to mirtazapine, fatigue or sexual dysfunction to bupropion, cardiac or overdose risk away from a TCA, the elderly to an SSRI watching hyponatraemia, pregnancy planning to sertraline.
- **Reassessment:** review by 2 to 4 weeks; switch or step up if there is no early improvement trajectory by 4 weeks.

MNEMONIC

PICO-SC

What drives the choice when efficacy is equal: **P**ast response, **I**nteractions, **C**omorbidity, **O**verdose safety, **S**ide-effect profile, **C**ost. Run the list and the "which antidepressant and why" answers itself.

HOLD THIS

First-line antidepressants are broadly equal in efficacy, so choose by the adverse-effect and comorbidity match, not by presumed potency: CANMAT leads with the SSRIs, SNRIs, mirtazapine, bupropion, vortioxetine and agomelatine, the IPS and NICE and the BAP agree the SSRIs come first for tolerability and overdose safety, and you review by 2 to 4 weeks and switch or step up if there is no early improvement trajectory by 4 weeks.

12 . Managing an acute depressive episode: the phases

Managing an **acute depressive episode** is not a drug list, it is a sequence: decide **where** to treat, then work through the **phases of treatment** in order, choosing the mode of treatment each phase asks for. This is the mood-block closer, and a high-yield theory question: the examiner rewards the LOCUS to FOCUS to MODUS spine and the exact phase durations, not a recitation of side effects. The deep drug pharmacology, dosing and adverse-effect profiles are owned by the earlier topics in these notes; the augmentation and treatment-resistance ladder is owned by the treatment-resistance topic. This topic carries the phased plan and the durations.

Lead the guideline answer with CANMAT (CANMAT 2016), then give the Indian Psychiatric Society position, now carried by the 2025 IPS depression update (IPS 2025, Tripathi et al., which supersedes the 2017 Gautam guideline), BAP (BAP 2015) and NICE positions. Across all four the single organising principle the exam tests is one instruction, not two: **treat to remission, then continue at the acute dose.** Response is not remission, and remission is not the end point.

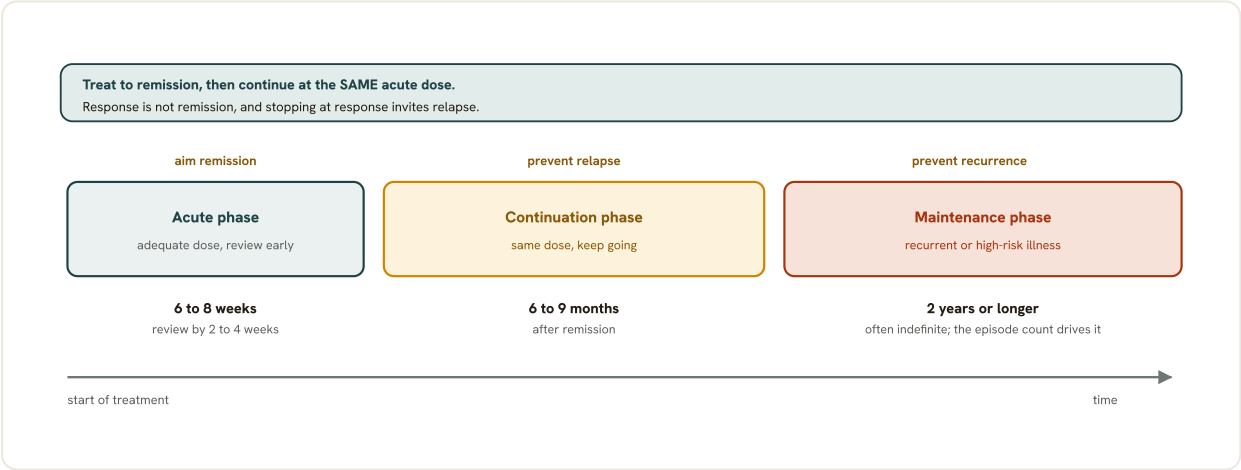

Fig 12.4 The phases and duration of treating an acute depressive episode. The acute phase runs about 6 to 8 weeks to remission, with an early review by 2 to 4 weeks; the continuation phase keeps the same acute dose for 6 to 9 months to prevent relapse; the maintenance phase extends to 2 years or longer, often indefinitely, for recurrent or high-risk depression. The cardinal rule is to treat to remission and continue at the acute dose, never to stop at response.

12.1 LOCUS: where to treat, and when to admit

Outpatient is the default. Most patients with an acute depressive episode are managed in the outpatient or the day care centre setting from the outset. Admission is reserved for a defined set of high-risk situations: **high suicide risk**, depression with **psychotic features**, severe **self-neglect** (not eating or drinking, dehydration), or the need for inpatient-level treatment such as ECT. The full clinical suicide risk assessment and safety planning that set the admission

threshold are owned by the Somatic-symptom, sexual, impulse-control disorders and suicide notes; the ECT technique itself is owned by the ECT and neurostimulation notes. Whatever the locus, care is delivered as **measurement-based care**: CANMAT specifies regular, frequent monitoring of clinical and functional outcomes with a validated scale such as the PHQ-9 or HAM-D, not clinical impression alone (CANMAT 2016; IPS 2017).

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

12.2 The ACUTE phase: aim remission, not response

The target of the acute phase is **remission**, the near-complete resolution of symptoms, not merely a partial **response** (conventionally a 50 percent symptom reduction). Stahl frames the whole plan around this: continue treatment until all symptoms are gone, that is remission, because residual symptoms predict relapse (Stahl 2021). Give an **adequate trial at an adequate dose**: a first-line antidepressant titrated to a therapeutic dose and continued for **6 to 8 weeks** before it can be called a failure. Review early: CANMAT and BAP advise reviewing the patient every **1 to 2 weeks** after starting (BAP 2015). Judge response on a trajectory. A lack of significant improvement by **2 to 4 weeks** substantially reduces the chance of eventual sustained response, so for a non-improver at 2 to 4 weeks you increase the dose if tolerated, or switch if tolerability is the problem (CANMAT 2016). BAP frames the same checkpoint as assessing response at 4 weeks and again at **6 to 8 weeks**, switching or stepping up if there is no improvement trajectory by 4 weeks or only minimal improvement by 6 to 8 weeks (BAP 2015). The IPS reappraises at 4 to 6 weeks (IPS 2017).

TRAP **Do not combine two antidepressants at initiation.** CANMAT states this explicitly: start one first-line agent, monitor, then optimise or switch. Combination belongs to the treatment-resistance step, not the start.

12.3 The CONTINUATION phase: protect the remission at the SAME dose

Once remission is achieved, do not stop. The **continuation** phase continues the antidepressant at the **same acute treatment dose** (not a reduced "maintenance" dose) for **6 to 9 months** after symptomatic remission, to prevent early relapse (CANMAT 2016). The IPS is explicit that the dose achieving response is continued and not reduced through the continuation phase, which the 2025 IPS update now sets at **4 to 9 months** (IPS 2025). BAP frames the lower bound as at least 1 year for anyone with an increased relapse risk (BAP 2015); NICE frames it as at least 6 months after symptoms remit (NICE 2022). This is the phase most often failed in practice: the patient feels well at week 8 and stops, and the relapse that follows is a continuation-phase relapse, not a genuinely new episode.

RULE **Continue at the acute dose through continuation; do not drop the dose or stop at response.** Continuation is 6 to 9 months at the same dose after remission (CANMAT 2016; IPS 2017).

12.4 The MAINTENANCE phase: prevent recurrence, and let the episode count set the duration

For recurrent, severe or high-risk depression the plan extends into a **maintenance** phase. CANMAT extends antidepressant treatment to **2 years or more** for patients with risk factors for recurrence (CANMAT 2016). The key examinable principle is that the number of prior episodes drives the **duration**: Stahl states that after a first episode you continue for about 1 year, but for a second and subsequent episodes treatment may need to be indefinite (Stahl 2021). The 2025 IPS update sets the maintenance phase at **6 to 24 months**, extended long-term for recurrent depression, with the probability of recurrence and the frequency and severity of past episodes driving the decision to continue (IPS 2025). BAP names the higher-risk group as, for example, more than five lifetime episodes or two episodes in recent years, and recommends at least 2 years and often long-term (BAP 2015). The maintenance-phase psychological options are CBT or mindfulness-based cognitive therapy (MBCT) to prevent relapse (CANMAT 2016); the technique of these therapies is owned by the Psychotherapies, clinical assessment, MSE and nosology notes.

MNEMONIC

FINISH

When the maintenance phase does end, taper slowly over several weeks to limit antidepressant discontinuation symptoms, which CANMAT summarises as FINISH: **F**lu-like symptoms, **I**nsomnia, **N**ausea, **I**mbalance, **S**ensory disturbances, **H**yperarousal (CANMAT 2016). Taper short half-life drugs (for example paroxetine, venlafaxine) more slowly. The discontinuation syndrome detail is owned by the discontinuation topic in these notes.

12.5 The MODUS: which mode of treatment each phase asks for

At guideline level the mode is an antidepressant, an evidence-based psychotherapy, or both. The **first-line** pharmacological agent is a **second-generation antidepressant**, individualised to the patient with measurement-based monitoring (CANMAT 2016). CANMAT's first-line agents (verified) include the SSRIs escitalopram (Nexito or S-Citadep; 10 to 20 mg/day), sertraline (Serta or Daxid; 50 to 200 mg/day), fluoxetine (Fludac; 20 to 60 mg/day) and the SNRI venlafaxine (Venlor; 75 to 225 mg/day), with bupropion (Bupron), mirtazapine (Mirtaz) and vortioxetine (Vortioxa) also first-line; the full per-agent dosing, mechanism and adverse-effect detail live in the earlier topics of these notes. The IPS names the SSRIs as first-line on grounds of tolerability and overdose safety (IPS 2017), NICE treats SSRIs as the first choice for most people, and BAP prefers newer antidepressants for tolerability and overdose safety (BAP 2015). The first-line psychotherapies for the acute phase are CBT, interpersonal therapy (IPT) and behavioural activation (BA); where feasible, combining a psychotherapy with an antidepressant is superior to either alone (CANMAT 2016; IPS 2017). The receptor-level pharmacology and CYP metabolism that underlie agent selection are cross-referred to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

RULE **First-line = one second-generation antidepressant, individualised, or an evidence-based psychotherapy.** Combination is superior for many, especially the more severe presentations.

12.6 The MODUS: the psychotic-depression rule

Psychotic depression is the one presentation with a fixed combination rule. Treat it with an **antidepressant plus an antipsychotic** from the outset, in preference to either drug alone, or use ECT (BAP 2015; IPS 2017). An antidepressant alone is inadequate here. The mood-with-psychotic-features entity itself is owned by the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes, and the ECT technique by the ECT and neurostimulation notes. One more selection rule sits behind the whole plan: a treatment-emergent switch to mania or hypomania on antidepressant monotherapy reclassifies the diagnosis as bipolar; stop or reduce the antidepressant and add a mood stabiliser (IPS 2017). Giving an antidepressant alone in what is really a bipolar depression is the classic error, and it is owned in full by the bipolar-management topics.

TRAP **Treating psychotic depression with an antidepressant alone.** The rule is antidepressant plus an antipsychotic from the outset, or ECT.

12.7 Putting the phases together: the phase-by-phase plan

The four phases and the locus decision assemble into one table. Learn the highlighted cell in each row: it is the fact the examiner tests.

6 to 8 wk	2 to 4 wk	6 to 9 mo	2 years+
ADEQUATE ACUTE TRIAL	NON-IMPROVER REVIEW POINT	CONTINUATION AT THE ACUTE DOSE	MAINTENANCE IF RECURRENT

PHASE	TARGET	DURATION / CHECKPOINT	GUIDELINE-FIRST MODE
Locus decision	Choose the safest adequate setting	**Admit for high suicide risk, psychosis, severe self-neglect, or the need for ECT**	Outpatient default; measurement-based care throughout (CANMAT 2016)
Acute	Remission (not just response)	**Adequate dose for 6 to 8 weeks; review every 1 to 2 weeks; judge by 2 to 4 weeks and switch or step up if no trajectory**	One second-generation antidepressant, individualised, and/or CBT, IPT or BA; combination superior for many (CANMAT 2016)
Continuation	Protect the remission	**Continue at the same acute dose for 6 to 9 months after remission**	Same acute-phase agent at the same dose; do not down-titrate (CANMAT 2016; IPS 2017)
Maintenance	Prevent recurrence	**Extend to 2 years or longer (often indefinite) for recurrent, severe or high-risk depression; the number of prior episodes drives the duration**	Continue antidepressant; CBT or MBCT to prevent relapse; taper slowly (FINISH) at stop (CANMAT 2016)

PHASE	TARGET	DURATION / CHECKPOINT	GUIDELINE-FIRST MODE
Psychotic depression	Remission with psychosis control	From the outset	**Antidepressant plus an antipsychotic, or ECT (BAP 2015)**
Inadequate response	Optimise, then augment or switch	Optimise dose first, then reassess	Augmentation or switch; the full ladder is owned by the treatment-resistance topic in these notes

The acute depressive episode managed by the phases of treatment on the LOCUS to FOCUS to MODUS spine; durations verified against CANMAT 2016, IPS 2017 and BAP 2015. Drug detail is cross-referred to the earlier topics in these notes.

INDIA

The Indian Psychiatric Society Clinical Practice Guideline for depression has been updated: the 2025 IPS depression update (IPS 2025, Tripathi et al., Indian J Psychiatry 2026;68:68-93) supersedes the 2017 Gautam guideline and is now the current examinable Indian reference. It sets the treatment phases as acute **8 to 16 weeks** (achieve remission), continuation **4 to 9 months** (consolidate remission, prevent relapse) and maintenance **6 to 24 months** (prevent recurrence, restore functioning), extended long-term for recurrent depression. It selects the initial treatment by severity: for mild low-risk depression, psychotherapy is preferred (pharmacotherapy is acceptable in the Indian setting given limited access to psychologists); for moderate depression, pharmacotherapy or psychotherapy, with pharmacotherapy slightly more efficacious, quicker and more cost-effective; for severe depression without psychosis, combined pharmacotherapy and psychotherapy; for severe depression with psychosis, an antidepressant plus an antipsychotic as first-line; and for life-threatening presentations, ECT with admission. The first-line SSRIs and their doses are unchanged (escitalopram 10 to 20 mg, sertraline 50 to 200 mg, fluoxetine 20 to 60 mg), and the update names vilazodone, vortioxetine and agomelatine among the newer options. All the first-line agents are inexpensive Indian brands: escitalopram (Nexito or S-Citadep), sertraline (Serta or Daxid), fluoxetine (Fludac), venlafaxine (Venlor), duloxetine (Duzela), mirtazapine (Mirtaz), bupropion (Bupron), vortioxetine (Vortioxa). ECT is widely available across Indian teaching hospitals and remains a mainstream option for severe, psychotic, suicidal or treatment-resistant depression rather than a last resort.

GOOD TO REMEMBER

- **LOCUS:** outpatient default; admit for high suicide risk, psychosis, severe self-neglect, or the need for ECT; measurement-based care throughout.
- **Acute phase:** aim **remission**, not response; adequate dose for **6 to 8 weeks**; review every 1 to 2 weeks; switch or step up if no trajectory by 2 to 4 weeks (CANMAT 2016; BAP 2015).
- **Continuation phase:** continue at the **same acute dose** for **6 to 9 months** after remission; do not down-titrate (CANMAT 2016; IPS 2017).
- **Maintenance phase: 2 years or longer** (often indefinite) for recurrent, severe or high-risk depression; the number of prior episodes drives the duration (Stahl 2021; IPS 2017).
- **MODUS:** one second-generation antidepressant, or an evidence-based psychotherapy (CBT, IPT, BA), or both; combination superior for many.
- **Psychotic depression:** antidepressant plus an antipsychotic from the outset, or ECT (BAP 2015).
- **Do-not-combine rule:** two antidepressants are not combined at initiation (CANMAT 2016).

WORKED EXAMPLE

A 38-year-old man with a second moderate-to-severe depressive episode, no psychosis and no active suicidal plan, is managed as an outpatient. He is started on a single first-line SSRI, escitalopram (Nexito or S-Citadep), titrated to a therapeutic dose, and offered CBT alongside because combination is superior to either alone. He is reviewed at 2 weeks and again at 4 weeks: there is a partial improvement trajectory, so the dose is optimised rather than switched, and the adequate trial is allowed to run to 6 to 8 weeks. He reaches remission by month 3. The escitalopram is continued at the same acute dose for 6 to 9 months in the continuation phase, not reduced. Because this is his second episode, the recurrence-risk conversation supports a maintenance phase of at least 1 to 2 years rather than stopping at the end of continuation.

PEARL

"Remission then continuation at the acute dose" is a single instruction. The dose that achieved remission is the dose that maintains it: the continuation phase is the acute-phase drug at the acute-phase dose for 6 to 9 months. Reducing the dose the moment the patient feels well is a common and avoidable cause of relapse.

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

HOLD THIS

Treat the acute depressive episode to remission on an adequate 6-to-8-week trial, continue at the same acute dose for 6 to 9 months after remission, and extend to 2 years or longer for recurrence, with the number of prior episodes setting the duration.

Mood stabilisers and lithium

13 . Lithium: mechanism and pharmacokinetics

Why this leads the block. Lithium is a monovalent cation with no receptor, no enzyme it was designed for, and no metabolism, yet it remains the gold-standard mood stabiliser and the only agent with a genuine anti-suicide signal (Maudsley 2021). The examiner reward here is mechanistic: two intracellular **mechanism of action** hypotheses that also explain the neuroprotective story, and a **pharmacokinetics** profile so unusual that the drug is effectively a sodium mimic cleared entirely by the kidney. Get the pharmacokinetics right and the interactions, the monitoring schedule and the toxicity all fall out of it; get them wrong and a stable patient tips into toxicity from nothing more than a stomach bug.

This fragment teaches the molecular targets, then the four pharmacokinetic facts a resident must hold, then the bridge that makes lithium's kinetics the source of its danger. The therapeutic ranges, the monitoring intervals and the drug interactions themselves are developed in the sibling topics; the deep monoamine and second-messenger anatomy sits in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

13.1 A drug with no obvious target

The framing problem. Lithium has "practically no acute effects in normal individuals" and is neither sedative nor euphoriant; the mood-stabilising action appears only on prolonged administration (KDT 2019). It does not bind a classical receptor. Instead it acts inside the cell on two enzymes that sit on second-messenger and signalling cascades, and it does so at the low millimolar concentrations reached therapeutically. The two dominant, exam-relevant hypotheses are **inositol** depletion and GSK-3 inhibition. Both converge on dampening an over-active signalling state and on downstream neurotrophic or neuroprotective effects (Stahl 2021).

RULE **Two targets, one theme.** Lithium works intracellularly on inositol monophosphatase and GSK-3 beta, not on a membrane receptor: it turns down an over-active signalling cascade and switches on neuroprotective genes.

13.2 The inositol depletion hypothesis

Inositol monophosphatase and the phosphatidylinositol cycle. Gq-coupled receptors activate phospholipase C, which hydrolyses membrane phosphatidylinositol to the second messengers inositol trisphosphate (IP3) and diacylglycerol. To regenerate the signalling lipid, the cell must recycle inositol, and the enzyme that liberates free **inositol** from inositol monophosphate is inositol monophosphatase (IMPase). Lithium is a powerful inhibitor of IMPase, so the phosphatidylinositol second-messenger cascade runs down as the cell is depleted of inositol (Berridge 1982; New Oxford 2020). Because the brain crosses the blood brain barrier poorly for inositol and is therefore uniquely dependent on recycling, it is selectively sensitive to this depletion (New Oxford 2020).

Uncompetitive inhibition is the elegant part. Lithium inhibits IMPase *uncompetitively*, meaning the block deepens as substrate rises. Lithium therefore acts most where a pathway is hyperfunctional and barely touches pathways ticking over at basal rates, which is exactly the selectivity you want in an anti-manic drug (New Oxford 2020). This "inhibition of inositol monophosphatase dampening the phosphatidylinositol second-messenger cascade" is the phrase to reproduce. Supporting the class relevance, valproate and carbamazepine also deplete brain inositol, though largely by inhibiting a synthetic enzyme rather than IMPase (New Oxford 2020).

MNEMONIC

"I MP-ede the cycle"

IMPase is the enzyme lithium blocks; blocking it *impedes* the phosphatidylinositol cycle by starving it of recycled inositol. Uncompetitive means the busier the pathway, the harder lithium hits.

13.3 GSK-3 beta inhibition and the neurotrophic story

The second target. Glycogen synthase kinase 3 beta (glycogen synthase kinase 3, GSK-3) is a constitutively active kinase that phosphorylates and inactivates a wide set of substrates. Lithium robustly inhibits GSK-3 beta, both directly and indirectly through the beta-arrestin 2 / Akt pathway that dopamine D2 signalling recruits (Companion 2010; Lithium Handbook 2023). Inhibiting GSK-3 releases its downstream substrates from suppression: Wnt / beta-catenin signalling, the cytoskeletal and tau proteins, and the transcription factors CREB and AP-1 (jun) (Companion 2010).

Downstream neurotrophic and neuroprotective effects. The net consequence is upregulation of neurotrophic and cytoprotective programmes, notably brain-derived neurotrophic factor (BDNF) and the anti-apoptotic protein bcl-2 (Kaplan 2024). This is the molecular basis usually invoked for lithium's neuroprotective and putative anti-dementia signal (Lithium Handbook 2023). GSK-3 also phosphorylates core clock proteins, so its inhibition feeds into the **circadian** and signalling pathways that are disordered in bipolar illness, one proposed route by which lithium lengthens and re-entrains the circadian period (Stahl 2021).

TARGET	WHAT LITHIUM DOES	DOWNSTREAM CONSEQUENCE
Inositol monophosphatase (IMPase)	**Uncompetitive inhibition**	Inositol depletion, phosphatidylinositol / IP3 cascade damped, most in hyperactive pathways
GSK-3 beta	**Direct and Akt/beta-arrestin inhibition**	Wnt/beta-catenin, CREB, BDNF, bcl-2 up; neuroprotection; circadian re-entrainment

The two dominant mechanism-of-action hypotheses for lithium and their downstream signalling effects.

PEARL

Both mood-stabiliser mechanisms fit a single idea: lithium quietens an over-active intracellular signal (inositol/PI cycle) while switching on survival and plasticity genes (via GSK-3 inhibition). This "dampen the noise, protect the cell" dual action distinguishes it from receptor-blocking drugs.

13.4 Absorption and distribution

A small ion that behaves like body water plus sodium. Lithium is well absorbed orally with peak plasma levels at **2 to 3 hours** for immediate-release salts, and it is not protein bound (KDT 2019). It first enters the extracellular water, then slowly crosses into cells, giving an apparent **volume of distribution** around **0.8 L/kg**, close to total body water and narrow compared with lipophilic psychotropics (KDT 2019). The slow intracellular equilibration matters clinically: after an acute overdose the plasma level can be alarmingly high while the patient is still asymptomatic, then deteriorate over hours as lithium loads into cells, which is why the serum level and the clinical picture can dissociate early (Kaplan 2024).

2 to 3	0.8	18 to 24
TIME TO PEAK, IR (HOURS)	VOLUME OF DISTRIBUTION (L/KG)	ELIMINATION HALF-LIFE (HOURS)

13.5 Not metabolised: entirely renal excretion

The single most important pharmacokinetic fact. Lithium is not metabolised by the liver and is not protein bound; it undergoes **renal excretion** essentially in its entirety, cleared unchanged by the kidney (KDT 2019; Kaplan 2024). It is filtered at the glomerulus and then handled by the proximal tubule "in much the same way as sodium," where roughly 80% of the filtered load is reabsorbed alongside sodium; its renal clearance is about one fifth of creatinine clearance (KDT 2019). The elimination half-life is of the order of **18 to 24 hours** in a patient with normal renal function, described by Kaplan as "about a day," which is what makes once-daily dosing feasible and why steady state and a valid trough level are reached only after several days at a fixed dose (Kaplan 2024).

WORKED EXAMPLE

A euthymic patient stable for years on a fixed lithium dose develops gastroenteritis, eats little, and becomes volume-deplete over a weekend. Sodium and water avidity rise, the proximal tubule reabsorbs more filtered sodium and therefore more lithium, renal lithium clearance falls, and the serum level climbs even though the dose has not changed. The stable patient is now heading into toxicity with no prescribing error at all.

13.6 The sodium link is the whole game

Why the kinetics drive the toxicity and the interactions. Because lithium is handled like sodium and cleared only by the kidney, anything that lowers total-body sodium or reduces renal clearance raises the level. Sodium depletion, dehydration and a low-salt diet all increase proximal reabsorption of lithium; renal impairment and a falling glomerular filtration rate reduce its excretion (Kaplan 2024; KDT 2019). This is the mechanistic root of the classic interactions developed in the interaction and monitoring topics: thiazide diuretics deplete sodium and raise

levels; NSAIDs and ACE inhibitors or ARBs cut renal perfusion or clearance and raise levels; sodium loading or osmotic diuresis lowers them. There is no hepatic escape route and no protein reservoir to buffer swings, so kinetic changes translate directly into level changes.

RULE **Lithium follows sodium and the kidney.** Lithium is renally cleared and sodium-linked, so anything that lowers sodium or lowers renal clearance raises the level. That single sentence predicts nearly every lithium interaction and every toxicity trigger.

TRAP **The "nothing changed" toxicity.** Forgetting that dehydration, a vomiting or diarrhoeal illness, a heat wave or a new low-salt diet can push a long-stable patient into toxicity with the dose untouched. The level moved because sodium and water moved, not because the prescription did.

13.7 Narrow therapeutic index: why monitoring is mandatory

The margin is thin and individual. Lithium has a **narrow therapeutic index**: therapeutic maintenance levels sit around **0.6 to 1.0 mEq/L** while toxicity appears not far above, with early features from roughly **1.5 mEq/L** and serious toxicity higher still (Meyer and Stahl / Lithium Handbook 2023; CANMAT 2018). Guideline targets are level-defined rather than dose-defined: CANMAT sets maintenance at 0.6 to 1.0 mEq/L and an acute-mania target of 0.8 to 1.2 mEq/L, and the Indian Psychiatric Society (IPS guidelines) similarly anchor maintenance around 0.6 to 1.0 mmol/L with acute targets up to about 1.2 mEq/L (CANMAT 2018; Shah, Grover et al. 2017). Because the same oral dose produces widely different levels between patients (large inter-individual variation in renal clearance) and the same patient's level moves with sodium and hydration, therapeutic drug monitoring of the serum level is not optional, it is the drug (Kaplan 2024; Lithium Handbook 2023). This is the bridge into the initiation, monitoring and toxicity topics.

INDIA

Lithium carbonate is widely available in India as immediate-release and sustained-release tablets, commonly branded Licab and Intalith CR (generic lithium carbonate stays primary in the prose). The narrow-index and sodium-link teaching is especially load-bearing in Indian practice: hot-climate dehydration, gastroenteritis, fasting and low-salt diets are common real-world triggers for a stable patient to drift into toxicity between clinic visits.

HOLD THIS

Lithium is not metabolised and is cleared entirely by the kidney where it is handled like sodium, so with a narrow therapeutic index any fall in sodium, hydration or renal clearance raises the level toward toxicity.

GOOD TO REMEMBER

- **Mechanism (inositol):** inhibits inositol monophosphatase, uncompetitively, depleting inositol and dampening the phosphatidylinositol / IP3 second-messenger cascade, most in hyperactive pathways.
- **Mechanism (GSK-3):** inhibits GSK-3 beta, releasing Wnt/beta-catenin, CREB, BDNF and bcl-2, giving downstream neurotrophic, neuroprotective and circadian effects.
- **Pharmacokinetics:** not protein bound, not metabolised, renal excretion entirely; handled like sodium (proximal reabsorption ~80%); Vd ~0.8 L/kg; half-life ~18 to 24 hours; peak at 2 to 3 hours (IR).
- **The clinical rule:** narrow therapeutic index (maintenance ~0.6 to 1.0 mEq/L) makes serum monitoring mandatory; sodium depletion, dehydration and renal impairment raise the level.

14 . Lithium: indications, initiation, dosing and range

Lithium is the oldest and still the single most important mood stabiliser, and the examiner treats it as a set-piece: the indications, the baseline work-up before the first tablet, the starting dose, and above all the **serum lithium** therapeutic range that differs between acute mania and maintenance. It is the gold-standard prophylactic agent in bipolar disorder and carries the strongest anti-suicidal evidence of any psychotropic (Maudsley 2021; CANMAT 2018), so a resident is expected to prescribe it correctly and to know its numbers cold. A wrong serum level or a skipped renal or thyroid baseline is the classic marked error.

Organise the topic around one idea: **aim high for acute mania, aim lower for maintenance**, and never start without a baseline renal, thyroid and calcium screen. The ranges below are verified against the Maudsley and the CANMAT and Indian Psychiatric Society guideline rows (Maudsley 2021; CANMAT 2018; IPS 2017); the neurobiology of mood and the wider guideline-anchored management PLAN belong to the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes, and the deep antimanic-antipsychotic detail to the Schizophrenia: management, antipsychotics and adverse effects notes.

14.1 Mechanism: a monovalent cation with intracellular targets

The molecular target. Lithium is a monovalent cation with no single agreed mechanism; the best-supported candidates are inhibition of glycogen synthase kinase 3 (GSK3-beta) and interference with the phosphatidylinositol second-messenger cycle through inhibition of inositol monophosphatase, together with effects on CREB and on neuronal sodium and calcium handling (Maudsley 2021; Stahl 2021). It also promotes hippocampal neurogenesis and has putative neuroprotective effects.

Why the narrow window matters. Lithium is not metabolised; the ion is handled entirely by the kidney and excreted with a half-life of about 24 hours, so anything that alters sodium handling or renal function moves the serum level directly (Kaplan and Sadock 2024). That renal-only clearance, and the fact that the therapeutic and toxic ranges nearly abut, is why serum monitoring is non-negotiable.

14.2 Lithium indications: mania, maintenance and augmentation

The core indications. The set of **lithium indications** a resident must recite: **acute mania** (a first-line antimanic agent), bipolar maintenance and **prophylaxis** (the gold-standard mood stabiliser for preventing both manic and depressive recurrence), augmentation of an antidepressant in treatment-resistant unipolar depression, and prophylaxis of recurrent unipolar depression (Maudsley 2021; CANMAT 2018).

Acute mania

First-line, alone or combined with an antipsychotic; a faster antimanic onset is gained by adding a dopamine antagonist (Maudsley 2021; CANMAT 2018).

Bipolar maintenance / prophylaxis

The best-performing single agent for long-term relapse prevention; in 2024 it remains the gold-standard maintenance treatment (Maudsley 2021).

Unipolar antidepressant augmentation

A first-choice augmenting agent in treatment-resistant depression, most effective at a serum level of 0.6 to 1.0 mmol/L (Maudsley 2021).

Recurrent unipolar depression

Prophylaxis is indicated after two depressive episodes in five years, or after one severe episode with strong suicide risk (Maudsley 2021).

The anti-suicidal signal. Lithium is the one psychotropic with dedicated anti-suicide evidence: a meta-analysis of clinical trials concluded it reduced attempted and completed suicide by roughly 80 percent in bipolar illness, and this protection extends to unipolar depression (Maudsley 2021; IPS 2017). About 15 percent of people with bipolar disorder die by suicide, which frames why this matters. The full clinical suicide risk assessment and safety planning belong to the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

RULE **Lithium is the anti-suicidal mood stabiliser.** In a bipolar patient with suicidality it is the preferred long-term agent for its specific, class-unique anti-suicide evidence.

14.3 Initiation: the baseline work-up before the first tablet

The pre-lithium screen. Because clearance is renal and the drug is a putative teratogen with thyroid, parathyroid and cardiac effects, a baseline work-up is mandatory before **initiation** (Maudsley 2021; IPS 2017). As a minimum, check: renal function (estimated GFR with urea and electrolytes), thyroid function (TSH), serum calcium, a baseline weight, and a pregnancy test with contraceptive counselling in women of child-bearing potential. An ECG is recommended in those with cardiovascular risk factors or established cardiac disease.

BASELINE TEST	WHY
Renal function (eGFR, U and Es)	Lithium is cleared only by the kidney; sets the safety floor and the interaction baseline
Thyroid function (TSH)	Lithium causes hypothyroidism (up to ~20 percent in middle-aged women over time)
Serum calcium	Hyperparathyroidism with hypercalcaemia occurs in about 4 percent
ECG (if cardiovascular risk)	Recommended where cardiac risk factors or disease exist
Weight / BMI	Weight gain is a common, adherence-limiting adverse effect
Pregnancy test / contraception	Putative teratogen (Ebstein anomaly with first-trimester exposure)

The pre-lithium baseline work-up (Maudsley 2021; IPS 2017). Renal, thyroid and calcium are the non-negotiable trio; ECG is conditional on cardiac risk. The perinatal detail is cross-referred.

TRAP **Starting lithium without baseline renal and thyroid function.** You lose the safety baseline, miss pre-existing renal impairment or hypothyroidism, and cannot later attribute change to the drug.

14.4 Dosing: starting dose and titration to the target level

Starting and titrating. The standard **dosing** approach: start lithium carbonate at **400 mg at night** in an adult, or **200 mg at night** in the elderly, then titrate against the serum level, not against a fixed milligram target (Maudsley 2021). Check the first plasma level after 7 days, and again 7 days after every dose change, until the desired level is reached; once stable it is checked every 6 months (Maudsley 2021; IPS 2017).

Timing the sample. The blood sample must be taken 12 hours after the last dose (the standardised 12-hour trough), because a sample drawn too early reads falsely high (Maudsley 2021). The usual maintenance dose lands around 600 to 1200 mg daily, but the number that matters is the serum level, not the dose.

RULE **Titrate to the level, and take the sample at 12 hours.** A lithium level drawn before the 12-hour trough overreads and can trigger a wrongful dose cut.

WORKED EXAMPLE

A 34-year-old man in acute mania is started on lithium carbonate 400 mg nocte after a normal baseline eGFR, TSH and calcium. A level after one week, drawn 12 hours post-dose, reads 0.6 mmol/L. Because the target for acute mania is higher, the dose is increased and a repeat level 7 days later reaches 0.9 mmol/L, within the 0.8 to 1.0 mmol/L acute band, with good tolerability. Had the day-7 sample been taken at 3 hours post-dose it would have read spuriously high and prompted an inappropriate dose reduction.

14.5 The therapeutic range: aim high for mania, lower for maintenance

The two targets. This is the single highest-yield fact of the topic. The **therapeutic range** is phase-dependent. For **acute mania** aim for a serum lithium of **0.8 to 1.0 mmol/L**, extending up to 1.2 mmol/L in difficult-to-treat mania (Maudsley 2021; CANMAT 2018; IPS 2017). For maintenance and prophylaxis aim lower, at **0.6 to 0.8 mmol/L**, with the option to go up to 1.0 mmol/L for insufficient response and good tolerance, or down to 0.4 to 0.6 mmol/L for good response but poor tolerance (Maudsley 2021; CANMAT 2018).

The elderly and the augmentation targets. In older adults a lower maintenance target of about **0.4 to 0.6 mmol/L** is often used, starting low (for example 150 to 200 mg at night) because renal clearance falls with age (Maudsley 2021; CANMAT 2018). For unipolar antidepressant augmentation the effective serum level is 0.6 to 1.0 mmol/L. The minimum effective prophylactic level is probably about 0.4 mmol/L, but the practical prophylaxis target remains 0.6 to 0.8 mmol/L (Maudsley 2021).

INDICATION / PHASE	SERUM LITHIUM TARGET (MMOL/L)	SOURCE
Acute mania	**0.8 to 1.0 (up to 1.2 in difficult mania)**	Maudsley 2021; CANMAT 2018; IPS 2017
Maintenance / prophylaxis (bipolar)	**0.6 to 0.8 (up to 1.0)**	Maudsley 2021; CANMAT 2018
Maintenance in the elderly	0.4 to 0.6	Maudsley 2021; CANMAT 2018
Unipolar antidepressant augmentation	0.6 to 1.0	Maudsley 2021
Toxicity threshold	above 1.5 (seizures usually above 2.0)	Maudsley 2021

Verified serum lithium targets by phase (mmol/L; for lithium, 1 mmol/L equals 1 mEq/L). The two highlighted rows are the must-hold numbers: higher for acute mania, lower for maintenance. Toxicity begins reliably above 1.5 mmol/L.

0.8 to 1.0	0.6 to 0.8	above 1.5
ACUTE MANIA TARGET (MMOL/L)	MAINTENANCE TARGET (MMOL/L)	TOXICITY THRESHOLD (MMOL/L)

TRAP **Using the maintenance range to treat acute mania.** A 0.6 to 0.8 mmol/L level undertreats an acute manic episode; the acute target is higher, 0.8 to 1.0 (up to 1.2) mmol/L.

14.6 The Indian brands and continued front-line use

What is prescribed here. In Indian practice lithium is prescribed as lithium carbonate, and remains a genuine first-line mood stabiliser rather than a legacy drug, endorsed as first-line for acute mania and as the primary maintenance agent in the Indian Psychiatric Society guidelines (the IPS guidelines; IPS 2017). Its low cost and the strength of the maintenance and anti-suicide evidence keep it front-line in a largely out-of-pocket health system.

INDIA

Lithium carbonate is marketed in India as Licab and as Intalith (both lithium carbonate), available as standard and sustained-release tablets. It stays a genuine front-line agent: the Indian Psychiatric Society guidelines place lithium first-line for acute mania (target 0.8 to 1.2 mmol/L) and as the primary maintenance mood stabiliser for preventing both manic and depressive recurrence, at a maintenance level of 0.6 to 1.0 mmol/L, with its specific anti-suicide evidence explicitly noted (IPS 2017). Serum-level access is widely available in district and teaching hospitals, and the drug is inexpensive, both of which support its continued heavy use in Indian outpatient departments.

GOOD TO REMEMBER

- **Lithium (Licab or Intalith):** monovalent cation, GSK3-beta and inositol-cycle effects; renal clearance only; first-line for acute mania and the gold-standard maintenance agent with unique anti-suicide evidence.
- **Acute mania target:** serum lithium **0.8 to 1.0 mmol/L** (up to 1.2 in difficult mania).
- **Maintenance / prophylaxis target:** serum lithium **0.6 to 0.8 mmol/L** (up to 1.0; 0.4 to 0.6 in the elderly).
- **Initiation:** baseline renal (eGFR, U and Es), thyroid (TSH), calcium, weight, ECG if cardiac risk, pregnancy test; start **400 mg nocte** (200 mg elderly).
- **Monitoring:** level at 7 days and 7 days after each change, sampled 12 hours post-dose, then 6-monthly with eGFR and TFTs.

HOLD THIS

Lithium is first-line for acute mania and the gold-standard maintenance mood stabiliser with the strongest anti-suicidal evidence: aim for a serum level of 0.8 to 1.0 mmol/L in acute mania and 0.6 to 0.8 mmol/L in maintenance, always after a baseline renal, thyroid and calcium screen, sampling the level 12 hours post-dose.

15 . Lithium monitoring

lithium monitoring is examined more precisely than almost any other prescribing topic, because lithium has the narrowest therapeutic index in psychiatry: the gap between an effective and a toxic level is small, so the drug is unusable without a disciplined monitoring routine. The two things the board rewards are the **sampling rule** (how and when to draw the level) and the **investigation schedule** (what to check at baseline and how often afterwards). Get the timing of the blood sample wrong and the number is meaningless; let the renal or thyroid checks lapse and you miss the two organ toxicities that end lithium therapy.

The whole topic hangs on one physiological fact: lithium is renally cleared with a long distribution phase, so the plasma level is only interpretable at a standardised time after the dose. That time is twelve hours. Everything below, the target ranges, the check after a dose change, the six-monthly organ panel, is verified against the Maudsley Prescribing Guidelines, Stahl's Prescriber's Guide, the CANMAT guideline and the Indian Psychiatric Society clinical practice guideline (Maudsley 2021; Stahl 2021; Yatham 2018; Shah 2017). The lithium initiation and toxicity detail sits alongside this in the mood-block pharmacotherapy notes; the guideline-

anchored management PLAN that puts lithium first-line is set out in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

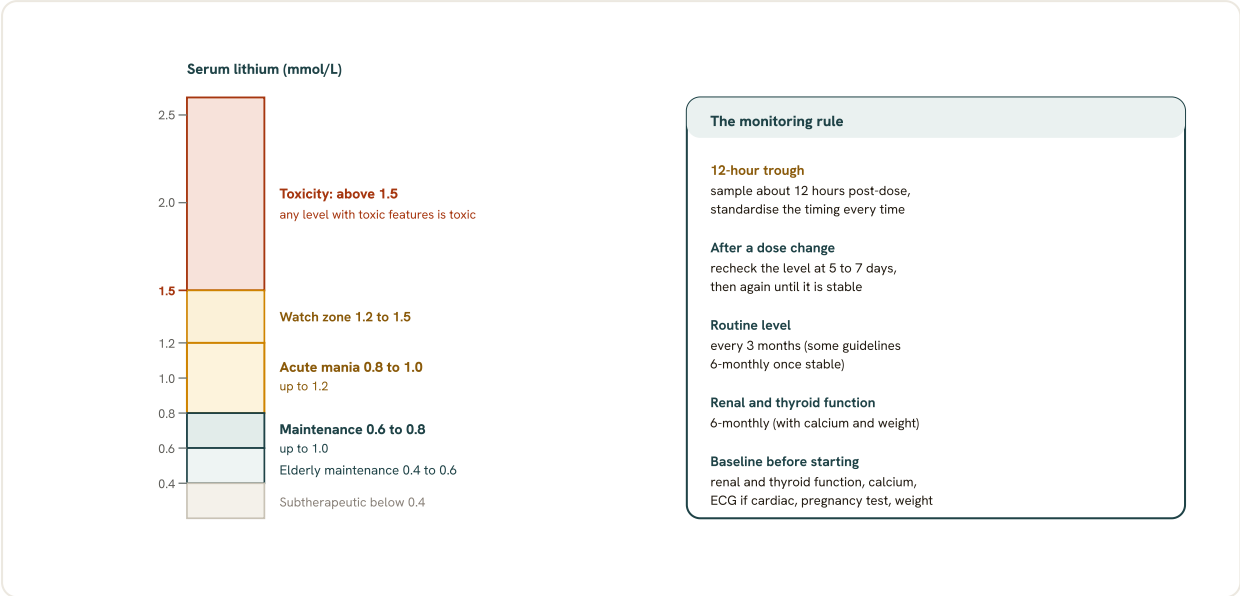

Fig 12.6 The lithium therapeutic window and the monitoring rule. The window is narrow: aim about 0.8 to 1.0 (up to 1.2) mmol/L for acute mania and 0.6 to 0.8 (up to 1.0) for maintenance, with a lower 0.4 to 0.6 target in the elderly; toxicity is expected above 1.5, though any level with toxic features counts as toxic. Sample as a 12-hour trough, recheck 5 to 7 days after any dose change, and monitor renal and thyroid function with the baseline work-up shown.

15.1 The sampling rule: the twelve-hour trough

Sample at the trough, twelve hours post-dose. The single most examined fact in **lithium monitoring** is when to draw the blood. Because lithium has a long distribution phase, an early sample catches the drug still redistributing and reads falsely high. The standard is the **twelve-hour trough**: the blood is taken as the **12-hour** post-dose sample, ideally 10 to 14 hours after the last dose, with 12 hours the target, in a patient on a once-daily bedtime regimen (Maudsley 2021). This is the **serum level** that every published target range refers to. In practice, for a patient who takes lithium at night, the sample is drawn the next morning before the day's dose.

Standardise the timing. Because the level changes across the dosing interval, the timing must be held constant from one sample to the next, so that a change in the number reflects a change in the patient and not a change in when you took the blood. A CANMAT and the Indian Psychiatric Society both anchor drug-level sampling to this trough point (Yatham 2018; Shah 2017).

RULE **Draw the lithium level as a twelve-hour trough.** The 12-hour post-dose sample, timed the same way each time, is the only interpretable serum level.

TRAP **Taking a random, non-trough level and acting on it.** A sample drawn a few hours after the dose reads spuriously high and invites a wrong dose cut, or a spuriously reassuring number if drawn late; always standardise to 12 hours.

15.2 The target ranges the level is read against

What number you are aiming for. The trough **serum level** is only useful against a target. For maintenance and prophylaxis in bipolar disorder the accepted range is **0.6 to 1.0 mmol/L**

(CANMAT keeps maintenance at 0.6 to 1.0 mEq/L; the Maudsley narrows the prophylactic optimum to 0.6 to 0.8 mmol/L) (Yatham 2018; Maudsley 2021). In acute mania a slightly higher level of **0.8 to 1.2 mmol/L** is targeted, and for lithium augmentation of an antidepressant in unipolar depression the target is **0.6 to 1.0 mmol/L**, the same as maintenance (Maudsley 2021). Toxic effects reliably appear above **1.5 mmol/L**, which is why the trough discipline matters so much.

0.6 to 1.0	0.8 to 1.2	1.5
MAINTENANCE LITHIUM (MMOL/L)	ACUTE MANIA TARGET (MMOL/L)	TOXICITY THRESHOLD (MMOL/L)

15.2b Checking the level after a dose change

Recheck 5 to 7 days after every dose change. Lithium reaches a new steady state roughly five half-lives after any change in dose, which is about 5 to 7 days in an adult with normal renal function. So after starting lithium or altering the dose you draw the next twelve-hour trough about 5 to 7 days later, and you repeat this after each successive change until the level is stable in the target range (Maudsley 2021; Shah 2017). The Maudsley states the interval as a level after 7 days and then 7 days after every dose change; the Indian Psychiatric Society states it as 5 to 7 days after a dose change, and CANMAT applies the same 5 to 7 day rule after any dose or interacting-drug change in older adults (Maudsley 2021; Shah 2017; Yatham 2018). Practically, hold 5 to 7 days.

RULE **After any dose change, recheck the trough level in 5 to 7 days.** Steady state is about five half-lives; repeat after each change until stable.

15.3 The frequency of level monitoring once stable

Frequent during titration, then every 3 months. During titration the level is checked every few days to a week as the dose is adjusted (each check 5 to 7 days after the preceding change). Once the patient is established on a stable dose with the level in range, routine **serum level** monitoring settles to **every 3 months** in the Indian Psychiatric Society schedule, while some guidelines including the Maudsley move to **6-monthly** lithium levels once the patient is stable (Shah 2017; Maudsley 2021). CANMAT sits between these, repeating levels every 3 to 6 months after two consecutive therapeutic acute-phase readings (Yatham 2018).

Check more often in the vulnerable. The interval shortens in the **elderly**, in anyone starting or stopping an interacting drug (see 15.6), in renal impairment or other relevant physical illness, and whenever toxicity is suspected clinically (Maudsley 2021). In these groups a routine 6-monthly level is not enough.

15.4 Baseline investigations before starting lithium

The pre-lithium work-up. The **baseline investigations** exist to establish the two organ functions lithium threatens and to flag cardiac risk. Before prescribing, check **renal function** (estimated glomerular filtration rate, that is eGFR, with urea and electrolytes and serum creatinine) and **thyroid function** (thyroid-stimulating hormone, that is TSH), together with a baseline serum calcium, a baseline weight or body mass index, and an ECG where the patient has

risk factors for or established cardiovascular disease (Maudsley 2021; Yatham 2018). Because lithium is a putative human teratogen, a woman of child-bearing potential should be counselled on reliable contraception and a pregnancy test considered at baseline (Maudsley 2021).

Renal function
eGFR, serum creatinine, urea and electrolytes; the organ that clears lithium and the one at long-term risk.

Thyroid function
TSH (with free T4 if abnormal); lithium causes hypothyroidism, up to about 20% in middle-aged women over time.

Calcium
baseline serum calcium; lithium can cause hyperparathyroidism and hypercalcaemia.

ECG
at baseline where cardiovascular risk factors or disease exist.

Weight / BMI
baseline, because lithium causes weight gain.

15.5 The follow-up panel: renal and thyroid roughly 6-monthly

Repeat renal and thyroid at 6 months. The on-treatment organ panel mirrors the baseline one. **Renal function** (eGFR and creatinine) and **thyroid function** (TSH) are rechecked roughly 6-monthly, along with serum calcium and weight, and at least annually thereafter or as clinically indicated; the Maudsley checks plasma lithium, eGFR, U&Es, TFTs and calcium every 6 months, CANMAT assesses thyroid and renal function and plasma calcium at 6 months and at least annually, and the Indian Psychiatric Society specifies baseline and 6-monthly TSH, creatinine, eGFR, calcium and weight (Maudsley 2021; Yatham 2018; Shah 2017). Thyroid function is often checked more frequently in the first year, when hypothyroidism most commonly emerges (Maudsley 2021).

Note that the follow-up level (15.3) and the follow-up organ panel run on slightly different clocks: the trough level is checked 3-monthly (some guidelines 6-monthly once stable), while the renal and thyroid panel is checked roughly 6-monthly. Both intervals shorten in the elderly and with interacting drugs.

INVESTIGATION	BASELINE	TITRATION	ONCE STABLE (INTERVAL)	NOTE
Serum lithium (12-hour trough)	not applicable	**5 to 7 days after each dose change**	**every 3 months (some guidelines 6-monthly)**	Draw 12 h post-dose; standardise timing
Renal function (eGFR, creatinine)	yes	if concern	**roughly 6-monthly**	More often in the elderly / interacting drugs / CKD
Thyroid function (TSH)	yes	if concern	**roughly 6-monthly**	Consider more often in first year

INVESTIGATION	BASELINE	TITRATION	ONCE STABLE (INTERVAL)	NOTE
Serum calcium	yes	if concern	roughly 6-monthly	Hyperparathyroidism / hypercalcaemia
Weight / BMI	yes	monitor	roughly 6-monthly	Lithium causes weight gain
ECG	where CV risk	not routine	as clinically indicated	Baseline if cardiovascular risk factors or disease

Lithium monitoring schedule: the twelve-hour trough serum level after each dose change and then 3-monthly (some guidelines 6-monthly), with renal and thyroid function roughly 6-monthly, plus calcium, weight and ECG where indicated (Maudsley 2021; Yatham 2018; Shah 2017). Highlighted cells are the board-critical intervals.

TRAP **Letting renal or thyroid monitoring lapse.** A patient stable for years still needs the roughly 6-monthly renal and thyroid panel; silent hypothyroidism or a creeping fall in eGFR is missed when the panel is dropped.

15.6 Interacting drugs that force closer monitoring

Anything that raises the lithium level tightens the schedule. Lithium sits on the renal sodium-handling system, so drugs that alter that system change its level and mandate more frequent checks. The classic culprits are thiazide diuretics, ACE inhibitors and angiotensin-receptor blockers, and NSAIDs, each of which raises the lithium level and can precipitate toxicity (Maudsley 2021). Whenever one of these is started, stopped or dose-adjusted, recheck the twelve-hour trough 5 to 7 days later and monitor renal function more closely; in the elderly, ACE inhibitors raise the risk of lithium-toxicity hospitalisation several-fold (Maudsley 2021).

COMMON TRAP

A stable lithium patient develops hypertension and is started on a thiazide or an ACE inhibitor by another clinician. Without a repeat trough level 5 to 7 days later, the rising lithium level goes unnoticed until the patient presents with tremor, ataxia and confusion. Any new interacting drug is a trigger to recheck the level, not to wait for the next routine appointment.

INDIA

Lithium is cheap, freely available and heavily prescribed in Indian practice; the generic is lithium carbonate, marketed as Licab and as the controlled-release Intalith CR. The serum level assay is inexpensive and widely available, but the twelve-hour trough discipline is easily lost in a busy outpatient department, so counsel the patient to attend fasting in the morning before the day's dose and to note the time of the last tablet. The Indian Psychiatric Society schedule (serum level 5 to 7 days after a dose change, then 3-monthly when stable, with baseline and 6-monthly TSH, creatinine, eGFR, calcium and weight) is the practical standard to memorise for Indian exams (Shah 2017).

MNEMONIC

TRoTTeR

What lithium monitoring turns on: **T**welve-hour trough (the sample timing), **R**echeck at 5 to 7 days after a dose change, **o**ngoing level every 3 months once stable, **T**hyroid (TSH) roughly 6-monthly, **T**ests of renal function (eGFR/creatinine) roughly 6-monthly, and **R**emember calcium, weight and ECG where indicated.

GOOD TO REMEMBER

- **Serum level timing:** twelve-hour trough, the 12-hour post-dose sample (ideally 10 to 14 hours), standardised each time.
- **After a dose change:** recheck the trough level in 5 to 7 days (about five half-lives to steady state), repeat until stable.
- **Routine level once stable:** every 3 months (some guidelines 6-monthly), more often in the elderly or with interacting drugs.
- **Renal function (eGFR/creatinine):** at baseline then roughly 6-monthly; the organ that clears lithium and the long-term risk.
- **Thyroid function (TSH):** at baseline then roughly 6-monthly (often more in the first year); lithium causes hypothyroidism.
- **Also:** baseline and 6-monthly calcium and weight; baseline ECG where cardiovascular risk exists.
- **Target ranges the level is read against:** maintenance **0.6 to 1.0 mmol/L**, acute mania **0.8 to 1.2 mmol/L**, toxicity above **1.5 mmol/L**.

HOLD THIS

Sample lithium as a standardised twelve-hour trough, recheck 5 to 7 days after every dose change until stable, then run the level 3-monthly (some guidelines 6-monthly) and the renal and thyroid panel roughly 6-monthly, checking more often in the elderly or on interacting drugs.

16 . Lithium toxicity

lithium toxicity is the one lithium emergency the board expects you to recognise on sight, grade, and manage in the right order. Lithium has the narrowest therapeutic index in psychiatry, so a patient sitting comfortably in the maintenance range of **0.6 to 1.0 mmol/L** can be pushed into toxicity by an ordinary intercurrent event: a bout of gastroenteritis, a hot spell with poor fluid intake, a new diuretic, or an NSAID bought over the counter. The examinable core is the **graded picture keyed to the serum level** and the **stepwise management**, because both are scored precisely and both save lives.

Everything below is keyed to the twelve-hour trough **serum level** and verified against the Maudsley Prescribing Guidelines, with the guideline-level counselling and threshold cross-checked against CANMAT and the Indian Psychiatric Society clinical practice guideline (Maudsley 2021; Yatham 2018; Shah 2017). The Maudsley states that toxic effects reliably occur at levels above **1.5 mmol/L**, that disorientation and seizures usually appear above 2 mmol/L progressing to coma and death, and that dialysis is often used above 3 mmol/L (Maudsley 2021). The sampling rule, target ranges and organ monitoring sit alongside this in the lithium initiation

and monitoring notes; the wider emergency frame for acute management and the perinatal picture is set out in the Perinatal/women's mental health and emergency psychiatry notes.

Fig 12.7 Lithium toxicity graded by serum level. Mild toxicity from 1.5 to 2.0 mmol/L gives coarse tremor, GI upset and lethargy; moderate toxicity (2.0 to 2.5) adds confusion, ataxia and dysarthria; severe toxicity above 2.5 brings seizures, coma and renal failure and needs haemodialysis. Any level with toxic features counts as toxicity, and dehydration or an interacting drug is the usual precipitant.

16.1 Why toxicity happens: the precipitants

Anything that raises the lithium level or the brain's exposure to it. Lithium is handled by the kidney exactly like sodium, so most precipitants act by changing sodium balance or renal clearance. The examinable list is: **dehydration** (vomiting, diarrhoea, fever, hot climate, reduced intake), **sodium loss** or a low-salt diet, **renal impairment** (which lowers clearance), **drug interactions**, and **overdose** (deliberate or accidental) (Maudsley 2021). The Maudsley notes that most risk factors involve a fall in sodium or a change in how the body handles sodium, for example low-salt diets, dehydration, drug interactions and uncommon illnesses such as Addison's disease (Maudsley 2021).

The interacting drugs to hold. Three classes raise the level and precipitate toxicity: thiazide diuretics, ACE inhibitors and angiotensin-receptor blockers, and NSAIDs (Maudsley 2021). Each reduces renal lithium clearance, so a stable patient started on any of them needs a repeat level and can tip into toxicity within days.

RULE **Any coarse tremor, ataxia or confusion in a patient on lithium is toxicity until the level proves otherwise.** Check the level before you look for another cause.

TRAP **Continuing lithium through an intercurrent illness with vomiting or dehydration.** Fluid loss concentrates the drug; the level climbs even though the dose has not changed. Withhold lithium and rehydrate.

16.2 The graded picture: mild, moderate, severe

Read the features against the level. Toxicity follows a **mild moderate severe** gradient that tracks the rising **serum level**, and the board rewards you for stating the **grading** with the

matching level band. The Maudsley anchors the two hard thresholds: toxic effects reliably occur above **1.5 mmol/L** (gastrointestinal upset plus early CNS signs), and above 2 mmol/L disorientation and seizures usually occur, progressing to coma and death (Maudsley 2021). The widely taught three-band scheme places mild toxicity from 1.5 to 2.0 mmol/L, moderate from 2.0 to 2.5 mmol/L, and severe above 2.5 mmol/L, consistent with the Maudsley anchors above (serious neurotoxicity and seizures usually appear above 2, and dialysis is often needed above 3).

Mild (1.5 to 2.0 mmol/L)
coarse **tremor** (the fine physiological tremor becomes coarse), gastrointestinal upset (anorexia, nausea, diarrhoea), lethargy and mild drowsiness.

Moderate (2.0 to 2.5 mmol/L)
confusion, **ataxia**, dysarthria, myoclonus and muscle twitching, worsening coarse tremor, marked drowsiness.

Severe (above 2.5 mmol/L)
seizure, coma, cardiovascular collapse, and renal failure; ultimately death.

The level is only a guide. The Maudsley cautions that these plasma levels are a guide only and individuals vary in susceptibility, and that neurotoxicity has been described even at normal plasma levels because brain lithium may not be reflected in the plasma concentration (Maudsley 2021). Treat the patient in front of you, not the number alone.

1.5 to 2.0	2.0 to 2.5	above 2.5
MILD TOXICITY (MMOL/L)	MODERATE TOXICITY (MMOL/L)	SEVERE TOXICITY (MMOL/L)

16.3 The graded table of level, features and management

The one table to hold for the viva. Grade, features and the corresponding management step line up as follows (Maudsley 2021).

GRADE	SERUM LEVEL (MMOL/L)	CLINICAL FEATURES	MANAGEMENT
Mild	**1.5 to 2.0**	coarse tremor, GI upset (anorexia, nausea, diarrhoea), lethargy	Stop lithium; check level, renal function and electrolytes; rehydrate; recheck level
Moderate	**2.0 to 2.5**	confusion, ataxia, dysarthria, myoclonus, coarse tremor	Stop lithium; admit; intravenous normal saline to restore volume and sodium; serial levels and renal function; supportive care
Severe	**above 2.5**	seizure, coma, cardiovascular collapse, renal failure	Stop lithium; medical/ICU care; correct volume; **haemodialysis** for severe features or renal failure, usually at levels above 2.5 to 3.0 mmol/L

Lithium toxicity grading: features and management keyed to the twelve-hour trough serum level, mild 1.5 to 2.0, moderate 2.0 to 2.5, severe above 2.5 mmol/L; haemodialysis is reserved for severe toxicity (Maudsley 2021). Highlighted cells are the board-critical level bands.

16.4 Management: stop, assess, rehydrate, dialyse if severe

Four steps in order. The management of **lithium toxicity** is a fixed sequence. First, **stop lithium** immediately. Second, **check the level and renal function and electrolytes** (serum lithium, creatinine and eGFR, urea and electrolytes) and repeat serially, because the level can keep rising as the drug redistributes. Third, **rehydrate with saline**: intravenous normal (0.9%) saline restores intravascular volume and sodium and promotes renal excretion of lithium. Fourth, use **haemodialysis** for severe toxicity, that is high levels, renal failure, or severe clinical features such as seizures, coma or haemodynamic collapse (Maudsley 2021). The Maudsley states that above 3 mmol/L peritoneal or haemodialysis is often used, and that in more severe symptomatic cases osmotic or forced alkaline diuresis has historically been used in a medical facility (Maudsley 2021).

Why dialysis, and why it may need repeating. Lithium is a small, non-protein-bound ion that dialyses readily, so haemodialysis rapidly clears it from plasma. But lithium leaves the intracellular and brain compartments slowly, so the plasma level can rebound after a session ends, and dialysis may need to be repeated until the post-dialysis rebound level stays below the toxic threshold. This is why serial levels continue after the first run.

RULE **Stop lithium, give saline, and dialyse the severe.** Haemodialysis is indicated for very high levels, renal failure, or severe neurological or cardiovascular features, regardless of the exact number.

16.5 The silent sequel: delayed and irreversible neurotoxicity

Recovery is not always complete. A minority of patients who survive significant neurotoxicity are left with persistent, sometimes permanent, cerebellar and other neurological deficits: the **silent** picture, described as the syndrome of irreversible lithium-effectuated neurotoxicity (SILENT). The hallmark is a persisting cerebellar syndrome, most often ataxia and dysarthria, that outlasts the acute episode and the fall in serum level. The teaching point is that lithium neurotoxicity is not always a fully reversible event, which is a further reason to act quickly and not to let a moderate picture drift toward the severe. Delayed neurotoxic sequelae can persist after the plasma level has normalised, consistent with the Maudsley observation that brain lithium is not reflected in the plasma (Maudsley 2021).

INDIA

Lithium is cheap, freely available and heavily prescribed in Indian practice, marketed as lithium carbonate (Licab, and the controlled-release Intalith CR). The commonest real-world precipitants here are summer dehydration, gastroenteritis with vomiting and diarrhoea, and over-the-counter NSAIDs bought without a prescription, so counsel every patient at initiation to withhold lithium and increase fluids during any vomiting, diarrhoea or febrile illness and to attend for a level. Serum lithium, creatinine and electrolyte assays are inexpensive and widely available; the practical management chain to hold is stop lithium, send a stat level with renal function and electrolytes, start intravenous normal saline, and refer for **haemodialysis** if the level is high, renal function is failing, or the patient has seizures or coma (Maudsley 2021; Shah 2017). Where dialysis is not immediately available, transfer the severely toxic patient to a centre that has it rather than waiting.

PEARL

The discriminator between a therapeutic tremor and toxicity is its character: lithium normally causes a fine physiological tremor, but a **tremor** that has become coarse, especially with any GI upset, ataxia or confusion, signals toxicity and demands a level. Do not attribute new ataxia or confusion in a lithium patient to age, alcohol or a virus until the level is back.

MNEMONIC

SALT loss climbs the level; STOP-SALINE-DIALYSE brings it down

Precipitants act through **SALT** and water: dehydration, sodium loss, NSAIDs and diuretics, renal impairment, overdose. Management is **STOP** lithium, check the level and renal function and electrolytes, **SALINE** (rehydrate with normal saline), and **DIALYSE** if severe (high level, renal failure or severe features).

GOOD TO REMEMBER

- **Mild toxicity (around 1.5 mmol/L):** coarse tremor, GI upset and lethargy; the earliest and commonest feature.
- **Moderate toxicity (around 1.5 to 2.5 mmol/L):** ataxia, dysarthria, confusion and myoclonus; the patient is now clearly encephalopathic.
- **Severe toxicity (above 2.5 mmol/L):** seizures, coma and cardiovascular collapse; a medical emergency.
- **Precipitants:** dehydration and NSAIDs are the classic ones; also sodium loss, diuretics, ACE inhibitors/ARBs, renal impairment and overdose.
- **First management step:** stop lithium, check level plus renal function and electrolytes, rehydrate with saline; dialyse if severe.
- **Discriminator (silent sequel):** haemodialysis for severe toxicity; a persisting cerebellar syndrome (silent, irreversible neurotoxicity) can outlast the normalised level.

HOLD THIS

Coarse tremor and GI upset at ~1.5, ataxia/dysarthria/confusion at 1.5 to 2.5, seizures/coma above 2.5 mmol/L: stop lithium, check level with renal function and electrolytes, rehydrate with saline, and haemodialyse the severe (Maudsley 2021).

17 . Lithium and the kidney

The kidney is where lithium is cleared and where lithium does its most talked-about harm, so **lithium and the kidney** is a favourite examiner theme. Two effects sit at opposite ends of the time axis: an **early, common, largely reversible** concentrating defect that the patient feels as thirst and frequent urination, and a **slow, long-term** decline in filtration that only a monitoring trend will reveal. The board rewards you for separating the two, for naming the drug that treats the first, and for knowing that the second is managed by watching the eGFR trend and taking a measured nephrology-guided decision rather than stopping lithium on a single reading.

The whole topic follows from one physiological fact set out in the Mood disorders: pharmacotherapy renal-handling detail: lithium enters collecting-duct principal cells through the epithelial sodium channel (ENaC), competing with sodium, and its intracellular accumulation inhibits the renal response to antidiuretic hormone and, over years, drives interstitial fibrosis (Meyer and Stahl 2023; Maudsley 2021). Everything below, the polyuria, the amiloride, the eGFR trend, the CKD risk-benefit, derives from that. The initiation, dosing and toxicity detail sits in the mood-block pharmacotherapy notes; the twelve-hour trough and the full baseline and follow-up panel are in the lithium monitoring topic; the guideline-anchored PLAN that keeps lithium first-line is in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes. The receptor and channel background is in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

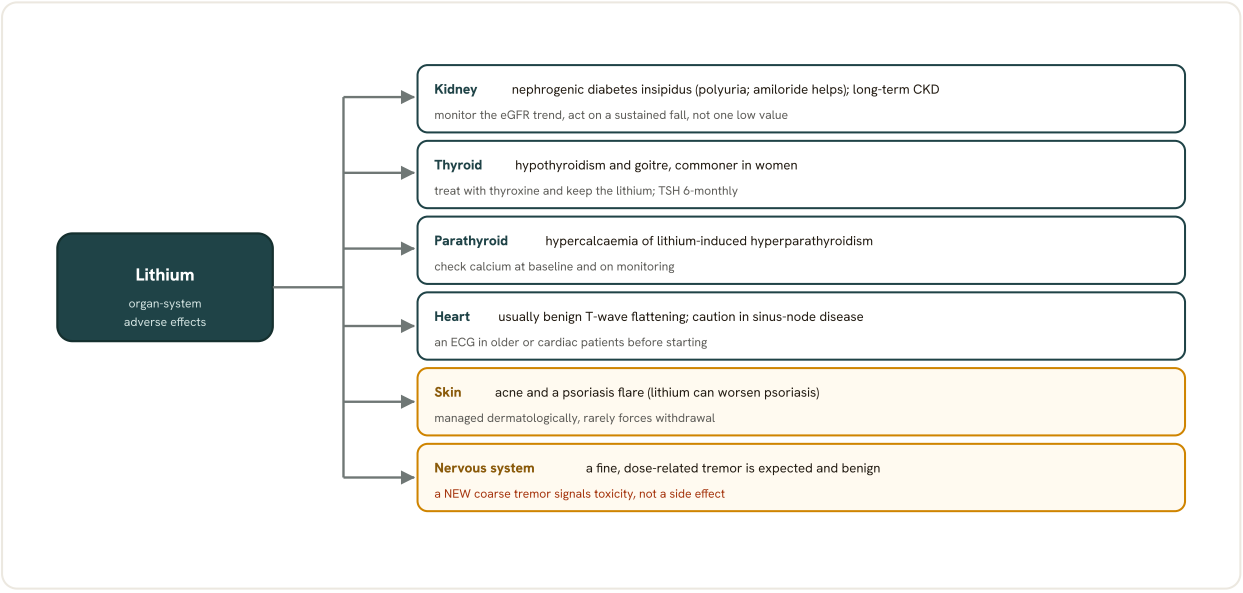

Fig 12.8 The organ-system adverse effects of lithium and their monitoring. The kidney (nephrogenic diabetes insipidus, long-term chronic kidney disease) and thyroid (hypothyroidism, goitre) are the load-bearing ones, caught by routine renal and thyroid monitoring; hypercalcaemia, benign cardiac T-wave changes, acne and psoriasis, and a fine dose-related tremor complete the picture. A new coarse tremor is the exception: it signals toxicity rather than a tolerable side effect.

17.1 Nephrogenic diabetes insipidus: the mechanism

Lithium blocks the renal response to ADH. The earliest and commonest renal effect is nephrogenic diabetes insipidus. Lithium entering the collecting-duct principal cell via ENaC accumulates intracellularly and, in roughly 20% of patients, produces insensitivity to antidiuretic

hormone (ADH, vasopressin) with downregulation of the water-absorbing aquaporin-2 channels on the apical surface (Meyer and Stahl 2023). The kidney can no longer concentrate the urine in response to ADH, so dilute urine is passed in large volume. The result is **polyuria** and, secondarily, **polydipsia** as the patient drinks to keep up. It is nephrogenic (the defect is at the kidney, the ADH itself is normal or high), which is why it is called nephrogenic diabetes insipidus rather than a central one.

Common, and usually reversible early. A reduction in urinary concentrating capacity is common on lithium and, in the short to medium term, is usually reversible on stopping or dose reduction; renal effects may become irreversible only after long-term treatment (Grierson and companion authors, Companion to Psychiatric Studies; Meyer and Stahl 2023). Polyuria is defined as a 24-hour urine output above **3 litres** (Meyer and Stahl 2023). It is the effect patients notice first and complain about most, and it is the single commonest cited reason for wanting to stop lithium, so recognising and treating it early forestalls unnecessary discontinuation.

RULE **Lithium polyuria is nephrogenic diabetes insipidus until proven otherwise.** ADH is normal, the kidney cannot respond, and the defect is usually reversible if caught early.

17.2 Assessing the polyuria

Ask at every visit, then quantify. Assessment of **polyuria** starts with routine inquiry at each office visit about excessive thirst and urination, because some patients underreport the functional impact (Meyer and Stahl 2023). Two office tools then quantify it. The 24-hour fluid intake record (FIR) is a simple screen the patient can keep: an intake below 2000 mL over 24 hours makes polyuria very unlikely, while an intake climbing towards 3000 to 3500 mL makes it likely. The early morning urine osmolality (EMUO) estimates concentrating ability directly and tracks response to treatment.

Polyuria (definition)
24-hour urine output above 3 litres; the standard threshold.

24-hour fluid intake record (FIR)
patient-kept screen; below 2000 mL/24 h makes polyuria unlikely, above 3500 mL/24 h makes it likely.

Early morning urine osmolality (EMUO)
direct measure of concentrating ability; normal exceeds about 850 mOsm/kg.

Full nephrogenic diabetes insipidus
EMUO below 300 mOsm/kg; treat regardless of how loudly the patient complains.

A normal EMUO is above about **850 mOsm/kg** after overnight water deprivation; a value below **300 mOsm/kg** represents full nephrogenic diabetes insipidus and warrants treatment whatever the patient reports, because it signals clear lithium accumulation in the principal cells (Meyer and Stahl 2023).

17.3 Managing nephrogenic diabetes insipidus: dose review, once-daily dosing, amiloride

First tighten the regimen, then add amiloride. Management of lithium-related **nephrogenic diabetes insipidus** proceeds in a logical order. First, review the dose and the serum level: keep the maintenance twelve-hour trough modest, and prefer once-daily dosing, because polyuria occurs more frequently with twice-daily than once-daily regimens and modern once-daily dosing lowers renal risk (Maudsley 2021; Meyer and Stahl 2023). Second, where polyuria persists, add amiloride.

Amiloride blocks lithium entry into the collecting duct. Amiloride is a potassium-sparing diuretic that specifically blocks ENaC, the very channel lithium uses to enter principal cells, so it reduces lithium's intracellular accumulation and improves urine concentrating ability (Meyer and Stahl 2023; Kortenoeven et al. 2009). It is the primary, best-evidenced treatment for lithium-related nephrogenic diabetes insipidus and should be started as soon as a concentrating problem is detected; the claim that the only option is to switch off lithium is simply untrue (Meyer and Stahl 2023). Importantly, amiloride is one of the diuretics whose effect on lithium clearance is clinically insignificant, so it does not itself push the lithium level up the way a thiazide does, though at least one repeat lithium level after starting it is prudent (Meyer and Stahl 2023).

TRAP **Reaching for a thiazide to treat lithium polyuria.** A thiazide reduces polyuria but raises the lithium level and risks toxicity; amiloride, an ENaC blocker, treats the concentrating defect at its mechanism without that hazard.

WORKED EXAMPLE

A patient stable on lithium complains of drinking constantly and passing urine through the night. You confirm a 24-hour fluid intake record above 3500 mL and an early morning urine osmolality of 250 mOsm/kg, which is full nephrogenic diabetes insipidus. You do not stop the lithium. You move the patient to once-daily bedtime dosing, keep the twelve-hour trough modest, and start amiloride, then track the early morning urine osmolality as it recovers. The patient stays on the drug that protects them from relapse.

17.4 The long-term risk: chronic kidney disease

A slow decline in eGFR over years. The second, separate concern is chronic kidney disease. Years of lithium exposure can be associated with a slow decline in the estimated glomerular filtration rate (eGFR), the histological substrate being a chronic interstitial nephropathy, that is proximal tubular atrophy and interstitial fibrosis driven by intracellular lithium inhibiting GSK-3-beta in principal cells (Meyer and Stahl 2023). Lithium can lead to a reduction in glomerular filtration rate, though the magnitude of the risk is uncertain; it is driven mainly by cumulative exposure, repeated episodes of toxicity, older multiple-daily dosing and comorbidity (hypertension, diabetes) rather than by any single therapeutic level (Companion to Psychiatric Studies; Meyer and Stahl 2023).

Lithium is not the whole story. The modern reframing matters for the exam. Much of the renal risk historically pinned on lithium alone actually reflects two things: old prescribing practices (multiple daily dosing, allowing trough levels to exceed 1.2 mEq/L) and the chronic kidney

disease risk factors, hypertension, metabolic syndrome, diabetes and smoking, that are disproportionately common in bipolar patients (Meyer and Stahl 2023). Having a bipolar diagnosis itself carries a roughly 3-fold increased CKD risk independent of drug treatment. With once-daily dosing and modest outpatient trough levels below about 1.0 mEq/L, progression to end-stage renal disease attributable to lithium has become very rare (Meyer and Stahl 2023). So chronic kidney disease is a real long-term risk that mandates monitoring, but not the near-inevitability it was once feared to be.

HOLD THIS

Lithium harms the kidney in two separable ways: an early, common, usually reversible nephrogenic diabetes insipidus (polyuria, treated with amiloride) and a slow, long-term chronic kidney disease seen as a declining eGFR trend, watched over time and never acted on from one low value.

17.5 Monitoring the eGFR trend, not a single value

Watch the trend. Because the long-term change is a gradual slope, the practical rule is to monitor the **eGFR trend** rather than react to any one reading. Renal function (eGFR and creatinine) is checked at baseline and then roughly 6-monthly on stable lithium, more often when eGFR is already reduced or an interacting drug is in play (Maudsley 2021; Meyer and Stahl 2023). What triggers action is not a value but a verified downward slope. The Lithium Handbook operationalises this: increase lab frequency to every 3 months when the eGFR is below **60 ml/min**, or when there is an initial decline of more than **2 ml/min over 6 months** or more than **4 ml/min over 12 months** confirmed on a repeat specimen (Meyer and Stahl 2023).

When to bring in nephrology. A nephrology review is warranted when the eGFR falls in a sustained way, not on a single blip: a second confirmed decline exceeding those thresholds, an eGFR below **45 ml/min** verified on repeat, progression of albuminuria to stage A3, or nephrogenic diabetes insipidus unresponsive to maximal amiloride plus adjunctive acetazolamide (Meyer and Stahl 2023). The point of the nephrology referral is a joint, measured decision, weighing the renal trajectory against lithium's mood-stabilising and anti-suicide benefit, rather than a reflex switch.

RULE **Monitor the eGFR trend on long-term lithium and act on a sustained fall, not a single value.** A confirmed decline (for example more than 4 ml/min over 12 months on repeat) triggers closer monitoring and nephrology review; one isolated low reading does not.

RENAL PARAMETER	BASELINE	STABLE FOLLOW-UP	ESCALATE FREQUENCY WHEN	REFER TO NEPHROLOGY WHEN
eGFR (with creatinine)	yes	**roughly 6-monthly**	**below 60 ml/min, or decline over 2 ml/min in 6 months / over 4 ml/min in 12 months (repeat-verified)**	**second confirmed decline, or eGFR below 45 ml/min on repeat**

RENAL PARAMETER	BASELINE	STABLE FOLLOW-UP	ESCALATE FREQUENCY WHEN	REFER TO NEPHROLOGY WHEN
Early morning urine osmolality (EMUO)	consider if over 50 years	if polyuria / on amiloride	new or increased polyuria, or EMUO below 300 mOsm/kg	full NDI unresponsive to maximal amiloride plus acetazolamide
Albumin-to-creatinine ratio (ACR)	as indicated	for CKD risk factors	progression from stage A1 to A2 (repeat-verified)	stage A3
24-hour fluid intake record (FIR)	not routine	periodic office screen	polyuria complaints	not a referral trigger by itself

Practical renal monitoring on long-term lithium: the eGFR trend is the spine, with EMUO and the fluid intake record tracking the concentrating defect and the ACR tracking glomerular injury from comorbid CKD risk factors (Meyer and Stahl 2023; Maudsley 2021). Highlighted cells are the trend-based triggers a resident must hold.

17.6 Do not stop abruptly: the rebound-mania trap

A low eGFR is not a reason to stop lithium overnight. The most dangerous reflex on this topic is to see one reduced eGFR and abruptly discontinue lithium. Abrupt cessation carries a much greater than expected incidence of manic relapse in the first few months, even in patients who have been symptom-free for years (Maudsley 2021). If a decision to withdraw lithium is genuinely reached, the dose should be reduced gradually over at least a month, preferably three, avoiding stepwise plasma-level reductions greater than 0.2 mmol/L, which lowers the relapse risk (Maudsley 2021). Where the concern is renal, the correct path is the eGFR trend and a nephrology-guided risk-benefit decision, continuing lithium unless the likelihood of progression to end-stage disease clearly outweighs its benefit (Meyer and Stahl 2023).

TRAP **Stopping lithium abruptly on one low eGFR.** That risks rebound mania; the measured move is to confirm the trend, involve nephrology, and if withdrawing at all, taper over at least a month.

3	60	45
POLYURIA THRESHOLD (LITRES/24 H)	ESCALATE LABS BELOW (EGFR ML/MIN)	NEPHROLOGY REVIEW BELOW (EGFR ML/MIN)

INDIA

Lithium carbonate (marketed as Licab and as the controlled-release Intalith CR) is cheap, freely available and heavily prescribed in Indian practice, so its renal monitoring falls to the psychiatrist. Serum creatinine and eGFR are inexpensive and widely available; amiloride is available and affordable. The Indian Psychiatric Society schedule builds the renal check into routine care: baseline and 6-monthly creatinine and eGFR alongside TSH, calcium and weight, with counselling on dehydration risk (Shah et al., Indian Psychiatric Society bipolar guideline). The practical Indian-exam point is that a falling eGFR trend, not a single value, drives escalation, and that amiloride, not switching off lithium, is the first answer to lithium polyuria.

MNEMONIC

PEAR-T

Lithium and the kidney: **P**olyuria and polydipsia are the early, common, usually reversible sign, **E**NaC entry drives it (so amiloride, an ENaC blocker, treats it), **A**miloride plus once-daily dosing and a dose review is the management, **R**enal trend (the eGFR slope) is what you watch long term for chronic kidney disease, and **T**aper never abruptly stop (rebound mania).

GOOD TO REMEMBER

- **Nephrogenic diabetes insipidus:** lithium blocks the renal response to ADH at the collecting duct (via ENaC entry, aquaporin-2 downregulation), causing polyuria and polydipsia; common (about 20%), usually reversible early.
- **Amiloride:** a potassium-sparing ENaC blocker that stops lithium entering the collecting duct; the first-line, best-evidenced treatment for lithium polyuria, alongside dose review and once-daily dosing, does not raise the lithium level.
- **Polyuria assessment:** ask at every visit; quantify with the 24-hour fluid intake record and early morning urine osmolality; polyuria is over 3 litres/24 h, full NDI is EMUO below 300 mOsm/kg.
- **Chronic kidney disease:** a slow, long-term eGFR decline (chronic interstitial nephropathy); real but modest with modern once-daily dosing and troughs below about 1.0 mEq/L, and partly driven by comorbid hypertension and diabetes.
- **Monitoring:** watch the eGFR trend, not a single value; escalate labs below eGFR 60 ml/min or a confirmed decline (over 4 ml/min in 12 months); nephrology review for a sustained fall or eGFR below 45 ml/min on repeat.
- **Do not stop abruptly:** one low eGFR is not grounds to stop; abrupt cessation risks rebound mania, so confirm the trend, involve nephrology, and if withdrawing, taper over at least a month.

18 . Lithium and the thyroid and parathyroid

Why it matters. lithium is the most effective long-term agent in bipolar disorder, yet clinician fear of its endocrine effects drives underuse (Meyer and Stahl 2020). The examinable point is that the two glandular effects, on the **thyroid** and the **parathyroid**, are common, detectable on routine bloods, and treatable without ever stopping the lithium. This is the topic where a resident must resist the reflex to withdraw an effective drug for a monitorable, correctable side effect.

Frame the whole topic around three verified truths: lithium accumulates in the thyroid and inhibits thyroid hormone release, producing **hypothyroidism** (often with a **goitre**) that is picked up by the routine TSH and corrected with levothyroxine; it also shifts the parathyroid calcium set point, producing hypercalcaemia of lithium-induced hyperparathyroidism, picked up by the routine serum calcium; and neither event, on its own, is a reason to discontinue lithium.

18.1 Mechanism at the thyroid follicle

Iodide trapping and hormone release. Lithium is a substrate for the sodium-iodide symporter (NIS) and concentrates in the thyroid gland at levels **3 to 4 times** those in plasma (Meyer and Stahl 2020). Its dominant action is **inhibition of T4 and T3 release** from the gland; it additionally alters thyroglobulin conformation so that coupling of iodinated tyrosine residues to form T4 and T3 is impaired. The net effect is a fall in circulating thyroid hormone, a

compensatory rise in TSH, and, over time, clinical hypothyroidism. Importantly, lithium is **not** associated with Hashimoto thyroiditis, Graves disease, an excess of antithyroid antibodies, or thyroid tumours (Meyer and Stahl 2020, Companion 2010).

RULE **Concentrate then throttle.** Lithium is trapped by the NIS and chiefly blocks thyroid hormone release, so TSH rises and hypothyroidism, not autoimmunity, is the signature.

18.2 Hypothyroidism: the common, treatable thyroid effect

Frequency and who is at risk. Slight falls in T4 with compensatory rises in TSH appear within a few months and usually stabilise within 12 months (Companion 2010). The annual incidence of new-onset **hypothyroidism** on lithium is about **1.5 percent**, and overt hypothyroidism occurs in roughly **8 to 19 percent** across long-term studies (Meyer and Stahl 2020). It is distinctly **commoner in women**, with female rates about three times those of men. The classic at-risk profile is a woman over 45 with circulating antithyroid antibodies and a slight but sustained TSH elevation (Companion 2010).

Detection and management. It is detected by the **routine TSH monitoring** already built into lithium follow-up: a sustained TSH elevation, even with a normal T4, is sufficient indication to supplement. It is managed with levothyroxine (L-thyroxine, Indian brand Thyronorm), titrated to the TSH, **without stopping lithium** (Meyer and Stahl 2020). A prior history of hypothyroidism is not a reason to withhold lithium, and new-onset hypothyroidism is not a reason to discontinue it.

HOLD THIS
Lithium hypothyroidism is a TSH diagnosis with a levothyroxine solution: supplement and keep the lithium, never stop the lithium to treat the thyroid.

18.3 The goitre, and the rarer hyperthyroidism

Goitre. Lithium-induced **goitre** is under-recognised on palpation but, on ultrasonography, is common, affecting over 50 percent of long-term users (Companion 2010). Most goitres are not palpable, and enlargement alone does not signify hypofunction. The mechanism reflects impaired iodine incorporation into thyroid hormone. Asymptomatic goitre, like biochemical or clinical hypothyroidism, is **not a contraindication** to continued lithium; only the rare multinodular goitre needing surgery is an exception, and long-term lithium does not increase thyroid carcinoma risk (Companion 2010).

Hyperthyroidism. Less commonly, patients may show hyperthyroidism, but on the best data this is rare and is likely **incidental** to lithium rather than caused by it (Meyer and Stahl 2020). In one large database analysis, lithium exposure was not significantly associated with hyperthyroidism after adjustment. The practical rule is unchanged: if TSH is low, continue lithium, confirm with T4 and T3, and work up Graves or Hashimoto disease on their own merits.

TRAP **Stopping the wrong drug.** Discontinuing an effective lithium to treat a hypothyroidism that levothyroxine would fully correct sacrifices the mood benefit for a problem that needed a second tablet, not withdrawal.

18.4 Hyperparathyroidism and hypercalcaemia: check calcium

Mechanism and picture. Lithium enters the parathyroid chief cell and, via GSK3-beta inhibition, disrupts the **calcium-sensing receptor** pathway, shifting the PTH set point to the right: a higher serum calcium is now required to suppress PTH. The earliest measurable change is therefore a rise in serum calcium, which is why routine monitoring includes **calcium** (Meyer and Stahl 2020). Chronic therapy in a subset unmasks a parathyroid adenoma or drives multiglandular hyperplasia; the clinical picture then is identical to primary **hyperparathyroidism**, is commoner in women, and may not reverse when lithium is stopped. A meta-analysis found total calcium raised by 0.09 mmol/L and PTH by 7.32 pg/mL on lithium (Meyer and Stahl 2020).

Detection and management. Sporadic elevated calcium is repeated in 3 to 6 months; persistent elevation is confirmed with an ionized calcium, then a PTH level, then endocrine referral. Because stopping lithium may not reverse established adenoma or hyperplasia, discontinuation is not the first move: symptomatic or criteria-meeting disease goes to parathyroid surgery, and calcimimetics such as cinacalcet allosterically activate the calcium-sensing receptor and offer a non-surgical option that lets lithium continue (Meyer and Stahl 2020).

GLAND	EFFECT	SCREENING TEST	MANAGEMENT (KEEP LITHIUM)
Thyroid	**Hypothyroidism, goitre (commoner in women)**	routine TSH	levothyroxine to TSH target
Thyroid	Hyperthyroidism (rare, usually incidental)	routine TSH (low)	confirm T4/T3, treat cause on merits
Parathyroid	**Hyperparathyroidism with hypercalcaemia**	routine serum calcium	surgery if criteria met, else cinacalcet

The two glandular effects of lithium, each caught by a routine test already in the monitoring panel, each treatable without withdrawing lithium.

18.5 Why this rarely forces lithium withdrawal, and where it sits in monitoring

The unifying principle. Thyroid and parathyroid dysfunction on lithium is **common, monitorable and treatable**, so it rarely forces lithium withdrawal. Hypothyroidism is not among the ten leading causes of lithium discontinuation and, in surveillance, accounts for only about a 2 percent discontinuation rate (Meyer and Stahl 2020). The guideline-anchored monitoring that catches both is standard: baseline TSH and calcium before starting, then thyroid and renal function plus plasma calcium checked at around 6 months and at least annually thereafter (CANMAT 2018). The Indian Psychiatric Society advises baseline and 6-monthly TSH, creatinine, eGFR and calcium, with TSH checked once or twice in the first 6 months then 6-monthly to yearly (IPS 2017); this could not be re-confirmed to the exact interval against the

primary IPS text here and is taken from the guideline digest. For the wider emergency frame around lithium and the perinatal frame, see the Perinatal/women's mental health and emergency psychiatry notes; for the initiation and toxicity detail, this note sits within the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes management thread.

8 to 19	1.5	6 to 12
OVERT HYPOTHYROIDISM ON LITHIUM (PERCENT)	ANNUAL INCIDENCE NEW HYPOTHYROIDISM (PERCENT)	TSH PLUS CALCIUM REVIEW INTERVAL (MONTHS)

GOOD TO REMEMBER

- **Lithium (thyroid):** concentrated by the NIS to 3 to 4 times plasma and inhibits T4/T3 release; signature effect is hypothyroidism with goitre, commoner in women; the one thing to hold is that a sustained TSH rise triggers supplementation, not withdrawal.
- **Hypothyroidism:** detected by routine TSH, managed with levothyroxine (Thyronorm) titrated to TSH; keep the lithium.
- **Goitre:** common on ultrasound (over 50 percent), usually impalpable and euthyroid; not a contraindication and no increase in thyroid carcinoma.
- **Hyperparathyroidism:** lithium shifts the parathyroid PTH set point rightward via the calcium-sensing receptor; discriminator on bloods is a rising serum calcium; confirm with ionized calcium then PTH, treat with surgery or cinacalcet, keep the lithium where possible.

INDIA

Lead with the Indian brand where you name one: lithium carbonate is Licab (Intas) or Intalith CR (Samarth); levothyroxine for the hypothyroidism is Thyronorm (Abbott) or Eltroxin. Generic names stay primary in prescribing; the brand is the parenthetical the patient will recognise on the strip.

PEARL

Both glandular effects are caught by tests you are already drawing: the TSH catches the thyroid, the serum calcium catches the parathyroid. Add calcium to the lithium panel and neither surprise you.

19 . Lithium: dermatological and cardiac effects

Two organ-system effects of **lithium** (Licab or Intalith; lithium carbonate) are examined less as reasons to stop the drug and more as things you must recognise, counsel about, and manage without reflex withdrawal. The **dermatological** effects are cosmetic and usually treatable topically, but they drive real-world non-adherence if missed; the **cardiac** effects are mostly benign ECG changes, with one genuine caution in sinus-node disease. The exam framing is: name the skin problems and the ECG changes, state that both are usually manageable, and know the single situation where the heart forces your hand (Maudsley 2021; Meyer and Stahl 2021).

Everything below is verified against the Meyer and Stahl Lithium Handbook for the detailed derm and cardiac profile, cross-checked against the Maudsley Prescribing Guidelines and Kaplan and Sadock for the class-level statements (Maudsley 2021; Meyer and Stahl 2021; Kaplan 2024).

The renal, thyroid, toxicity and monitoring picture sits alongside this in the lithium initiation and monitoring notes; the baseline pre-lithium ECG rule is set out there too.

19.1 Dermatological effects: acne, psoriasis, and hair thinning

Skin and hair problems are new-onset or an exacerbation of what was already there. The **dermatological** set that the board expects is: acne (an acneiform eruption, new or worsened), a **psoriasiform rash**, the **exacerbation of psoriasis** (lithium can worsen or unmask psoriasis), and diffuse hair thinning (alopecia). Folliculitis and a maculopapular rash also occur (Meyer and Stahl 2021). The Maudsley states plainly that some skin conditions such as psoriasis and acne can be aggravated by lithium therapy (Maudsley 2021). The true incidence is uncertain because the literature is mostly case reports, and controlled data have not clearly separated lithium from placebo, but the association is real enough that you counsel about it and ask at every visit (Meyer and Stahl 2021).

Managed dermatologically, rarely forcing withdrawal. The governing principle is that lithium discontinuation is not always necessary for these problems. Acne responds to topical benzoyl peroxide (2 to 10 percent) and, if needed, topical retinoids or a dermatology referral; a psoriasis flare is discussed honestly and co-managed with a dermatologist, and modern biologic therapy may let some patients stay on lithium; hair thinning is treated as any pattern hair loss, with topical minoxidil (5 percent), remembering that regrowth is slow, so early detection by routine inquiry is the real intervention (Meyer and Stahl 2021). Only a problem with no obvious option other than stopping, such as a persistent maculopapular rash, prompts a slow taper with dermatology input if you wish to rechallenge (Meyer and Stahl 2021).

RULE **Ask about skin eruptions and hair loss at every visit and manage them dermatologically, not by stopping lithium.** Most respond to topical treatment; discontinuation is the exception, not the rule.

TRAP **Stopping lithium reflexively for acne or a psoriasis flare in a patient it has stabilised.** You trade a treatable, cosmetic problem for a real relapse risk; treat the skin and keep the mood stabiliser.

19.2 Cardiac effects: benign T-wave changes, and the sinus-node caution

The common ECG changes are benign. The usual **cardiac** finding on the ECG is a benign, reversible **T-wave** flattening or inversion, reflecting an effect on ventricular repolarisation; long-term treatment can also produce benign PR-interval prolongation and U-waves that resemble those of hypokalaemia (Meyer and Stahl 2021; Kaplan 2024). These reflect the chronicity of lithium exposure and do not carry sudden-death risk, so a novel benign ECG finding is not a reason to stop the drug; any real impact on cardiac conduction is unlikely at therapeutic serum levels and becomes prominent mainly in toxicity (Meyer and Stahl 2021). Lithium, unlike antipsychotics, tricyclics, citalopram, escitalopram and lamotrigine, carries no routine QT-monitoring warning outside overdose (Meyer and Stahl 2021).

The one genuine caution: sinus-node dysfunction. Lithium can worsen or unmask sick sinus syndrome, so it is associated with bradycardia, **sinus node** dysfunction, sinus block and sinus arrest (Meyer and Stahl 2021; Kaplan 2024). The mechanism is not that lithium creates the pathology but that it hastens the appearance of an underlying, often age-related, degenerative sinus-node disease; the rare patient who develops symptomatic bradycardia at therapeutic levels represents unmasked sick sinus syndrome and may need lithium interrupted until a pacemaker is placed (Meyer and Stahl 2021). This is why a baseline ECG is advised in the older or cardiac patient, that is roughly above age 40 or with cardiovascular risk factors, syncope or a family history of sudden cardiac death, before starting lithium (Meyer and Stahl 2021).

toxic or chronic	above 40
EXPOSURE DRIVING ANY CONDUCTION EFFECT	BASELINE ECG ADVISED FROM THIS AGE (YEARS)

RULE **Lithium ECG changes are usually benign, but avoid lithium in sinus-node dysfunction.** Benign T-wave changes are no reason to stop; symptomatic sick sinus syndrome is.

TRAP **Starting lithium in significant conduction disease without a cardiology view.** In an older or cardiac patient, get a baseline ECG first; unmasked sinus-node disease can present with symptomatic bradycardia and near-syncope.

HOLD THIS

Lithium's skin effects (acne, psoriasis flare, hair thinning) are treated dermatologically and rarely force withdrawal; its ECG changes (T-wave flattening or inversion) are usually benign, and the one real caution is sinus-node disease, where lithium can unmask sick sinus syndrome, so get a baseline ECG in the older or cardiac patient.

GOOD TO REMEMBER

- **Dermatological (lithium):** acne, a psoriasiform rash and exacerbation of psoriasis, plus hair thinning; managed dermatologically (topical benzoyl peroxide, minoxidil, dermatology co-management), rarely forcing withdrawal (Meyer and Stahl 2021; Maudsley 2021).
- **Cardiac (lithium):** usually benign T-wave flattening or inversion on the ECG (a benign t-wave change on the ecg, plus benign PR prolongation and U-waves); not a reason to stop (Meyer and Stahl 2021; Kaplan 2024).
- **The discriminator to hold:** benign ECG change means continue; symptomatic bradycardia at therapeutic level means unmasked sick sinus syndrome, so interrupt lithium and involve cardiology.
- **The one caution:** caution with sinus node dysfunction; lithium can worsen sick sinus syndrome, so an ECG in the older or cardiac patient before starting (Meyer and Stahl 2021).

20 · Lithium drug interactions

Lithium is renally cleared, has a narrow therapeutic index and is handled by the kidney exactly like sodium. That single fact drives almost every clinically important interaction: any drug or state that makes the proximal tubule reabsorb more sodium, or that drops the glomerular filtration rate, drags lithium up with it and can tip a stable patient into toxicity. Because the safe window is so tight (**0.6 to 1.0 mmol/L** maintenance, toxicity from about **1.5 mmol/L**), a change

that would be trivial for most drugs is dangerous here. Examiners test this as a keyed direction question: does the drug **raise** or **lower** the level, and what do you do about it.

This note teaches the **lithium drug interactions** as a two-column split (drugs that raise versus drugs and states that lower the level), then the pharmacodynamic combinations that are dangerous even at a normal level, then the one practical monitoring rule that ties it together. Verify the direction of every interaction; a swapped direction is a critical error. For the wider prescribing frame, initiation and the toxicity syndrome, see the mood-block pharmacotherapy notes; for the renal and thyroid monitoring schedule and teratogenicity, cross to those; the receptor and CYP background sits in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

20.1 Why lithium interacts: the renal mechanism

Sodium mimicry. About 70 percent of filtered lithium is reabsorbed in the proximal tubule through the sodium/hydrogen exchanger (NHE3), where lithium competes with sodium for uptake (The Lithium Handbook 2023). When the body senses sodium or volume depletion it up-regulates proximal reabsorption, and lithium is reabsorbed alongside the sodium, so the serum level climbs. Anything that cuts the glomerular filtration rate does the same by reducing clearance. Lithium is not metabolised and not protein-bound, so there are essentially no cytochrome interactions: the interactions are pharmacokinetic-renal (level-changing) or pharmacodynamic (toxicity-adding at any level).

RULE **Sodium and lithium move together.** Volume depletion, a low-salt state, or any fall in GFR raises the lithium level, because the kidney reabsorbs lithium wherever it reabsorbs sodium.

20.2 Drugs that RAISE the level (the dangerous ones)

Reduced renal clearance. Three classes are the classic level-raisers a resident must hold, plus metronidazole. NSAIDs inhibit renal prostaglandins, constrict the afferent arteriole and cut renal blood flow, raising the level (Maudsley 2021); the effect is class-wide but aspirin and sulindac raise it less (The Lithium Handbook 2023). Thiazide diuretics deplete sodium, driving compensatory proximal reabsorption of lithium and a substantial rise. ACE inhibitors and ARBs limit angiotensin II mediated efferent arteriolar tone and cause volume depletion, both dropping GFR and raising the level. Metronidazole raises the level by reducing renal clearance.

CLASS / DRUG	DIRECTION	MECHANISM	PRACTICAL NOTE
NSAIDs (ibuprofen, diclofenac, indomethacin, naproxen, celecoxib)	**RAISE**	Inhibit renal prostaglandins, afferent vasoconstriction, reduced clearance	Includes over-the-counter ibuprofen; aspirin and sulindac raise it less
Thiazide diuretics (hydrochlorothiazide, chlorthalidone)	**RAISE**	Sodium depletion drives proximal lithium reabsorption	The strongest, most predictable diuretic riser
ACE inhibitors (enalapril, ramipril, lisinopril)	**RAISE**	Reduced efferent tone and volume depletion, lower GFR	Elderly especially vulnerable
ARBs (losartan, telmisartan, valsartan)	**RAISE**	Same efferent / volume mechanism as ACE inhibitors	Treat as equivalent to ACE inhibitors
Metronidazole	**RAISE**	Reduces renal lithium clearance	Recheck if a course is started

The four level-raisers to hold: NSAIDs, thiazides, ACE inhibitors and ARBs, plus metronidazole; each reduces clearance or depletes sodium.

TRAP **The over-the-counter NSAID.** A stable patient buys ibuprofen for backache, no prescriber is told, the level climbs over days and toxicity is precipitated. NSAID access is the commonest hidden riser.

20.3 A note on loop diuretics and potassium-sparing agents

Not all diuretics behave alike. Thiazides are the reliable, dangerous risers. Loop diuretics (furosemide) also reduce clearance and can raise the level, but the effect is more variable and less pronounced than with a thiazide. The safest rule for the exam and the clinic is to treat any diuretic start or stop as a level-changing event and recheck, rather than trusting one class to be neutral.

20.4 Drugs and states that LOWER the level

Increased clearance. The mirror image: anything that increases renal lithium clearance drops the level and risks loss of prophylaxis. Osmotic diuretics (mannitol) and, classically, the carbonic-anhydrase and osmotic agents increase lithium excretion. Theophylline and aminophylline increase renal clearance and lower the level. Caffeine, in the same way, modestly increases clearance, so a big swing in caffeine intake shifts the level. A high sodium intake competes lithium out of the proximal tubule and lowers the level, which is the flip side of the salt-restriction rule: a patient who suddenly increases dietary salt may lose efficacy, and one who crash-diets on salt may become toxic.

AGENT / STATE	DIRECTION	MECHANISM
Osmotic diuretics (mannitol)	**LOWER**	Increase lithium excretion
Theophylline / aminophylline	**LOWER**	Increase renal lithium clearance
Caffeine (sustained high intake)	**LOWER**	Increases clearance; abrupt cessation can raise the level
High sodium intake	**LOWER**	Sodium competes lithium out of proximal reabsorption
Low sodium intake / dehydration	RAISE	Volume/sodium depletion drives proximal lithium reabsorption

The level-lowering agents and the salt paradox: high salt lowers the level, low salt or dehydration raises it.

20.5 Pharmacodynamic interactions: toxicity added at a normal level

Danger without a level change. Some combinations are hazardous even when the serum level reads normal, because the toxicity is additive at the target rather than through clearance. First, the neurotoxicity risk with a high-dose antipsychotic: reports of lithium plus a high-dose antipsychotic (historically haloperidol) producing an encephalopathic, delirious, sometimes irreversible neurotoxic picture relate largely to the excessive antipsychotic doses used in earlier decades, and many such cases were actually neuroleptic malignant syndrome (The Lithium Handbook 2023). The practical message is caution and dose restraint, not absolute avoidance. Second, the serotonin-syndrome risk with serotonergic drugs: lithium is pro-serotonergic, so combining it with an SSRI, an SNRI (venlafaxine) or other serotonergic agents raises the risk of serotonin syndrome, and lithium augmentation of an antidepressant should be started low and titrated slowly (Shorter Oxford 2018). Third, the additive tremor: lithium tremor stacks with the tremor of an SSRI, valproate or a beta-agonist, worsening a benign but distressing side effect.

WORKED EXAMPLE

A woman stable at **0.7 mmol/L** on lithium and sertraline is prescribed hydrochlorothiazide for hypertension by her GP. Over the next week she develops a coarse tremor, nausea and unsteadiness. The thiazide has raised the lithium level; the additive serotonergic and tremor load with sertraline makes her more symptomatic. Withhold lithium, check the level and renal function, and rethink the antihypertensive.

20.6 The practical monitoring rule

Recheck around any interacting drug. The one rule that operationalises all of the above: whenever an interacting drug, especially an NSAID, a thiazide or an ACE inhibitor, is **started or stopped**, recheck the lithium level. Stopping a riser is as important as starting one, because a level that was in range only because of the interaction will fall. The verified interval is a trough (12 hours post-dose) level about **5 to 7 days** after any dose change or interacting-drug change (CANMAT 2018; Maudsley 2021). Counsel every patient not to buy over-the-counter NSAIDs, and to flag any new blood-pressure or water tablet, before it is dispensed.

0.6 to 1.0	1.5	5 to 7
MAINTENANCE LITHIUM (MMOL/L)	TOXICITY THRESHOLD (MMOL/L)	RECHECK AFTER INTERACTING-DRUG CHANGE (DAYS)

RULE **An NSAID, a thiazide or an ACE inhibitor raises the lithium level, so recheck it.** Recheck a trough level 5 to 7 days after any interacting drug is started or stopped.

HOLD THIS

NSAIDs, thiazides and ACE inhibitors / ARBs all RAISE the lithium level by cutting renal clearance; theophylline, caffeine and high sodium LOWER it; recheck a trough level 5 to 7 days after any interacting drug starts or stops.

MNEMONIC

NTA raises, CATS lowers

NSAID, **T**hiazide, **A**CE inhibitor (and ARB) RAISE the level. **C**affeine, **A**minophylline/theophylline, **T**oo much **S**alt LOWER it.

INDIA

Lithium carbonate is marketed in India as Licab (Torrent) and Intalith, among others; the generic stays primary in prescribing. The interaction trap is amplified here by easy over-the-counter access to NSAIDs (ibuprofen, diclofenac) and to combination analgesic and cold preparations, so explicit counselling to avoid self-medicated painkillers is essential.

PEARL

Caffeine cuts both ways: a heavy coffee drinker may run a lower level, and abruptly stopping caffeine (for example on admission) can nudge the level up. Ask about caffeine and salt habits when a level drifts without an obvious drug cause.

GOOD TO REMEMBER

- **NSAIDs:** inhibit renal prostaglandins and reduce clearance, so they RAISE the level; aspirin and sulindac raise it less; over-the-counter ibuprofen is the classic hidden precipitant.
- **Thiazide diuretics:** deplete sodium, drive proximal lithium reabsorption, RAISE the level; the strongest, most predictable diuretic riser.
- **ACE inhibitors / ARBs:** lower GFR via efferent tone and volume depletion, RAISE the level; the elderly are most vulnerable.
- **Metronidazole:** reduces renal clearance, RAISES the level; recheck if a course is started.
- **Theophylline / caffeine:** increase renal clearance, LOWER the level; a big change in caffeine intake shifts the level.
- **High sodium intake:** competes lithium out of the proximal tubule, LOWERS the level; low salt or dehydration does the opposite and RAISES it.
- **High-dose antipsychotic:** caution for a neurotoxic encephalopathy at a normal level; restrain the dose rather than avoid absolutely.
- **Serotonergic drugs (SSRI, venlafaxine):** additive serotonin-syndrome risk; start lithium augmentation low and titrate slowly.
- **The one rule:** recheck a trough lithium level 5 to 7 days after any interacting drug, especially an NSAID, thiazide or ACE inhibitor, is started or stopped.

21 . Lithium in pregnancy and lactation

Reproductive-age women make up a large share of the bipolar caseload, and **lithium in pregnancy** is the single most examined perinatal prescribing decision in psychiatry. The board wants three things from you: the specific **teratogenicity** signal (the first-trimester link with Ebstein anomaly), the way lithium pharmacokinetics shift across pregnancy and swing sharply at delivery, and the guideline-anchored logic of a planned risk-benefit discussion rather than a reflex stop. The whole topic is a study in numbers that are **small but raised**: the absolute risk to the fetus is low, yet it is high enough that continuation demands fetal echocardiography and closer level monitoring.

Everything below is verified against the Maudsley Prescribing Guidelines and the Meyer and Stahl Lithium Handbook for the pharmacology and monitoring, with the class detail cross-checked against Kaplan and Sadock and the Companion to Psychiatric Studies (Maudsley 2021; Meyer 2023; Sadock 2024; Johnstone 2010). The wider perinatal frame, including relapse-prevention planning and postpartum psychosis, sits in the Perinatal/women's mental health and emergency psychiatry notes; the toxicity grading it references is in the lithium toxicity notes. Lithium is dispensed in Indian practice as lithium carbonate (Licab, and the controlled-release Intalith CR).

21.1 Teratogenicity: the Ebstein anomaly signal

The classic association is with a right-sided cardiac malformation. First-trimester **lithium in pregnancy** carries a well-known association with Ebstein anomaly, a malformation in which the tricuspid valve is displaced downward into the right ventricle (a right-sided cardiac lesion causing tricuspid regurgitation and a small, functionally impaired right ventricle) (Maudsley 2021; Sadock 2024). The historical Register of Lithium Babies vastly overstated this because uneventful pregnancies went unreported; corrected estimates put the risk of Ebstein anomaly with first-

trimester exposure at roughly **0.05 to 0.1%**, a roughly 10- to 20-fold rise over the very low population baseline, but still an absolute risk well under 1% (Johnstone 2010).

Small but raised is the phrase to hold. The Maudsley notes that more recent data suggest the magnitude of the effect is much smaller than previously estimated, and that a surveillance study of 5.6 million births found Ebstein anomaly linked to maternal mental illness generally rather than specifically to lithium; the Lithium Handbook gives a number needed to harm of 37 for any major malformation from first-trimester exposure (Maudsley 2021; Meyer 2023). The overall risk of major malformation, and of atrial and ventricular septal defects, is raised but low. The period of maximum fetal risk is **2 to 6 weeks after conception**, before many women know they are pregnant (Maudsley 2021). Because the risk is real but small, the decision is a risk-benefit one, and if lithium is continued the woman is offered fetal echocardiography and high-resolution ultrasound in liaison with fetal-medicine obstetric services.

RULE **If lithium is continued in pregnancy, monitor the level closely and offer fetal echocardiography.** The first-trimester Ebstein signal is screened for with high-resolution ultrasound and fetal echocardiography in liaison with fetal medicine.

TRAP **Stopping lithium abruptly on discovering the pregnancy.** Abrupt discontinuation carries a very high relapse risk (postpartum relapse up to 70% in women who stop before conception); the correct move is a planned risk-benefit discussion, not a reflex stop (Maudsley 2021).

0.05 to 0.1	10 to 20	2 to 6
EBSTEIN RISK, FIRST-TRIMESTER LITHIUM (%)	FOLD RISE OVER BASELINE	WEEKS POST-CONCEPTION: PEAK FETAL RISK

21.2 Pharmacokinetic shifts across pregnancy

The level falls as pregnancy advances, then rebounds at delivery. Renal plasma flow and glomerular filtration rise across pregnancy and total body water expands, so lithium clearance increases and the serum level falls; an increasing dose is needed to hold the level in the therapeutic range, and the level must be monitored more often (Maudsley 2021; Sadock 2024). This is why the sample cannot be taken at pre-pregnancy intervals. NICE recommends checking the plasma lithium level **every 4 weeks**, then **weekly from week 36**, adjusting the dose to keep the level in the woman's therapeutic range while maintaining adequate fluid balance (Maudsley 2021).

At delivery the requirement snaps back to pre-pregnancy levels. The raised clearance reverses abruptly the moment the baby is delivered, so a dose that was correct in the third trimester becomes an overdose within a day, and the large intercompartmental electrolyte and fluid shifts around labour make sudden maternal toxicity possible (Maudsley 2021; Johnstone 2010). The dose is therefore adjusted around the birth: the woman delivers in hospital where fluid balance can be monitored, lithium is stopped during labour, and the plasma level is checked **12 hours after the last dose**; the pre-pregnancy dose is resumed post-delivery with a level check (Maudsley 2021).

RULE **Monitor levels more often in pregnancy and adjust the dose around delivery.** The level falls as renal clearance rises antenatally, then rebounds sharply postpartum; deliver in hospital, hold lithium in labour, and check the level 12 hours after the last dose.

21.3 The peripartum neonate: floppy baby and toxicity

Lithium equilibrates fully across the placenta, so the neonate is exposed. Lithium completely crosses the placenta, and peripartum exposure produces the **floppy baby** picture: neonatal hypotonia and lethargy, poor feeding and low Apgar scores, together with reported neonatal goitre, cardiac arrhythmia and respiratory symptoms (Maudsley 2021). Neonatal lithium toxicity is a real peripartum risk because the newborn's immature renal function clears lithium slowly; the Lithium Handbook notes that newborn reactivity is better when the maternal level at birth is below about **0.64 mEq/L**, which is one rationale for a modest dose reduction in the week before delivery (Meyer 2023).

Balance the neonatal risk against the maternal relapse risk. The counterweight is that lithium is the drug most likely to keep the mother well, and abrupt discontinuation drives a very high peripartum and postpartum relapse rate; lithium probably does not affect neonatal brain development (Maudsley 2021). The floppy, poorly feeding neonate is managed supportively with a neonatal lithium level and fluid attention, and typically resolves as the infant's renal function matures.

21.4 Lactation: passes into milk, generally cautioned

Lithium enters breast milk and is a relative contraindication in many guidelines. Lithium passes into breast milk and is renally cleared by an infant whose kidneys are still maturing, so **lactation** on lithium is generally cautioned; the Maudsley advises that lithium should be continued in the mother but that breastfeeding should not be permitted, treating it as the exception among the mood stabilisers (Maudsley 2021). The Companion likewise states that because lithium passes into breast milk, breastfeeding should be avoided (Johnstone 2010).

The position is individualised, not absolute. Newer data soften the older blanket prohibition: a systematic review and the Lithium Handbook report that infant lithium levels fall significantly after the second week of life as renal function matures, and that breastfeeding while taking lithium does not pose a risk to the majority of infants under close monitoring, so lithium-treated women need not be automatically discouraged from breastfeeding provided infant growth and lithium-related bloods are tracked, especially in the early weeks (Meyer 2023). The exam-safe line is that lactation on lithium is a relative contraindication decided case by case; the wider perinatal decision frame is set out in the Perinatal/women's mental health and emergency psychiatry notes.

TRAP **Treating breastfeeding on lithium as absolutely forbidden or as freely permitted.** The Maudsley cautions against breastfeeding while newer monitored-cohort data are reassuring; the answer is an individualised, monitored decision, not a blanket rule either way.

21.5 The management algorithm: a planned risk-benefit decision

Guideline-level logic, not a reflex. The framework is consistent across sources (Maudsley 2021; NICE 2014; Yatham 2018). No mood stabiliser is clearly safe, and the decision turns on how well and how quickly the woman relapses off treatment.

SCENARIO	GUIDELINE-LEVEL ACTION
Planning pregnancy, long remission, low relapse risk	**Consider slow discontinuation before conception, or switch to a mood-stabilising antipsychotic; taper over about 4 weeks, never abruptly**
Becomes pregnant, well, lower risk	Consider stopping lithium gradually over 4 weeks; explain the postnatal relapse risk
Severe illness or rapid relapse off treatment	**Continue lithium after a documented risk-benefit discussion; offer fetal echocardiography and high-resolution ultrasound**
If lithium continued	Level every 4 weeks, then weekly from week 36; deliver in hospital; hold lithium in labour; check level 12 hours after last dose
Breastfeeding	Generally cautioned (relative contraindication); individualise with infant monitoring

Guideline-anchored algorithm for lithium in pregnancy and lactation: the decision keys to relapse risk, and continuation triggers fetal echocardiography plus intensified level monitoring (Maudsley 2021; NICE 2014). Highlighted cells are the board-critical branch points.

Where the guidelines converge. NICE advises considering a gradual stop over 4 weeks if the woman is well, switching to an antipsychotic or restarting in the second trimester if she is at higher risk, and continuing lithium where relapse risk is high and an antipsychotic is unlikely to work (Maudsley 2021; NICE 2014). CANMAT frames the perinatal period as one of very high bipolar relapse risk and prioritises maintaining prophylaxis in women who relapse quickly, with lithium among the first-line maintenance options (Yatham 2018). The Indian Psychiatric Society bipolar clinical practice guideline (Shah et al.) similarly counsels a planned pre-conception risk-benefit discussion rather than abrupt cessation; the precise IPS wording on breastfeeding could not be confirmed from the parsed sources and is flagged under gaps.

WORKED EXAMPLE

A 29-year-old woman with bipolar I disorder, well on lithium for four years with two severe manic relapses whenever she has stopped it, presents at 7 weeks pregnant, having just found out. The wrong move is to stop lithium today. The right move is a documented risk-benefit discussion: her rapid, severe relapse pattern favours continuation; she is counselled on the small but raised Ebstein risk, referred for fetal echocardiography and high-resolution ultrasound, her level is checked every 4 weeks and weekly from week 36, she is booked to deliver in hospital with lithium held in labour and a level 12 hours after her last dose, and breastfeeding is discussed as a cautioned, individualised decision (Maudsley 2021).

INDIA

Lithium carbonate (Licab, Intalith CR) is cheap and widely used in Indian bipolar practice, and reproductive-age women are a large part of the caseload, so this decision is common. The practical points that matter here: many pregnancies are unplanned and present after the 2 to 6 week window of peak risk has already passed, so counsel women of childbearing potential about the plan at initiation, not at conception. Serum lithium, creatinine and TSH assays are inexpensive and available; fetal echocardiography and high-resolution anomaly scanning are available in most tertiary and many secondary obstetric units and should be arranged in liaison with the obstetric team if lithium is continued. Deliver in hospital, hold lithium in labour, and check a level after delivery because the dose requirement drops back to pre-pregnancy levels at once (Maudsley 2021; Shah 2017).

PEARL

The two numbers that decide the antenatal plan pull in opposite directions: the Ebstein absolute risk is tiny (well under 1%), while the postpartum relapse risk after abrupt discontinuation is huge (up to 70%). Stated side by side they explain why guidelines lean toward a planned continuation-with-monitoring in women who relapse quickly, rather than a reflex stop.

MNEMONIC

ECHO: Ebstein, Clearance rises, Hold in labour, Off breastfeeding (cautioned)

Ebstein anomaly is the first-trimester teratogenic signal (small but raised); **C**learance rises antenatally so the level falls and is checked more often, then rebounds at delivery; **H**old lithium in labour, deliver in hospital, check the level 12 hours after the last dose; breastfeeding is generally **O**ff / cautioned (relative contraindication, individualised). ECHO also cues the fetal echocardiography offered on continuation.

GOOD TO REMEMBER

- **Teratogenicity:** first-trimester lithium associates with Ebstein anomaly (a right-sided cardiac malformation); absolute risk about 0.05 to 0.1%, small but raised (10- to 20-fold over baseline).
- **If continued:** monitor the level closely and offer fetal echocardiography plus high-resolution ultrasound; peak fetal risk is 2 to 6 weeks post-conception.
- **Pharmacokinetics:** the level falls as renal clearance rises in pregnancy (check every 4 weeks, then weekly from week 36), then rebounds sharply at delivery; adjust the dose around the birth.
- **Peripartum neonate:** floppy baby (hypotonia, lethargy, poor feeding) and neonatal toxicity risk; deliver in hospital, hold lithium in labour, check the level 12 hours after the last dose.
- **Lactation:** lithium passes into breast milk and is generally cautioned (a relative contraindication in many guidelines, individualised with infant monitoring).
- **The trap:** do not stop lithium abruptly on discovering pregnancy (relapse up to 70%); make it a planned risk-benefit decision.

HOLD THIS

First-trimester lithium raises the risk of Ebstein anomaly (small but raised, about 0.05 to 0.1%): if continued, monitor levels closely and offer fetal echocardiography; the level falls as clearance rises antenatally and rebounds at delivery, so adjust the dose around the birth; breastfeeding is generally cautioned; never stop abruptly (Maudsley 2021).

22 . Valproate

Valproate is the second workhorse mood stabiliser after lithium, and the examiner treats it as a paired set-piece: a genuinely effective antimanic and maintenance agent that carries the single worst reproductive-safety profile of any mood stabiliser. The whole topic hangs on two axes, the drug pharmacology (mechanism, forms, dose, the serum range, the adverse-effect set and monitoring) and the **teratogenicity**, which is a marked-error magnet: neural-tube defects, a dose-related fall in IQ, and an autism signal (Maudsley 2021). A resident is expected to prescribe it competently in a man or a woman past childbearing, and to know that in a woman who could become pregnant it is effectively contraindicated unless a formal pregnancy-prevention programme is running.

Organise the topic around one idea: **valproate is anti-manic and a maintenance agent, not a bipolar-depression monotherapy, and it is the drug you do not give to a woman who could conceive without counselling and a pregnancy-prevention programme.** Every dose, serum level and teratogenicity fact below is verified against the Maudsley, the CANMAT and Indian Psychiatric Society rows and Stahl (Maudsley 2021; CANMAT 2018; IPS 2017; Stahl 2021). The neurobiology of mood and the wider guideline-anchored management PLAN belong to the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; the perinatal frame and acute emergency management belong to the Perinatal/women's mental health and emergency psychiatry notes.

22.1 Mechanism: GABA potentiation, sodium-channel block and more

The molecular target. Valproate is a simple branched-chain fatty acid whose mechanism is multiple and incompletely understood (Maudsley 2021; Stahl 2021). The best-taught actions are potentiation of GABA: it inhibits the catabolism of gamma-aminobutyric acid (by inhibiting GABA-transaminase) and probably increases GABA synthesis, raising inhibitory tone; and a phenytoin-like, use-dependent blockade of voltage-gated sodium channels that dampens high-frequency neuronal firing (Maudsley 2021; Stahl 2021).

The downstream and neuroplastic actions. Beyond GABA and sodium channels, valproate weakly attenuates calcium T-currents, reduces the turnover of arachidonic acid, depletes inositol, activates the ERK pathway and promotes brain-derived neurotrophic factor expression while reducing protein kinase C, and it acts as a histone deacetylase inhibitor altering gene transcription (Maudsley 2021; Stahl 2021). These signalling and epigenetic effects are the presumed substrate of its mood-stabilising and neuroplastic actions.

22.2 The forms: sodium valproate, valproic acid and divalproex

Three interchangeable forms of one active moiety. Valproate is dispensed in three forms, all metabolised to **valproic acid**, which is the pharmacologically active species (Maudsley 2021). Distinguish them by name because the examiner will: **sodium valproate** and valproic acid (classically licensed for epilepsy), and **divalproex** (semi-sodium valproate, the 1:1 coordination compound of valproic acid and sodium valproate, classically licensed for acute mania) (Maudsley 2021). There are no important efficacy differences between the forms; divalproex may have marginally better gastric tolerability.

Sodium valproate

The sodium salt; the controlled-release form can be given once daily, other forms at least twice daily (Maudsley 2021).

Valproic acid

The free acid and the active moiety to which all forms are metabolised (Maudsley 2021).

Divalproex (semi-sodium valproate)

A 1:1 compound of valproic acid and sodium valproate; the form used in most mania trials, slower-absorbed, possibly better tolerated (Maudsley 2021).

INDIA

Lead with the Indian brand, then the generic. Sodium valproate is marketed in India as **Valprol-CR**, **Encorate** or Valparin Chrono (sodium valproate); divalproex as **Valance** or Divaa (divalproex) (KDT 2019). All three chemical forms convert to valproic acid, so brand choice is driven by formulation (once-daily controlled-release versus twice-daily) and tolerability, not by a difference in the active drug.

22.3 Indications: acute mania and maintenance, not bipolar depression alone

Where it works. The core **indications**: **acute mania** (a first-line antimanic agent, response rate around 50 percent, number needed to treat 2 to 4) and **bipolar maintenance** or prophylaxis, best supported when it was the agent that worked in the acute manic episode (Maudsley 2021; CANMAT 2018; IPS 2017). CANMAT lists divalproex as a first-line monotherapy for acute mania and among first-line maintenance monotherapies for bipolar I disorder (CANMAT 2018). The Indian Psychiatric Society names valproate as a first-line monotherapy for acute mania and, with lithium, as a best-evidenced maintenance agent, and the IPS guidelines quote an acute-mania serum target of 50 to 125 mcg/mL (IPS 2017).

Where it is not first choice. Valproate is **not for bipolar depression as monotherapy**: the evidence in bipolar depression is at best a small-to-medium effect and it is not a first-line agent for the depressive pole (Maudsley 2021; CANMAT 2018). It has limited utility in rapid-cycling illness. A hard practice point: NICE recommends against starting valproate for bipolar disorder in primary care, and both NICE and the Indian Psychiatric Society bar its use to treat bipolar illness in women of childbearing age (NICE 2014; IPS 2017).

RULE **Valproate is an anti-manic and maintenance agent, not a bipolar-depression monotherapy.** Reach for it in mania and for relapse prevention, not to lift the depressive pole on its own.

22.4 Initiation, dosing and the serum range

Starting and titrating. Titrate the dose upward against response and adverse effects; loading-dose regimens are generally well tolerated and give a faster antimanic response (Maudsley 2021). A common adult approach starts around 500 mg twice daily (or a weight-based load of roughly 20 to 30 mg/kg/day) and increases every few days. Controlled-release sodium valproate can be given once daily; other formulations require at least twice-daily dosing (Maudsley 2021).

The serum level, held more loosely than lithium. Plasma level monitoring is of more limited use than with lithium, but there is a linear relationship in acute mania: levels below **55 mg/L** are no more effective than placebo, and levels above **94 mg/L** give the most robust response (Maudsley 2021). The practical acute-mania target is a serum valproate of about **50 to 100 mg/L** (CANMAT: 350 to 700 micromol/L; IPS quotes 50 to 125 mcg/mL), taken as a trough immediately before the next dose (CANMAT 2018; IPS 2017; Maudsley 2021). Adverse effects and toxicity rise sharply once the level exceeds 100 mg/L.

PARAMETER	VALUE	SOURCE
Acute-mania serum target	**50 to 100 (levels below 55 no better than placebo; above 94 most robust)**	Maudsley 2021
CANMAT acute-mania target	**350 to 700 micromol/L (50 to 100 microg/mL)**	CANMAT 2018
IPS acute-mania target	50 to 125 mcg/mL	IPS 2017
Sample timing	trough, immediately before the next dose	Maudsley 2021
Adverse effects escalate above	100	Maudsley 2021

Valproate serum monitoring, in mg/L (equivalently microg/mL or mcg/mL) unless stated. Used more loosely than the lithium level; the number that matters most is the acute-mania trough (Maudsley 2021; CANMAT 2018; IPS 2017).

50 to 100	below 55	above 100
ACUTE-MANIA SERUM VALPROATE (MG/L)	SERUM NO BETTER THAN PLACEBO (MG/L)	ADVERSE EFFECTS ESCALATE (MG/L)

22.5 Adverse effects: the common set and the dangerous ones

The everyday set. The common, adherence-limiting adverse effects: **weight gain** (can be marked, worse when combined with clozapine or olanzapine), a dose-related **tremor** (intention or postural, in up to a quarter of patients), **hair loss** with curly regrowth, **sedation** and lethargy (especially at starting doses above 750 mg/day), gastric irritation and nausea (Maudsley 2021). Peripheral oedema also occurs.

The haematological and metabolic dangers. Valproate can cause **thrombocytopenia** (also leucopenia and red-cell hypoplasia), and **hyperammonaemia**, which can produce nausea and, when marked, an encephalopathy even with normal liver enzymes (Maudsley 2021). Two organ-

threatening reactions dominate the safety picture: **hepatotoxicity**, ranging from the common early asymptomatic transaminase rise to rare fulminant hepatic failure (young children on multiple anticonvulsants are at greatest risk), and **pancreatitis** (Maudsley 2021; KDT 2019). Any patient with rising liver enzymes should be evaluated clinically, with albumin and clotting checked.

ADVERSE EFFECT	NOTE
Weight gain	Can be significant; worse with clozapine or olanzapine (Maudsley 2021)
Tremor	Dose-related, in up to a quarter; intention or postural (Maudsley 2021)
Hair loss	With characteristic curly regrowth (Maudsley 2021)
Sedation / lethargy	Especially at starting doses above 750 mg/day (Maudsley 2021)
Thrombocytopenia	Also leucopenia, red-cell hypoplasia; drives the FBC monitoring (Maudsley 2021)
Hyperammonaemia	Nausea, and an encephalopathy that can occur with normal LFTs (Maudsley 2021)
Hepatotoxicity	Common early transaminase rise; rare fulminant hepatic failure, highest in young children on polytherapy (Maudsley 2021)
Pancreatitis	Rare but serious; drives the low threshold to investigate abdominal pain (Maudsley 2021)

The valproate adverse-effect set. The four highlighted rows are the ones that drive baseline and periodic FBC and LFTs (Maudsley 2021).

MNEMONIC

VALPROATE

Weight gain, Ammonia (hyperammonaemia), Liver toxicity (hepatotoxicity), Pancreatitis, Reduced platelets (thrombocytopenia), Oedema, Alopecia (curly regrowth), Tremor, teratogen: a memory hook for the adverse-effect and reproductive-risk set to hold cold.

22.6 Monitoring: baseline and periodic LFTs and FBC

The pre-treatment work-up. Because the organ dangers are hepatic and haematological, the baseline screen is a **full blood count** and **liver function tests**, with a baseline weight or BMI (Maudsley 2021; NICE 2014). Take a menstrual history and a pregnancy test with contraceptive counselling in any woman of childbearing potential before the first tablet.

On-treatment monitoring. NICE recommends repeating the **FBC and LFTs** at 6 months and monitoring BMI; the product characteristics advise more frequent LFTs in the first 6 months, with albumin and clotting if enzymes are abnormal (Maudsley 2021; NICE 2014). CANMAT frames it as menstrual history, haematology and liver function at 3-to-6-month intervals in the

first year on maintenance divalproex, then yearly, alongside serum valproate levels (CANMAT 2018).

TRAP **Starting valproate without baseline FBC and LFTs.** You lose the safety baseline for the two organ-threatening reactions, hepatotoxicity and thrombocytopenia, and cannot later attribute a change to the drug.

22.7 Teratogenicity: the highest-risk mood stabiliser

The malformation risk. Valproate is an established major human teratogen and the single worst mood stabiliser in pregnancy. It has a clear causal link with **neural tube** defects including spina bifida, and the overall major-malformation rate is around **10 percent**, higher than carbamazepine (Maudsley 2021). It is also linked to atrial septal defects, cleft palate, hypospadias, polydactyly, craniosynostosis and reduced neonatal head circumference (Maudsley 2021). Folate does not reliably prevent anticonvulsant-induced neural-tube defects once pregnancy is established because the tube closes within about twenty-eight days, in the fourth week, so folate must be given before conception.

The neurodevelopmental risk, and its dose-dependence. Beyond structural malformation there is a clear causal association with **neurodevelopmental** harm: a European Medicines Agency review found that up to **40 percent** of pre-school children exposed in utero had some developmental delay (delayed walking and talking, memory, speech and language problems, lower intellectual ability), with lower IQ and an increased rate of autism-spectrum diagnosis, and the processing, working-memory and learning deficits are dose-related (Maudsley 2021). This IQ and autism signal, dose-related and lasting, is the fact the examiner most wants verified.

~10%	up to 40%	5 mg/day
MAJOR MALFORMATION RATE (MAUDSLEY)	PRE-SCHOOL DEVELOPMENTAL DELAY AFTER IN-UTERO EXPOSURE	HIGH-DOSE PRE-CONCEPTION FOLIC ACID

The prescribing rule that follows. Because of this, valproate is contraindicated in women of childbearing potential unless a formal pregnancy-prevention programme is in place (Maudsley 2021; NICE 2014; IPS 2017). If a woman planning pregnancy is already on it, withdraw it gradually (over at least 4 weeks, or 2 to 4 weeks per the perinatal guidance) while she uses effective contraception, adding high-dose folic acid **5 mg/day** continued through the first trimester (Maudsley 2021; CANMAT 2018; BAP 2016). If she becomes pregnant on valproate it should generally be stopped. In the UK it may not be initiated in patients under 55 or continued in a woman of childbearing potential unless two specialists agree no other treatment is effective or tolerated (Maudsley 2021).

RULE **Do not use valproate in a woman who could become pregnant without a pregnancy-prevention programme.** The neural-tube and dose-related IQ and autism risk makes it the mood stabiliser to avoid in childbearing-potential women.

TRAP **Prescribing valproate to a young woman for bipolar disorder without counselling the teratogenicity.** It is the classic marked error: no discussion of neural-tube defects, the IQ and autism risk, contraception or pre-conception folate.

INDIA

The childbearing-potential rule applies squarely in Indian practice: valproate (Valprol-CR, Encorate; divalproex Valance) is common and cheap, but in a woman who could conceive it should not be started for bipolar disorder without a documented pregnancy-prevention plan and explicit counselling on neural-tube and neurodevelopmental risk (IPS 2017; NICE 2014). The Indian Psychiatric Society explicitly advises avoiding valproate in pregnancy for its high teratogenicity, neural-tube defects and neurodevelopmental harm (IPS 2017).

22.8 PCOS, menstrual disturbance and other reproductive effects

The endocrine effect in women. Separate from teratogenicity, valproate causes hyperandrogenism in women and is linked to **pcos** (polycystic ovary syndrome) with menstrual disturbance, weight gain and metabolic features, though the strength of the association is debated (Maudsley 2021). This is a further reason to take and monitor a menstrual history in women on valproate, and to prefer an alternative in a young woman where reproductive and metabolic concerns weigh heavily (CANMAT 2018).

PEARL

Two distinct reproductive harms travel together for valproate: the in-utero **teratogenicity** (neural-tube and neurodevelopmental), which threatens a future fetus, and **pcos** with menstrual disturbance, which affects the woman herself. Both push toward avoiding valproate in young women of childbearing potential.

22.9 Interactions: protein binding, enzyme inhibition and glucuronidation

The key interactions. Valproate is highly protein-bound and can be displaced by other protein-bound drugs such as aspirin, raising free levels toward toxicity; aspirin also inhibits its metabolism (Maudsley 2021). Conversely valproate can displace warfarin, raising the free anticoagulant level. As an enzyme inhibitor of glucuronidation it raises the levels of several drugs, most importantly lamotrigine (valproate roughly doubles lamotrigine exposure, hence the halved lamotrigine titration and the raised rash risk), and also tricyclics such as clomipramine, quetiapine and phenobarbital (Maudsley 2021). Drugs that inhibit CYP enzymes (erythromycin, fluoxetine, cimetidine) can raise valproate levels in turn.

INTERACTING DRUG	EFFECT
Lamotrigine	Valproate inhibits its glucuronidation, roughly doubling levels; halve the lamotrigine dose and titrate slowly (raised rash risk) (Maudsley 2021)
Aspirin	Displaces protein-bound valproate and inhibits its metabolism, raising free valproate toward toxicity (Maudsley 2021)
Warfarin	Displaced by valproate, raising free anticoagulant level (Maudsley 2021)
Erythromycin, fluoxetine, cimetidine	CYP inhibition raises valproate levels (Maudsley 2021)
Carbapenems	Sharply lower valproate levels (a well-known interaction to avoid) (KDT 2019)

The high-yield valproate interactions. The lamotrigine interaction is the one most often examined, because it dictates the halved lamotrigine titration (Maudsley 2021).

HOLD THIS

Valproate is an effective anti-manic and maintenance mood stabiliser, but with the worst reproductive profile of the class: a roughly 10 percent major-malformation rate with neural-tube defects and a dose-related fall in IQ with an autism signal, so it is contraindicated in women of childbearing potential without a pregnancy-prevention programme.

GOOD TO REMEMBER

- **Mechanism:** GABA potentiation (inhibits GABA-transaminase) plus use-dependent sodium-channel blockade, with histone-deacetylase and neuroplastic effects (Maudsley 2021; Stahl 2021).
- **Indications:** anti-manic and maintenance mood stabiliser (first-line acute mania, first-line maintenance), NOT bipolar depression as monotherapy (CANMAT 2018; IPS 2017).
- **Forms and Indian brands:** sodium valproate (Valprol-CR, Encorate), valproic acid, divalproex/semi-sodium valproate (Valance); all become valproic acid (KDT 2019; Maudsley 2021).
- **Serum target:** acute-mania trough around 50 to 100 mg/L (CANMAT 350 to 700 micromol/L; IPS 50 to 125 mcg/mL), held more loosely than the lithium level (Maudsley 2021; CANMAT 2018; IPS 2017).
- **Signature adverse effects:** weight gain, tremor, hair loss, sedation, thrombocytopenia, hyperammonaemia, and the organ-threatening hepatotoxicity and pancreatitis (Maudsley 2021).
- **Monitoring:** baseline and periodic FBC and LFTs, plus weight or BMI (Maudsley 2021; NICE 2014).
- **Teratogenicity:** the highest-risk mood stabiliser, around 10 percent major malformations with neural-tube defects and up to 40 percent developmental delay, dose-related IQ loss and autism risk; contraindicated in women of childbearing potential without a pregnancy-prevention programme, with pre-conception folic acid 5 mg/day (Maudsley 2021; NICE 2014; IPS 2017).
- **PCOS:** hyperandrogenism, polycystic ovary syndrome and menstrual disturbance in women (Maudsley 2021).
- **Key interaction:** inhibits glucuronidation of lamotrigine, roughly doubling its level, so halve and slow the lamotrigine titration (Maudsley 2021).

23 · Carbamazepine and oxcarbazepine

Carbamazepine is the interaction-heavy mood stabiliser: an anticonvulsant that works but is a second-line anti-manic and a third-line prophylactic agent, chosen after lithium and valproate have failed or are unsuitable. Examiners rarely ask you to reach for it; they ask you to survive it. The whole topic is really three keyed facts: it blocks sodium channels (the mechanism it shares with phenytoin and lamotrigine), it is a potent CYP3A4 inducer that **induces its own metabolism** so the level falls over the first few weeks, and it carries a distinctive safety set of hyponatraemia, blood dyscrasias and the HLA-B*1502 Stevens-Johnson association. Get those three right and the question is yours.

This note teaches **carbamazepine** and its better-tolerated analogue **oxcarbazepine** as mood stabilisers: the mechanism, the dose and plasma level, the pharmacokinetic headache of enzyme induction, the adverse-effect set with its monitoring, and where each sits in the guideline algorithm. Verify every level and interaction; a swapped direction or a forgotten contraceptive failure is a critical error. For where mood stabilisers sit in the acute-mania and maintenance algorithm see the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; the CYP background sits in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

23.1 What it is and where it sits

A second-line stabiliser. Carbamazepine (Tegretol or Mazetol) is an iminostilbene anticonvulsant, structurally related to the tricyclics, licensed for bipolar illness in patients who do not respond to lithium (Maudsley 2021). Two placebo-controlled trials of the extended-release formulation confirm efficacy in acute mania, with roughly double the placebo response, but it is not well tolerated and NICE does not recommend it first-line for mania (Maudsley 2021, NICE 2014). CANMAT places carbamazepine as a second-line monotherapy for acute mania and as a recommended (not first-line) maintenance agent (CANMAT 2018). It is thus the agent you reach for when lithium and valproate have failed, not the agent you start with.

RULE **Second line, not first.** Carbamazepine is a second-line anti-manic and a later-line maintenance stabiliser, used after lithium and valproate, not instead of them.

23.2 Mechanism: sodium-channel blockade

Use-dependent sodium-channel blockade. The core action is blockade of voltage-dependent (voltage-gated) sodium channels, stabilising the inactivated state and dampening high-frequency repetitive firing (Stahl 2021). This is the same molecular target as phenytoin and lamotrigine, and it is thought to underlie both the anticonvulsant and the mood-stabilising effect. Oxcarbazepine (Oxetol), a structural derivative of carbamazepine, blocks the same voltage-dependent sodium channels but in addition increases potassium conductance and modulates high-voltage-activated calcium channels (Maudsley 2021). Its active moiety is the monohydroxy metabolite (licarbazepine), which is why oxcarbazepine avoids the epoxide metabolite responsible for much of carbamazepine's toxicity and much of its enzyme induction.

23.3 Dose and plasma level

Titrate low and slow, monitor the trough. Start at **100 to 200 mg** twice daily and titrate against response and tolerability towards **400 mg** twice daily, higher in some patients; controlled clinical trials of efficacy in bipolar disorder use **800 to 1200 mg/day** (Maudsley 2021). The modified-release preparation (Tegretol Retard) gives smoother levels and is better tolerated. The therapeutic plasma range used as an anticonvulsant is **4 to 12 mg/L** (evidence in affective illness is weaker; a level of at least 7 mg/L may be needed), sampled as a trough immediately before the first dose of the day (Maudsley 2021). Levels above 12 mg/L carry a higher side-effect burden. Carbamazepine cannot be loaded, and rapid titration provokes sedation and ataxia (Goodman and Gilman 2018).

PARAMETER	CARBAMAZEPINE	NOTE
Starting dose (mg twice daily)	**100 to 200**	Titrate slowly; cannot be loaded
Usual target (mg twice daily)	400	Trial doses often 800 to 1200 mg/day total
Therapeutic plasma level (mg/L)	**4 to 12**	Trough, before the morning dose; anticonvulsant range
When to recheck the level	**2 to 4 weeks after a dose change**	Because autoinduction moves the level

Carbamazepine dosing and plasma monitoring: start low, target a trough of 4 to 12 mg/L, and recheck after autoinduction settles.

23.4 The pharmacokinetic headache: enzyme induction and autoinduction

A potent CYP3A4 inducer that induces its own metabolism. This is the single most examined fact. Carbamazepine is a hepatic **enzyme induction** agent, a potent inducer of CYP3A4 (and P-glycoprotein), and it induces the very enzymes that metabolise itself. An initial plasma half-life of around **30 hours** falls to around **12 hours** on chronic dosing, so the level a resident measures in week one drifts downward over the first few weeks even on a fixed dose (Maudsley 2021, K&S 2024). This is why the level must be re-checked **2 to 4 weeks** after any dose increase: the target may no longer be met once autoinduction is complete. Because CYP3A4 handles a large fraction of drugs, carbamazepine lowers the plasma level of many co-prescribed agents, making it one of the most interaction-heavy drugs in psychiatry.

RULE **Carbamazepine induces CYP3A4, including its own metabolism and the pill.** The level falls over the first weeks, and the level of many co-drugs (oral contraceptives, other psychotropics) falls with it; watch the level and the interactions.

23.5 The interactions that matter: the oral contraceptive and the psychotropics

Induction lowers other drug levels. As a CYP3A4 inducer, carbamazepine accelerates the metabolism of oral contraceptives, reducing their plasma concentration and causing contraceptive failure and unplanned pregnancy; adequate non-hormonal or higher-oestrogen contraception must be ensured, and prophylactic folate given, if it cannot be avoided in a woman of childbearing potential (Maudsley 2021). It similarly lowers the levels of many psychotropics

metabolised by CYP3A4, including some antipsychotics and other anticonvulsants (for example it lowers plasma lamotrigine and, by inducing UGT and CYP, valproate). Pharmacodynamically, its anticonvulsant effect is opposed by seizure-threshold-lowering drugs, its marrow-suppressing potential is amplified by clozapine, and its hyponatraemic tendency is worsened by sodium-depleting diuretics; rare neurotoxicity is reported when combined with lithium (Maudsley 2021).

CO-DRUG	EFFECT OF CARBAMAZEPINE	CONSEQUENCE
Oral contraceptive	**Level LOWERED (CYP3A4 induction)**	Contraceptive failure, unplanned pregnancy
Lamotrigine	Level LOWERED	Loss of stabiliser cover; lamotrigine dose may need raising
Some antipsychotics (CYP3A4 substrates)	Level LOWERED	Reduced efficacy; monitor clinically
Clozapine	**Additive marrow suppression**	Avoid combination; agranulocytosis risk
Diuretics	Additive sodium depletion	Worse hyponatraemia
Lithium	Pharmacodynamic	Rare neurotoxicity reported

Carbamazepine as an enzyme inducer: it lowers the level of the pill and CYP3A4-handled psychotropics, and stacks marrow-suppression and hyponatraemia risks.

TRAP **Forgetting that carbamazepine makes the oral contraceptive fail.** A woman started on carbamazepine, still on the combined pill, is now unprotected; the classic missed interaction is contraceptive failure and pregnancy on a teratogenic drug.

23.6 Hyponatraemia (SIADH)

A common, sometimes dangerous, electrolyte effect. Carbamazepine has vasopressin-like (antidiuretic) effects, promoting water resorption and producing dilutional hyponatraemia, an SIADH-like picture (K&S 2024). Older adults, women and higher doses are the vulnerability factors, and co-prescribed sodium-depleting diuretics worsen it. Severe hyponatraemia can present as confusion or delirium. Baseline and on-treatment urea and electrolytes are checked, at least annually and whenever clinically suspected (CANMAT 2018, NICE 2014). This is the one area where oxcarbazepine is worse: it causes hyponatraemia more often, in roughly **3 to 5 percent** of patients (K&S 2024).

23.7 Blood dyscrasias and FBC monitoring

Benign leucopenia is common; aplastic anaemia and agranulocytosis are rare but fatal. Carbamazepine commonly causes a chronic, usually clinically insignificant fall in the white cell count (benign leucopenia), through inhibition of colony-stimulating factor, and lithium can reverse it (K&S 2024). The dangerous events are idiosyncratic: aplastic anaemia, agranulocytosis and pancytopenia occur in roughly **1 in 25,000 to 100,000** patients (K&S 2024; the Maudsley cites about 1 in 20,000 for agranulocytosis and/or aplastic anaemia). Because routine full blood count (FBC) monitoring poorly predicts these rare events, the practical rule is a baseline FBC plus firm counselling that fever, sore throat, rash, bruising or bleeding demand an immediate FBC and

medical review (Maudsley 2021, K&S 2024). Baseline and periodic FBC and liver function tests are standard; a raised GGT or a GGT two to three times normal is rarely a concern.

WORKED EXAMPLE

A man three weeks into carbamazepine for treatment-resistant mania develops fever, mouth ulcers and a sore throat. This is not a viral illness to be observed; it is a potential agranulocytosis until proven otherwise. Stop the drug, take an urgent FBC, and manage the neutropenia. The counselling given at the outset (report fever or sore throat at once) is what makes this catch possible.

23.8 Rash and the HLA-B*1502 Stevens-Johnson association

Screen at-risk ancestry before prescribing. About 3 percent of patients develop a benign erythematous rash, but carbamazepine can rarely progress to Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The vulnerability is genetically determined: the HLA-B*1502 allele is strongly associated with carbamazepine-induced SJS/TEN, and it is prevalent in Han Chinese, Thai and some other Southeast Asian populations (Maudsley 2021, K&S 2024, Goodman and Gilman 2018). Genetic testing of people of Han Chinese or Thai origin is recommended before carbamazepine is started, and the drug is avoided if the patient is HLA-B*1502 positive. Because any carbamazepine rash may be the early phase of a serious reaction, most clinicians stop the drug even on a benign-looking rash; oxcarbazepine, which cross-reacts less, is a common switch (roughly two-thirds do not re-rash) (K&S 2024).

TRAP **Skipping the HLA-B*1502 screen in an at-risk patient.** In a Han Chinese or Thai patient, prescribing carbamazepine without genotyping risks a preventable Stevens-Johnson syndrome; the allele must be checked first.

23.9 Teratogenicity and the monitoring headline

An established human teratogen. Carbamazepine is a known human teratogen, associated with neural tube defects (spina bifida, of the order of 1 percent) and craniofacial abnormalities; folate pretreatment is advised and the combination with valproate is especially avoided (K&S 2024, CANMAT 2018). CANMAT and NICE advise avoiding it in pregnancy where possible; if used in a woman of childbearing potential the contraceptive interaction makes reliable non-hormonal contraception essential. The maintenance monitoring headline that CANMAT specifies: before and during carbamazepine, genotype at-risk Asian ancestry for HLA-B*1502, educate about rash and SJS, and check serum sodium at least annually, alongside baseline and periodic FBC and LFTs (CANMAT 2018).

4 to 12	30 to 12	2 to 4
THERAPEUTIC LEVEL (MG/L, TROUGH)	HALF-LIFE FALL ON AUTOINDUCTION (HOURS)	RECHECK LEVEL AFTER DOSE CHANGE (WEEKS)

23.10 Oxcarbazepine: the better-tolerated analogue

Less induction, more hyponatraemia, weaker evidence. Oxcarbazepine (Oxetol) shares the sodium-channel mechanism but is metabolised to licarbazepine without the toxic epoxide, so the

toxic effects due to the epoxide metabolite are avoided; separately it is a much weaker enzyme inducer and better tolerated: less rash, no routine benign WBC suppression, and no elevated serious blood-dyscrasia rate (K&S 2024). The two trade-offs are that it causes hyponatraemia more often (about 3 to 5 percent) and that the trial evidence in bipolar disorder is thin: a Cochrane review found insufficient adequate-quality trials to judge its efficacy or acceptability in acute bipolar episodes, and only small studies support adjunctive prophylactic use (Maudsley 2021). It is therefore a tolerability-driven alternative rather than a stronger drug. Typical tablet strengths in India are 150, 300 and 600 mg (KDT 2019).

FEATURE	CARBAMAZEPINE	OXCARBAZEPINE
Mechanism	Na-channel blockade	Na-channel blockade plus K conductance / Ca modulation
Enzyme induction	**Potent CYP3A4 inducer, autoinducing**	Much weaker inducer
Hyponatraemia	Common	**More common (about 3 to 5 percent)**
Blood dyscrasias	**Benign leucopenia; rare aplastic anaemia / agranulocytosis**	No routine WBC suppression; serious dyscrasia not elevated
Rash / SJS	HLA-B*1502 associated SJS/TEN	Lower rash frequency; many carbamazepine-rash patients tolerate it
Bipolar evidence	Second-line, RCT-supported for mania	**Insufficient adequate-quality trials (Cochrane)**

Carbamazepine versus oxcarbazepine: oxcarbazepine trades away potent induction and most of the blood and skin risk, at the cost of more hyponatraemia and weaker bipolar evidence.

HOLD THIS

Carbamazepine is a second-line stabiliser that blocks sodium channels, is a potent autoinducing CYP3A4 inducer (its own level and the pill both fall), and carries hyponatraemia, benign leucopenia with rare aplastic anaemia / agranulocytosis, and HLA-B*1502-linked Stevens-Johnson syndrome; oxcarbazepine is the better-tolerated analogue with less induction but more hyponatraemia.

INDIA

Carbamazepine is marketed in India as Tegretol (Novartis) and Mazetol, and oxcarbazepine as Oxetol; the generic stays primary in prescribing. The HLA-B*1502 point is not only a Han Chinese or Thai concern: the allele is present across parts of South and Southeast Asia, so ancestry-informed caution and a low threshold to stop on any rash are practical rules in Indian practice.

MNEMONIC

CBZ: Cuts Blood, Zaps sodium and the pill

Cuts **B**lood counts (leucopenia, rare aplastic anaemia and agranulocytosis), **Z**aps sodium (hyponatraemia) and the pill (CYP3A4 induction, contraceptive failure); plus HLA-B*1502 Stevens-Johnson syndrome. Autoinducing, so the level falls.

GOOD TO REMEMBER

- **Carbamazepine:** voltage-dependent sodium-channel blocker; potent autoinducing CYP3A4 inducer whose signature harm is the enzyme induction that fails the oral contraceptive; second-line for mania, trough level 4 to 12 mg/L.
- **Enzyme induction:** half-life falls from about 30 to 12 hours over the first weeks, so recheck the level 2 to 4 weeks after any dose change; it lowers oral contraceptive and many psychotropic levels.
- **Hyponatraemia (SIADH):** common, SIADH-like, worse with diuretics and in older women; check serum sodium at least annually.
- **Blood dyscrasias:** benign leucopenia is common; aplastic anaemia and agranulocytosis are rare (about 1 in 25,000 to 100,000) but fatal, so do a baseline FBC and counsel to report fever, sore throat or bruising at once.
- **HLA-B*1502:** allele linked to Stevens-Johnson syndrome and toxic epidermal necrolysis; screen at-risk Han Chinese, Thai and some Asian ancestry before prescribing and avoid if positive.
- **Teratogenicity:** established human teratogen (neural tube defects, craniofacial); avoid in pregnancy where possible, give folate, and never rely on a hormonal contraceptive it induces.
- **Oxcarbazepine (Oxetol):** same sodium-channel mechanism, much weaker inducer, better tolerated with no routine WBC suppression; the one drug where hyponatraemia (about 3 to 5 percent) is more frequent, and bipolar evidence is thin.

24 . Lamotrigine

lamotrigine (Lamitor, Lametec) is the mood stabiliser the board most wants tied to one clinical fact: it is the agent with the best evidence for **bipolar depression** and for maintenance, especially the prevention of depressive relapse, yet it is weak against acute mania. That split personality, strong on the depressive pole and prophylaxis but not a drug you reach for to break a manic episode, is the whole examinable point and the reason it is never used as monotherapy for acute mania (Stahl 2021). Every other high-yield fact about the drug flows from a single pharmacokinetic vulnerability: it must be introduced by **slow titration** to avoid a serious rash, and that titration is halved by valproate and roughly doubled by an enzyme inducer.

This is a pharmacology topic, so the marks are in the mechanism, the titration schedule, the interaction with valproate, and the **rash** stop-rule. The doses, the halving with valproate, the enzyme-inducer doubling and the benign-versus-serious rash distinction below are verified against Stahl's Prescriber's Guide, the Maudsley Prescribing Guidelines, the CANMAT guideline, the Indian Psychiatric Society clinical practice guideline (Stahl 2021; Maudsley 2021; Yatham 2018; Shah 2017). The guideline-anchored place of lamotrigine within the full bipolar management PLAN is set out in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; the CYP and metabolism background sits in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

Week	Standard mg/day	With valproate mg/day, halved	With an enzyme inducer mg/day (e.g. carbamazepine)
Weeks 1 to 2	25 once daily	25 on alternate days	50 once daily
Weeks 3 to 4	50 once daily	25 once daily	100 (in divided doses)
Week 5	100 once daily	50 once daily	increase by 100 each week
Week 6	200 once daily	100 once daily	up toward 400 (divided)
Usual target	100 to 200	100	400

Stevens-Johnson stop-rule
STOP at any confluent, purpuric or tender rash, any mucosal involvement (eyes, lips, mouth), or a rash with fever or malaise. The slow titration, and halving it with valproate, are what keep the serious-rash risk low.

Fig 12.10 Lamotrigine titration and the Stevens-Johnson risk. Lamotrigine must be titrated slowly over about six weeks; the schedule is halved when combined with valproate (which raises the lamotrigine level) and roughly doubled with an enzyme inducer such as carbamazepine. The rash risk is highest with fast titration and with valproate co-therapy, so a confluent, purpuric, tender or mucosal rash, or a rash with fever, is a stop signal.

24.1 The place: best for bipolar depression and maintenance, weak for mania

Strong on the depressive pole, weak on mania. Lamotrigine has FDA and guideline standing for the **maintenance** of bipolar I disorder, where its particular strength is preventing the depressive relapse rather than the manic one (Stahl 2021; Yatham 2018). It is a first-line option (monotherapy or adjunctive) for acute **bipolar depression**, and both CANMAT and the Indian Psychiatric Society name lithium or lamotrigine among the first-line agents for that indication, particularly where antipsychotic burden is undesirable (Yatham 2018; Shah 2017). What it does **not** do is treat acute mania: onset is far too slow for a manic emergency and the evidence is weak, so it is at best adjunctive and second-line there and never a mania monotherapy (Stahl 2021).

Guideline anchoring. CANMAT lists lamotrigine (monotherapy or adjunctive) for acute bipolar I depression, targeting a minimum of 200 mg/day with slow titration from 25 mg, and lists it among first-line maintenance monotherapies for bipolar I disorder; the Indian Psychiatric Society places lamotrigine as a first-line alternative for acute bipolar depression and as a maintenance agent that is better for depressive-recurrence prevention (Yatham 2018; Shah 2017). The mirror-image caution belongs here: an antidepressant given alone in a bipolar depression risks a switch, whereas lamotrigine treats the depressive pole without that manic-switch liability.

RULE **Reach for lamotrigine for the depressive pole and for maintenance, not for acute mania.** Best evidence is in bipolar depression and depressive-relapse prevention; it is weak and slow against mania.

TRAP **Starting lamotrigine to control an acute manic episode.** It is too slow and too weak for mania; use an antimanic (lithium, valproate, or an antipsychotic) and reserve lamotrigine for the depressive pole and maintenance.

24.2 Mechanism: sodium-channel blockade and glutamate modulation

A use-dependent sodium-channel blocker that damps glutamate. In the Neuroscience-based Nomenclature lamotrigine is a glutamate voltage-gated sodium channel blocker (Glu-CB) (Stahl 2021). It acts as a **use-dependent blocker of voltage-sensitive sodium channels**, binding the open-channel conformation at the alpha pore-forming subunit; by stabilising the inactivated state of the channel it reduces the presynaptic release of the excitatory neurotransmitters glutamate and aspartate (Stahl 2021). This glutamate-modulating action is the proposed basis of its mood-stabilising, and specifically its antidepressant-in-bipolar, effect, and distinguishes its profile from the antimanic anticonvulsants.

PEARL

The mechanism explains the clinical split. Sodium-channel blockade with downstream reduction of glutamate release maps onto relapse prevention and the depressive pole rather than onto the rapid dopaminergic damping needed to abort mania, which is why lamotrigine prevents and treats bipolar depression but is a poor antimanic.

24.3 The slow titration: why it takes weeks

Titrate over weeks, not days. Lamotrigine must be introduced by **slow titration** over several weeks: the incidence of serious rash rises steeply with a fast start and with high initial doses, so the standard monotherapy schedule creeps up from 25 mg/day to a target of 200 mg/day over about six weeks (Stahl 2021; Maudsley 2021). The dose should never be escalated faster than recommended, because the excess risk is not of a trivial side effect but of Stevens-Johnson syndrome. If the patient stops the drug for 5 days or more, the titration is restarted from the beginning, as rashes have been reported on re-exposure (Stahl 2021).

Two modifiers rewrite the schedule. Valproate roughly doubles the lamotrigine level, so the schedule is **halved** when the two are combined; an enzyme inducer such as carbamazepine lowers the level, so the schedule is roughly **doubled** (higher steps, higher target) (Stahl 2021). The monotherapy, with-valproate and with-inducer schedules are set out in the table below.

PHASE	MONOTHERAPY (MG/DAY)	WITH VALPROATE, HALVED (MG/DAY)	WITH ENZYME INDUCER, DOUBLED (MG/DAY)
Weeks 1 to 2	25 daily	**25 on alternate days**	50 daily
Weeks 3 to 4	50 daily	**25 daily**	100 daily (divided)
Week 5	100 daily	50 daily	increase by 100 each week
Week 6	200 daily	100 daily	up towards 400 (divided)
Usual target	**100 to 200**	**100**	**400**

Lamotrigine bipolar titration: the monotherapy schedule creeps 25 to 200 over about 6 weeks; valproate halves every step and the target (start at 25 on alternate days, target 100); an enzyme inducer such as carbamazepine roughly doubles the schedule (start 50, target 400) (Stahl 2021; Maudsley 2021). Highlighted cells are the board-critical numbers.

25	100 to 200	6
MONOTHERAPY STARTING DOSE (MG/DAY)	MONOTHERAPY BIPOLAR TARGET (MG/DAY)	TITRATION LENGTH (WEEKS)

RULE **Titrate lamotrigine slowly and halve the schedule with valproate.** Creep 25 to 200 over about six weeks; with valproate start at 25 on alternate days and target 100.

24.4 The valproate interaction: halve the dose

Valproate can double the lamotrigine level. This is the single most examined interaction of the drug. Valproate inhibits the glucuronidation that clears lamotrigine, so it roughly **doubles** the lamotrigine plasma level; the titration rate and the ultimate dose must therefore be **reduced by 50%** to hold down the rash risk (Stahl 2021). Concretely, in the presence of valproate the start is 25 mg on alternate days (not 25 mg daily), the steps are half-sized, and the usual target falls to about 100 mg/day (Stahl 2021; Maudsley 2021). The mirror rule matters too: if valproate is later stopped once lamotrigine is stabilised, the lamotrigine dose is cautiously doubled over at least two weeks to keep it therapeutic (Stahl 2021).

The enzyme-inducer direction. Carbamazepine and the other enzyme-inducing antiepileptics (phenytoin, phenobarbital, primidone) do the opposite, lowering the lamotrigine level, so the schedule and target are roughly doubled (start 50 mg/day, target up to 400 mg/day in divided doses) (Stahl 2021). Oral contraceptives and pregnancy also lower lamotrigine levels, so the maintenance dose needs review around starting or stopping the pill and around delivery (Stahl 2021).

WORKED EXAMPLE

A woman on maintenance divalproex for bipolar I has a breakthrough depression and lamotrigine is added. Because valproate doubles the lamotrigine level, you do not use the standard 25 mg daily start: you begin lamotrigine at 25 mg on alternate days, increase in half-sized steps, and aim for about 100 mg/day rather than 200 mg/day, watching closely for rash. Using the monotherapy schedule here would roughly double the true lamotrigine exposure and sharply raise the Stevens-Johnson risk.

24.5 Stevens-Johnson syndrome and the serious rash: the stop-rule

The dangerous adverse effect is the rash. Lamotrigine can cause a **rash** in roughly 10% of patients, and the great majority of these are benign; the fear is the small minority that are a serious cutaneous reaction, namely stevens-johnson syndrome or toxic epidermal necrolysis, sometimes with multi-organ hypersensitivity (Stahl 2021). The risk of a serious rash is highest with a fast titration, with high starting doses, in children, and with valproate co-therapy, which is precisely why the schedule is slow and is halved with valproate (Stahl 2021). Most serious rashes appear early, within the first 8 weeks or so of treatment, which is the window the slow titration is designed to cover.

Tell the benign rash from the serious one. A **benign** rash peaks within days, settles in about 10 to 14 days, is spotty, non-confluent, non-tender, has no systemic features and normal bloods; here

you may reduce the dose or hold the increase, warn the patient, and monitor. A **serious** rash is confluent and widespread, or purpuric or tender, involves the neck or upper trunk, or involves the eyes, lips or mouth (mucosal involvement), or carries fever, malaise, pharyngitis, anorexia or lymphadenopathy, or abnormal blood counts or liver function (Stahl 2021). The stop-rule follows: at any sign of a serious or mucosal rash, **stop lamotrigine at once** (and stop concomitant valproate), investigate for organ involvement and admit if needed (Stahl 2021).

COMMON TRAP

A patient a fortnight into lamotrigine develops a rash with sores at the lips and mouth and a low-grade fever. Treating this as the common benign rash and merely holding the dose is the error: mucosal involvement plus systemic features is a serious rash, and the correct action is to stop lamotrigine (and valproate) immediately and investigate, not to wait and watch.

TRAP **Titrating lamotrigine too fast, or ignoring the valproate interaction, and precipitating Stevens-Johnson syndrome.** A fast start or a full monotherapy schedule on top of valproate drives the serious-rash risk; go slow and halve with valproate.

FEATURE	BENIGN RASH	SERIOUS RASH (STOP THE DRUG)
Time course	peaks in days, settles 10 to 14 days	confluent, widespread, progressive
Appearance	spotty, non-confluent, non-tender	**confluent, purpuric or tender**
Site	trunk and limbs, no mucosa	**neck / upper trunk; eyes, lips, mouth (mucosal)**
Systemic features	none	**fever, malaise, pharyngitis, anorexia, lymphadenopathy**
Bloods	normal	abnormal FBC, LFTs, urea/creatinine
Action	reduce dose / hold increase, monitor	**stop lamotrigine (and valproate); investigate; admit if needed**

Benign-versus-serious rash on lamotrigine: any mucosal involvement, systemic features or abnormal bloods marks a serious rash and mandates immediate cessation (Stahl 2021). The wider acute management of a serious drug reaction is in the Perinatal/women's mental health and emergency psychiatry notes.

INDIA

Lamotrigine is widely available in India as the generic and under brands such as Lamitor and Lametec; the tablet strengths (25, 50, 100, 200 mg) suit the six-week creep, and a 25 mg tablet on alternate days is the practical with-valproate start. The same two examinable points hold for Indian practice: lamotrigine is particularly effective for bipolar depression, and the skin-rash risk is higher with faster dose escalation and with valproate co-prescription, so titrate very gradually as per the summary of product characteristics. Note that carbamazepine-linked Stevens-Johnson syndrome is separately tied to the HLA-B*1502 allele common in Asian ancestry; the lamotrigine rash is not gene-tested that way, but the slow-titration discipline is the safeguard.

MNEMONIC

SLOW

What lamotrigine turns on: **S**tevens-Johnson risk is the danger (go slow to avoid it), **L**ow and slow titration (25 to 200 over about six weeks), **O**ne interaction to halve for (valproate doubles the level, so halve the schedule), **W**eak against mania but best for the depressive pole and maintenance.

GOOD TO REMEMBER

- **Lamotrigine (Lamitor, Lametec):** use-dependent voltage-gated sodium-channel blocker that reduces glutamate release; best evidence in bipolar depression and maintenance (depressive-relapse prevention), weak for acute mania.
- **Slow titration:** monotherapy 25 mg/day creeping to a target of 100 to 200 mg/day over about six weeks; never faster than recommended.
- **Valproate interaction:** valproate roughly doubles the lamotrigine level, so halve the titration and the target (start 25 mg on alternate days, target about 100 mg/day).
- **Enzyme inducer (carbamazepine):** lowers the level, so roughly double the schedule and target (start 50 mg/day, up to 400 mg/day).
- **Serious rash / Stevens-Johnson syndrome and toxic epidermal necrolysis:** highest risk with fast titration and valproate co-therapy; stop the drug at any serious or mucosal rash.
- **Monitoring:** no routine serum-level or blood monitoring is required; the safeguard is the slow titration and rash vigilance.

HOLD THIS

Lamotrigine is the mood stabiliser for bipolar depression and maintenance but weak for mania: titrate it slowly from 25 to 200 mg/day over about six weeks, halve the schedule and target with valproate (which doubles the level) and double it with an enzyme inducer, and stop the drug at any sign of a serious or mucosal rash because of Stevens-Johnson syndrome.

25 . Antipsychotics as mood stabilisers

The **atypical** second-generation antipsychotics are no longer bit-players in bipolar disorder: several are guideline first-line agents across one or more phases, and the whole modern algorithm for mania and bipolar depression is built on them (CANMAT 2018; Maudsley 2021). The examiner treats **antipsychotics as mood stabilisers** as a phase-matching problem. You are expected to know which atypical is first-line for mania, which for bipolar depression, which for

maintenance, why they work (a fast anti-manic effect plus, for some, a genuine antidepressant and relapse-prevention effect), and the price you pay for them (the metabolic, extrapyramidal and prolactin burden).

Organise the topic around one idea: **match the atypical to the phase, then monitor the metabolic cost for as long as the drug is used.** Every phase indication, dose and monitoring interval below is verified against the CANMAT and Indian Psychiatric Society rows, the Maudsley and Stahl (CANMAT 2018; IPS 2017; Maudsley 2021; Stahl 2021). The deep receptor pharmacology, the full adverse-effect detail and the metabolic-monitoring schedule are the property of the Schizophrenia: management, antipsychotics and adverse effects notes; this fragment carries only what is load-bearing for mood, and cross-refers the rest there. The neurobiology of mood and the wider guideline-anchored management PLAN belong to the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

25.1 Why antipsychotics stabilise mood: the mechanism and the trade-off

What they do at the synapse. Antipsychotics are not merely anti-psychotic: individual agents variously possess sedative, anxiolytic, anti-manic, mood-stabilising and antidepressant properties, and a few (quetiapine and olanzapine) show all of these (Stahl 2021). The shared anti-manic action is **dopamine D2 blockade or partial agonism** in the mesolimbic pathway, which rapidly damps the elevated dopaminergic drive of mania (Stahl 2021; Maudsley 2021). The antidepressant and mood-lifting actions of the broader agents come from additional targets: 5-HT2A antagonism, 5-HT7 antagonism, 5-HT1A partial agonism, alpha-2 blockade and, for quetiapine, potent noradrenaline-reuptake inhibition via its norquetiapine metabolite (Stahl 2021). The full receptor map is developed in the Schizophrenia: management, antipsychotics and adverse effects notes.

Why we reach for them, and what it costs. They are used because the anti-manic effect is fast (useful in an agitated, sleepless, high-risk manic patient) and because, unlike a pure antimanic anticonvulsant, several have real efficacy in bipolar depression and in maintenance (Maudsley 2021; CANMAT 2018). The trade-off is the class burden: **metabolic** harm (weight gain, dyslipidaemia, hyperglycaemia, worst with olanzapine), **extrapyramidal** effects and akathisia, sedation, and prolactin elevation (marked with risperidone and paliperidone) (Stahl 2021; Maudsley 2021). Because bipolar treatment is long-term, that burden is carried for years, which is exactly why the metabolic monitoring is non-negotiable.

RULE **Match the atypical to the phase.** Quetiapine is the broad one (mania, bipolar depression, maintenance); lurasidone and cariprazine are the bipolar-depression agents; aripiprazole and risperidone/paliperidone are mania and maintenance workhorses.

25.2 The FDA phase map: which atypical is licensed for which pole

The set-piece table. The cleanest way to hold this is the FDA-indication-by-phase map (Stahl 2021; Maudsley 2021). Aripiprazole covers mania, mixed episodes and maintenance; asenapine mania and mixed states; olanzapine mania, mixed episodes and maintenance, and (as the olanzapine-fluoxetine combination) bipolar depression; quetiapine spans mania, maintenance

and bipolar depression; risperidone mania and mixed episodes (and, as risperidone LAI, maintenance); cariprazine and lurasidone are the bipolar-depression agents (cariprazine also covers mania); ziprasidone mania and maintenance (Stahl 2021).

ATYPICAL (GENERIC)	MANIA / MIXED	BIPOLAR DEPRESSION	MAINTENANCE	SIGNATURE TRADE-OFF
Quetiapine (Qutipin)	**Yes**	**Yes (300 mg/day)**	**Yes**	Sedation, weight gain, moderate metabolic
Olanzapine (Oleanz)	Yes	Yes (with fluoxetine)	Yes	**Highest metabolic burden**
Aripiprazole	Yes	No (as monotherapy)	Yes (manic relapse)	Akathisia; weight-neutral
Risperidone (Sizodon)	Yes	No	Yes (as LAI)	**Prolactin elevation**
Paliperidone	Yes	No	LAI option	**Prolactin elevation**
Cariprazine	Yes	**Yes**	-	Akathisia; low metabolic
Lurasidone	No	**Yes**	-	Akathisia, nausea; low metabolic; take with food
Asenapine	Yes (incl. mixed)	No	-	Sublingual; oral hypoaesthesia

Atypical antipsychotics by bipolar phase (FDA-indication map, Stahl 2021; Maudsley 2021). The highlighted cells are the phase-defining facts to hold: quetiapine across all three poles, olanzapine's metabolic cost, the depression pair (cariprazine, lurasidone), and the prolactin pair (risperidone, paliperidone).

25.3 Quetiapine: the broadest, works across all phases

Why it is the broad one. Quetiapine (Qutipin, quetiapine) is the single atypical effective across all three bipolar phases: acute mania, acute bipolar I depression and maintenance (Stahl 2021; CANMAT 2018). Its breadth is mechanistic: D2 and 5-HT2A antagonism for the anti-manic and antipsychotic effect, and an active metabolite (norquetiapine) that is a potent noradrenaline-reuptake inhibitor and 5-HT2C antagonist, underpinning a genuine antidepressant action (Stahl 2021). CANMAT names quetiapine as a first-line monotherapy for acute mania, a first-line monotherapy for acute bipolar I depression at a target of **300 mg/day**, and a first-line maintenance monotherapy for bipolar I disorder (CANMAT 2018).

The dose and the cost. Mania and maintenance use higher divided doses (commonly around 400 to 800 mg/day); bipolar depression is treated at the lower **300 mg/day** (CANMAT 2018; Maudsley 2021). It carries moderate metabolic risk and is sedating, so it is often dosed at night (Stahl 2021). In India it is marketed as Qutipin (quetiapine), available as 25, 50, 100, 200 and 400 mg tablets (KDT 2019).

GOOD TO REMEMBER

- **Quetiapine (Qutipin):** D2/5-HT2A antagonist whose norquetiapine metabolite is a noradrenaline-reuptake inhibitor; signature cost is sedation and weight gain; the one to hold is that it is first-line across all three phases and bipolar depression is treated at 300 mg/day (CANMAT 2018; Stahl 2021).

25.4 Olanzapine: mania and maintenance, and the OFC for bipolar depression

Its place. Olanzapine (Oleanz, olanzapine) is effective in acute mania, mixed episodes and maintenance, and the **olanzapine-fluoxetine combination** (OFC) is a recognised treatment for bipolar I depression (Stahl 2021; CANMAT 2018). CANMAT places olanzapine as a first-line option for acute mania but downgrades it in maintenance and lists the OFC as a second-line option for acute bipolar I depression, both because of its metabolic profile (CANMAT 2018). It is a D2 and 5-HT2A antagonist; the fluoxetine partner adds the serotonergic antidepressant drive that olanzapine alone lacks.

The catch. Olanzapine carries the **highest metabolic** burden of the atypicals used in mood disorder, alongside clozapine: substantial weight gain, dyslipidaemia and hyperglycaemia (Stahl 2021). This is why guidelines that rank it first-line for the manic pole still demote it for long-term use. Indian brand: Oleanz (olanzapine), 2.5 to 20 mg tablets (KDT 2019).

TRAP **Ignoring the metabolic monitoring when an atypical is used long-term for mood.** Olanzapine on maintenance without weight, glucose and lipid tracking is the classic error; the drug that controlled the mania quietly builds the metabolic syndrome.

GOOD TO REMEMBER

- **Olanzapine (Oleanz):** D2/5-HT2A antagonist; signature cost is the highest metabolic burden of the mood atypicals; the one to hold is that it covers mania and maintenance, and bipolar depression only as the olanzapine-fluoxetine combination (CANMAT 2018; Stahl 2021).

25.5 Aripiprazole: mania and maintenance, weight-neutral

The mechanism that sets it apart. Aripiprazole (aripiprazole) is a **D2 partial agonist** (and 5-HT1A partial agonist, 5-HT2A antagonist), which gives it a fast anti-manic effect with a low metabolic and prolactin profile (Stahl 2021; KDT 2019). CANMAT lists it as a first-line agent for acute mania and, importantly, as a first-line maintenance monotherapy, available oral or as a once-monthly long-acting injectable, with the caveat that it prevents manic but not depressive episodes (CANMAT 2018). It is not a bipolar-depression monotherapy.

Dose and tolerability. The usual bipolar dose range is roughly **15 to 30 mg/day** (Indian dosing 5 to 30 mg/day; KDT 2019). It is essentially **weight-neutral** and carries low metabolic risk, but akathisia is its characteristic and often dose-limiting adverse effect (Stahl 2021).

GOOD TO REMEMBER

- **Aripiprazole:** D2 partial agonist; signature cost is akathisia (but weight-neutral and low prolactin); the one to hold is that it is first-line for mania and for maintenance (oral or once-monthly LAI) but prevents only the manic pole, not the depressive one (CANMAT 2018; Stahl 2021).

25.6 Risperidone and paliperidone: mania and the LAI option, at a prolactin cost

What they cover. Risperidone (Sizodon, risperidone) is a potent D2 and 5-HT2A antagonist, first-line for acute mania and mixed episodes; paliperidone (paliperidone), its active 9-hydroxy metabolite, is likewise used in mania (Stahl 2021; CANMAT 2018). Their standout maintenance role is as the **long-acting injectable** option: CANMAT recommends a long-acting injectable antipsychotic (risperidone LAI every two weeks or aripiprazole once-monthly) for the non-adherent bipolar patient to prevent relapse (CANMAT 2018).

The cost. Both are the class leaders for **prolactin elevation** (galactorrhoea, menstrual disturbance, sexual dysfunction) and carry moderate metabolic risk, more than the partial agonists (Stahl 2021). Risperidone is dosed around 1 to 6 mg/day in mania; Indian brands include Sizodon and Respidon (risperidone), 1 to 4 mg tablets (KDT 2019).

GOOD TO REMEMBER

- **Risperidone (Sizodon) and paliperidone:** potent D2/5-HT2A antagonists (paliperidone is risperidone's 9-OH metabolite); signature cost is prolactin elevation; the one to hold is mania first-line, and the long-acting injectable (risperidone LAI two-weekly) as the maintenance option for non-adherence (CANMAT 2018; Stahl 2021).

25.7 Cariprazine: mania and bipolar depression, the D3-preferring partial agonist

Why it reaches the depressive pole. Cariprazine (cariprazine) is a D2 and D3 partial agonist that is unique in being the **most potent available agent at the D3 receptor**, more potent than dopamine itself, together with 5-HT1A partial agonism (Stahl 2021). This D3-preferring profile is the presumed basis of its efficacy across both poles. CANMAT names cariprazine among the first-line options for acute mania, and lists cariprazine (with the olanzapine-fluoxetine combination) as a second-line option for acute bipolar I depression when a rapid response is desirable (CANMAT 2018).

Tolerability. It sits in the low-metabolic-risk tier (with lurasidone and aripiprazole) but, like the other partial agonists, akathisia is its characteristic adverse effect (Stahl 2021). Its long half-life and active metabolites mean effects and adverse effects accumulate over weeks.

GOOD TO REMEMBER

- **Cariprazine:** D3-preferring D2/D3 partial agonist (the most potent D3 agent available); signature cost is akathisia (low metabolic); the one to hold is that it works in both mania and bipolar depression, unusual for an anti-manic atypical (CANMAT 2018; Stahl 2021).

25.8 Lurasidone: the bipolar-depression agent

Its niche. Lurasidone (lurasidone) is a potent antagonist at 5-HT2A, D2 and 5-HT7 receptors and a 5-HT1A partial agonist (Kaplan and Sadock 2024; Stahl 2021). Its distinctive place is

bipolar depression: CANMAT lists it as a first-line treatment for acute bipolar I depression, as monotherapy or adjunctive to lithium or divalproex (CANMAT 2018). It is not licensed for acute mania. It sits with cariprazine and aripiprazole in the low-metabolic-risk tier (Stahl 2021).

The practical points. Its commonest adverse effects are sedation, akathisia and nausea, and it has a firm pharmacokinetic quirk: it must be **taken with food** (at least 350 kcal) to be adequately absorbed, and it is a CYP3A4 substrate, so it is contraindicated with strong CYP3A4 inhibitors and inducers (Kaplan and Sadock 2024; Stahl 2021). The receptor and interaction detail is developed in the Schizophrenia: management, antipsychotics and adverse effects notes.

RULE **Lurasidone and cariprazine for bipolar depression.** When the pole to treat is the depressive one, these two (plus quetiapine and the olanzapine-fluoxetine combination) are the atypicals with the evidence, not the pure anti-manic agents.

GOOD TO REMEMBER

- **Lurasidone:** 5-HT2A/D2/5-HT7 antagonist and 5-HT1A partial agonist; signature cost is akathisia and nausea (low metabolic) plus the take-with-food requirement; the one to hold is that it is first-line for bipolar depression and has no mania licence (CANMAT 2018; Kaplan and Sadock 2024).

25.9 Asenapine: mania, including mixed features

Its place. Asenapine (asenapine) is a high-affinity 5-HT2A and D2 antagonist (with broad serotonergic, dopaminergic and adrenergic actions) licensed for acute **mania and mixed states**, and it is one of the agents named first-line for acute mania by CANMAT (Kaplan and Sadock 2024; CANMAT 2018). Its usefulness in **mixed features** is the fact worth holding.

The formulation quirk. Asenapine is given **sublingually** because oral bioavailability is negligible; the patient must avoid food and drink for 10 minutes afterwards, and it commonly causes oral hypoaesthesia (Kaplan and Sadock 2024). It carries moderate metabolic risk (Stahl 2021).

GOOD TO REMEMBER

- **Asenapine:** high-affinity 5-HT2A/D2 antagonist given sublingually; signature cost is oral hypoaesthesia (and no food or drink for 10 minutes); the one to hold is mania first-line, particularly useful for mixed features (CANMAT 2018; Kaplan and Sadock 2024).

25.10 Phase-matching and the metabolic monitoring: pulling it together

The selection logic, previewing the choosing topic. The whole class resolves into a phase-matching decision (CANMAT 2018; Stahl 2021). For **acute mania**, CANMAT offers quetiapine, aripiprazole, risperidone, paliperidone, cariprazine or asenapine (alone or combined with lithium or divalproex), with an atypical-plus-mood-stabiliser combination first-line in severe presentations. For **acute bipolar I depression**, the atypical options are quetiapine, lurasidone (monotherapy or adjunctive to lithium or divalproex), the olanzapine-fluoxetine combination and cariprazine. For **maintenance**, quetiapine, aripiprazole and asenapine are first-line monotherapies, with olanzapine and paliperidone (and risperidone LAI) as second-line,

olanzapine downgraded for its metabolic risk. The **Indian Psychiatric Society** position aligns: the IPS guidelines name quetiapine, aripiprazole, risperidone, asenapine or cariprazine (with lithium or divalproex) among first-line monotherapies for acute mania and place olanzapine and ziprasidone second-line, name the olanzapine-fluoxetine combination, quetiapine, lurasidone or cariprazine as first-line for acute bipolar depression, and quetiapine and lamotrigine alongside lithium and divalproex as first-line maintenance agents, with olanzapine, carbamazepine, ziprasidone and risperidone second-line (IPS 2025). NICE recommends offering an antipsychotic (asenapine, aripiprazole, olanzapine, quetiapine or risperidone) where lithium is unsuitable for maintenance (NICE 2014). The full agent-versus-agent selection is developed in the choosing topic.

The monitoring headline. Whenever an atypical is used long-term for mood, the metabolic monitoring runs for as long as the drug does: CANMAT advises weight monthly for the first three months then every three months, with blood pressure, fasting glucose and a fasting lipid profile at 3 and 6 months then yearly, on top of the baseline metabolic and prolactin screen (CANMAT 2018). The receptor-level basis and the full adverse-effect and monitoring schedule are the property of the Schizophrenia: management, antipsychotics and adverse effects notes.

300	3	3 and 6
QUETIAPINE BIPOLAR DEPRESSION (MG/DAY)	WEIGHT CHECK FOR FIRST MONTHS (MONTHLY, THEN 3-MONTHLY)	GLUCOSE AND LIPIDS THEN YEARLY (MONTHS)

PEARL

The two atypicals that reach the depressive pole in bipolar I as first-line (lurasidone and, with quetiapine, cariprazine second-line) are exactly the ones in the low-metabolic-risk tier: the drugs you most want to keep a patient on long-term for the harder-to-treat depressive phase happen to be the metabolically kindest, which is a rare alignment of efficacy and tolerability (Stahl 2021; CANMAT 2018).

INDIA

Lead with the Indian brand where one is confirmed: quetiapine as **Qutipin** (25 to 400 mg), olanzapine as **Oleanz** (2.5 to 20 mg), risperidone as **Sizodon** or Respidon (1 to 4 mg) (KDT 2019). Aripiprazole, paliperidone, cariprazine, lurasidone and asenapine are all marketed in India but a specific brand could not be confirmed from the parsed library, so the generic is given for those (flagged under gaps). All of these are widely available and used as mood stabilisers in Indian bipolar practice.

GOOD TO REMEMBER

- **Mania (first-line atypicals):** quetiapine, aripiprazole, risperidone, paliperidone, cariprazine, asenapine, alone or with lithium/divalproex (CANMAT 2018).
- **Bipolar depression:** quetiapine and lurasidone are first-line; cariprazine and the olanzapine-fluoxetine combination are second-line (CANMAT 2018).
- **Maintenance:** quetiapine, aripiprazole, asenapine first-line; aripiprazole prevents manic (not depressive) relapse; risperidone LAI or aripiprazole once-monthly for non-adherence (CANMAT 2018).
- **The trade-off:** the metabolic burden (worst with olanzapine), extrapyramidal effects/akathisia (the partial agonists) and prolactin (risperidone, paliperidone) must be monitored for as long as the drug is used (Stahl 2021; CANMAT 2018).

HOLD THIS

Quetiapine works across all three phases; lurasidone and cariprazine are the bipolar-depression agents; and any atypical used long-term for mood earns lifelong metabolic monitoring.

26 . Choosing a mood stabiliser: the algorithms

Choosing a mood stabiliser is not a single decision, it is a decision that is remade at every phase of bipolar disorder: the agent that is first-line for **acute mania** is not the same agent that is first-line for the depressive pole, and the **maintenance algorithm** is anchored by yet another logic. This is the mood-block closer and a reliable theory question: the examiner rewards the guideline-anchored **phase-then-polarity** spine and the exact serum-level targets, not a recitation of side effects. The deep pharmacology, dosing, monitoring and teratogenicity of each agent are owned by the dedicated lithium, valproate, carbamazepine and lamotrigine topics in these notes; this topic carries the **selection algorithm**.

Lead the guideline answer with CANMAT, specifically the CANMAT and ISBD 2018 bipolar guidelines (Yatham 2018), then give the Indian Psychiatric Society (IPS 2025, Menon et al.), NICE (NICE 2014) and BAP (BAP 2016, Goodwin) positions. Across all four the organising principle the exam tests is one instruction: **pick the stabiliser by phase and by predominant polarity, with lithium anchoring maintenance and lamotrigine covering the depressive pole.**

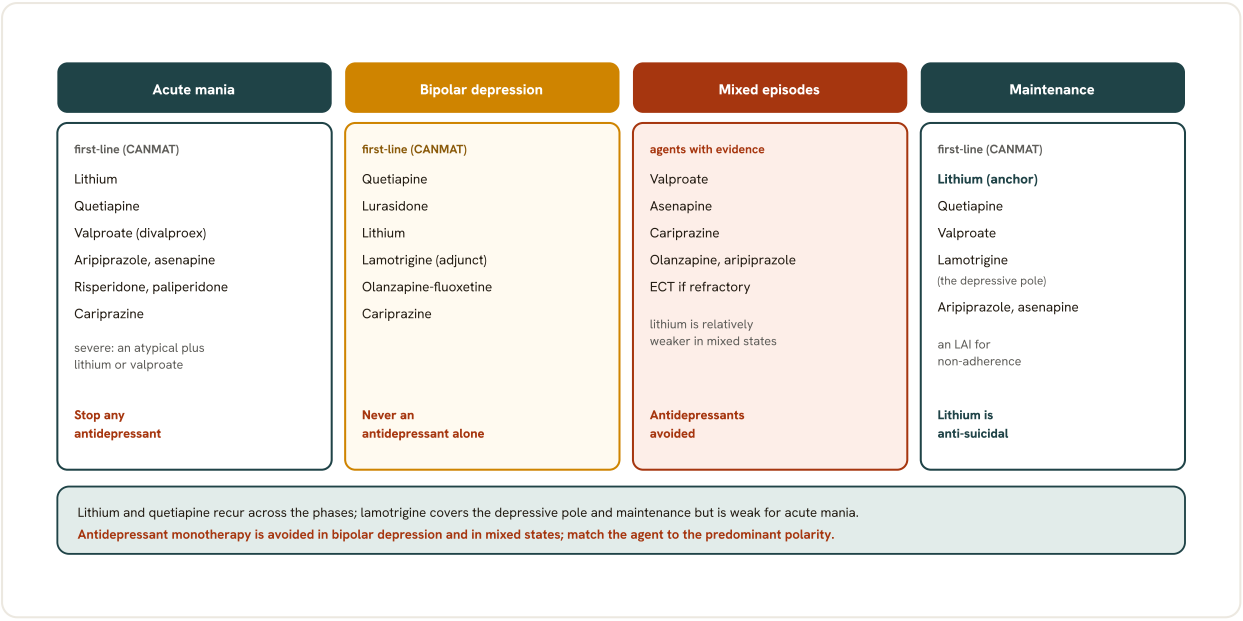

Fig 12.9 Choosing a mood stabiliser by phase, led by the CANMAT recommendations. Lithium, quetiapine and valproate anchor acute mania; quetiapine, lurasidone, lithium and lamotrigine cover bipolar depression; valproate and the atypicals (asenapine, cariprazine) with ECT cover mixed episodes; and lithium anchors maintenance with lamotrigine for the depressive pole. Antidepressant monotherapy is avoided in bipolar depression and mixed states, and any antidepressant is stopped in acute mania.

26.1 The selection logic: phase first, then predominant polarity

Phase before drug. The single most examinable idea is that you choose the agent by the phase you are treating, not by a generic label of "mood stabiliser". A drug that is genuinely first-line for mania (for example an antipsychotic or valproate) may be weak or useless for the depressive pole, and a drug that covers the depressive pole (lamotrigine) is weak for acute mania. Layered on top of phase is **predominant polarity**: a patient whose recurrences are mostly depressive is steered toward agents with depressive-pole efficacy (lamotrigine, quetiapine, lithium), whereas a mostly-manic course is steered toward lithium and the antimanic antipsychotics. The receptor-level pharmacology that underlies these differences is cross-referred to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

RULE **Pick the stabiliser by phase and predominant polarity.** Lithium anchors maintenance; lamotrigine covers the depressive pole; the antimanic antipsychotics and valproate cover mania.

26.2 ACUTE MANIA: the CANMAT first-line monotherapies

For **acute mania**, CANMAT offers a defined first-line monotherapy list (Yatham 2018): lithium (Licab or Intalith), quetiapine (Qutipin), divalproex (Valance or Valprol), asenapine, aripiprazole, paliperidone, risperidone and cariprazine, given alone or in combination. Note what is *not* on this list: lamotrigine, carbamazepine and the antidepressants. The choice among the first-line agents is individualised on prior response, tolerability, comorbidity and the need for sedation. The IPS names essentially the same set, listing lithium, divalproex, risperidone, quetiapine, aripiprazole, asenapine or cariprazine monotherapy as first-line for acute mania, with carbamazepine, olanzapine, ziprasidone and haloperidol second-line on grounds of a less favourable safety profile (IPS 2025). NICE, for a person not already on treatment, offers haloperidol, olanzapine, quetiapine or risperidone (NICE 2014).

RULE **Acute mania first-line = lithium, an antimanic atypical (quetiapine, asenapine, aripiprazole, paliperidone, risperidone, cariprazine) or divalproex.** Individualise on tolerability and comorbidity (CANMAT 2018).

26.3 ACUTE MANIA: the first-line combination and the antidepressant rule

For severe mania, CANMAT's **first-line combination** is an atypical antipsychotic (quetiapine, aripiprazole, risperidone or asenapine) plus lithium or divalproex, preferred in severe presentations over monotherapy (Yatham 2018). The IPS agrees: combine a mood stabiliser with a second-generation antipsychotic for severe mania (IPS 2017). Two selection rules sit alongside this. First, **discontinue any antidepressant** in a patient presenting with mania, and reassess the diagnosis before starting antimanic agents in a first-episode presentation (CANMAT 2018; IPS 2017). Second, if response to an optimally dosed first-line agent is inadequate after 2 weeks, optimise the dose and address non-adherence and substance use before switching to or adding another first-line agent (CANMAT 2018). The serum-level target for lithium in acute mania is **0.8 to 1.2 mEq/L** (Yatham 2018).

TRAP **Leaving an antidepressant running in acute mania.** Antidepressants are discontinued when a patient presents in mania; continuing one is a selection error.

WORKED EXAMPLE

A 27-year-old man presents with a first severe manic episode with psychotic features while taking sertraline for a presumed depression. The sertraline is discontinued. Because the mania is severe, he is started not on monotherapy but on the first-line combination: an atypical antipsychotic, risperidone (Sizodon or Risdone), plus a mood stabiliser, lithium (Licab or Intalith), titrated to an acute-phase serum lithium of 0.8 to 1.2 mEq/L. He is reviewed at 2 weeks; because the response is only partial, the dose is optimised and adherence checked before any switch. The diagnosis is reassessed as bipolar I disorder once the episode settles, which sets up the maintenance decision.

26.4 BIPOLAR DEPRESSION: a different first-line list

The depressive pole has its own first-line set, and it is the reason lamotrigine exists in this algorithm. For acute bipolar I depression, CANMAT's first-line options are quetiapine (Qutipin), lurasidone (as monotherapy or added to lithium or divalproex), lithium, and lamotrigine (Lamitor or Lametec) as monotherapy or adjunct (Yatham 2018). Lamotrigine is titrated slowly from **25 mg** to a minimum target of **200 mg/day** to limit the rash risk; the full titration schedule and the Stevens-Johnson syndrome caution are owned by the lamotrigine topic in these notes. The IPS names the olanzapine-fluoxetine combination, quetiapine, lurasidone and cariprazine as first-line for acute bipolar depression, and is explicit that lithium is not approved as a first-line treatment here and that lamotrigine is usually not preferred for the acute phase because of its prolonged titration (IPS 2025). NICE offers fluoxetine combined with olanzapine, quetiapine alone, olanzapine alone, or lamotrigine alone (NICE 2014). A hard rule governs the whole pole: **do not use an antidepressant as monotherapy in bipolar depression**; if one is used it is only on a background mood stabiliser, paroxetine is avoided, and bupropion is preferred (IPS 2017). The management of each bipolar phase in full is owned by the dedicated bipolar-management topics.

TRAP **An antidepressant alone in a bipolar patient.** Antidepressant monotherapy is not used in bipolar depression; cover it with a mood stabiliser, and never use lamotrigine to treat acute mania (it is weak there).

26.5 MAINTENANCE ALGORITHM: lithium leads, lamotrigine for the depressive pole

The **maintenance algorithm** is where lithium is the anchor. CANMAT's first-line maintenance monotherapies for bipolar I are lithium, quetiapine, divalproex, lamotrigine, asenapine and aripiprazole, alone or in combination (Yatham 2018). Two polarity facts drive the choice: **lamotrigine is the maintenance agent for the depressive pole** and is weak against manic recurrence, whereas **aripiprazole prevents manic but not depressive episodes**. Lithium is the broadest, preventing both poles, and carries specific anti-suicide evidence (IPS 2017). A rational default is to continue into maintenance the agent that worked in the acute phase (BAP 2016; IPS 2017). The maintenance serum-level target for lithium is **0.6 to 1.0 mEq/L** (Yatham 2018); NICE and BAP frame a slightly narrower **0.6 to 0.8 mmol/L** range (NICE 2014; BAP 2016). NICE is explicit that lithium is the first-line long-term treatment, with an antipsychotic (asenapine, aripiprazole, olanzapine, quetiapine or risperidone) if lithium is unsuitable (NICE 2014). The IPS guidelines name lithium and valproate as the best-evidenced maintenance agents (IPS 2017).

RULE **Lithium leads maintenance and prevents both poles; lamotrigine covers the depressive pole; aripiprazole covers the manic pole only.** Continue what worked acutely (CANMAT 2018; NICE 2014).

26.6 MAINTENANCE: the LAI option for non-adherence

Non-adherence is the commonest cause of maintenance failure, and the algorithm has a defined answer. In a non-adherent patient, CANMAT offers a **long-acting injectable** antipsychotic as first-line to prevent relapse, specifically risperidone LAI every 2 weeks or aripiprazole once-monthly (Yatham 2018). BAP frames the same option as depot antipsychotics for prophylaxis against manic recurrence when oral adherence is erratic or injection is preferred (BAP 2016). This is a selection rule the exam likes because it links a clinical problem (non-adherence) to a specific pharmacological form; the deep antipsychotic pharmacology behind these agents is cross-referred to the Schizophrenia: management, antipsychotics and adverse effects notes.

RULE **Non-adherence in maintenance = a long-acting injectable.** Risperidone LAI two-weekly or aripiprazole once-monthly is first-line for the non-adherent patient (CANMAT 2018).

26.7 The stabiliser-selection algorithm assembled by phase

The phases and their first-line agents assemble into one table. Learn the highlighted cell in each row: it is the first-line fact the examiner tests. Each phase links to the dedicated bipolar-management topics for the full plan.

0.8 to 1.2 ACUTE-MANIA LITHIUM (MEQ/L)	**0.6 to 1.0** MAINTENANCE LITHIUM (MEQ/L)	**200** LAMOTRIGINE MINIMUM TARGET (MG/DAY)	**2 wk** REASSESS BEFORE SWITCHING IN MANIA

PHASE	CANMAT FIRST-LINE (LEAD)	FIRST-LINE COMBINATION / NEXT STEP	IPS / NICE / BAP HEADLINE
Acute mania	**Lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone, cariprazine (monotherapy) (CANMAT 2018)**	Atypical (quetiapine, aripiprazole, risperidone, asenapine) plus lithium or divalproex for severe mania; discontinue any antidepressant; lithium 0.8 to 1.2 mEq/L	IPS: lithium, divalproex, risperidone, quetiapine, aripiprazole, asenapine, cariprazine first-line, with olanzapine, ziprasidone and haloperidol second-line; NICE: haloperidol, olanzapine, quetiapine, risperidone (IPS 2025; NICE 2014)
Bipolar depression	**Quetiapine, lurasidone (plus lithium or divalproex), lithium, lamotrigine (CANMAT 2018)**	Lamotrigine titrated 25 to 200 mg/day; no antidepressant monotherapy; olanzapine-fluoxetine an option	IPS: olanzapine-fluoxetine, quetiapine, lurasidone or cariprazine first-line, lithium not first-line here; NICE: fluoxetine plus olanzapine, or quetiapine, or lamotrigine (IPS 2025; NICE 2014)
Mixed features	**Antimanic agents; antidepressants avoided (treat the manic pole) (CANMAT 2018)**	Lithium, valproate or an antimanic atypical; do not use an antidepressant in a mixed state (IPS 2017)	IPS: no antidepressant monotherapy in mixed episodes; consider ECT if severe (IPS 2017)
Maintenance	**Lithium, quetiapine, divalproex, lamotrigine, asenapine, aripiprazole (CANMAT 2018)**	Lamotrigine for the depressive pole; aripiprazole for the manic pole only; LAI (risperidone two-weekly or aripiprazole monthly) for nonadherence; lithium 0.6 to 1.0 mEq/L	NICE: lithium first-line long-term; IPS/BAP: lithium and valproate best-evidenced, continue what worked acutely (NICE 2014; IPS 2017; BAP 2016)

The mood-stabiliser selection algorithm by phase; first-line agents verified against CANMAT and ISBD 2018 (Yatham 2018), IPS 2017, NICE 2014 and BAP 2016. Each phase is owned in full by the dedicated bipolar-management topics.

INDIA

The Indian Psychiatric Society Clinical Practice Guidelines for bipolar disorder (IPS 2025, Menon et al.) are the guideline most likely to be named in Indian postgraduate examinations, and they map cleanly onto the phases: lithium, divalproex or a first-line antipsychotic (risperidone, quetiapine, aripiprazole, asenapine, cariprazine) for acute mania, with olanzapine, ziprasidone and haloperidol second-line; the olanzapine-fluoxetine combination, quetiapine, lurasidone or cariprazine first-line for bipolar depression; lithium and valproate as the best-evidenced maintenance agents with lithium first-line for preventing recurrence at both poles and specific anti-suicide evidence. Every agent named here is available as an inexpensive Indian brand: lithium carbonate (Licab or Intalith), sodium valproate (Valprol or Encorate), divalproex (Valance or Divaa), quetiapine (Qutipin), olanzapine (Oleanz), lamotrigine (Lamitor or Lametec) and carbamazepine (Tegretol or Mazetol). The IPS avoids antidepressant monotherapy in bipolar depression, prefers bupropion if an antidepressant is unavoidable, and avoids paroxetine.

GOOD TO REMEMBER

- **Lithium (Licab or Intalith):** broad-spectrum anchor; prevents both poles and has anti-suicide evidence; acute-mania target **0.8 to 1.2 mEq/L**, maintenance **0.6 to 1.0 mEq/L** (CANMAT 2018).
- **Quetiapine (Qutipin):** the one atypical that is first-line across mania, bipolar depression and maintenance; signature adverse effect is metabolic and sedation.
- **Divalproex / valproate (Valprol or Encorate):** first-line for acute mania and maintenance; teratogenic, so avoided in women of childbearing potential; not first-line for bipolar depression.
- **Lamotrigine (Lamitor or Lametec):** the depressive-pole agent for bipolar depression and maintenance; weak for acute mania; titrate slowly from 25 mg to a minimum of **200 mg/day** for rash risk.
- **Aripiprazole:** first-line for mania and maintenance but prevents the manic pole only, not the depressive; available as a once-monthly LAI for non-adherence.
- **The antidepressant rule:** discontinue an antidepressant in acute mania, and never use antidepressant monotherapy in bipolar depression (CANMAT 2018; IPS 2017).

PEARL

Read the algorithm as three lists that overlap but are not identical. Only a handful of agents (lithium, quetiapine, divalproex, aripiprazole, asenapine) appear on both the mania and the maintenance first-line lists; lamotrigine appears on the depression and maintenance lists but never on the mania list; lurasidone appears on the depression list. The overlap is why lithium is the safest single answer when a question does not specify the phase.

HOLD THIS

Choose the mood stabiliser by phase and predominant polarity: for acute mania give lithium, an antimanic atypical or divalproex and stop any antidepressant; for bipolar depression reach for quetiapine, lurasidone, lithium or lamotrigine and never an antidepressant alone; for maintenance lithium leads and prevents both poles while lamotrigine covers the depressive pole, with CANMAT 2018 as the lead guideline.

Treatment resistance, augmentation and special populations

27 . Treatment-resistant depression

Some depressions do not lift on the first, or even the second, well-chosen antidepressant. **Treatment-resistant depression** is the label for that clinical situation, and it is one of the highest-yield theory topics in the mood block because the examiner is testing a discipline, not a drug list: before you escalate treatment, you must prove the depression is genuinely resistant and not merely under-treated. This topic teaches the **definition** of treatment-resistant depression, how to **staging** the degree of resistance, and the evaluation that must precede the label. The augmentation ladder that follows a confirmed diagnosis (which agent, which line) is the next topic; this topic carries the definition, the staging and the pre-escalation work-up.

The single organising idea is that resistance is a matter of *degree*, not a binary switch, and that it is over-diagnosed. Most apparent resistance is **pseudoresistance**, an inadequate dose, an inadequate duration, poor adherence or the wrong diagnosis, and every guideline (CANMAT 2016; BAP 2015; IPS 2017) opens the treatment-resistant depression pathway with a mandatory review of adequacy and diagnosis before any escalation.

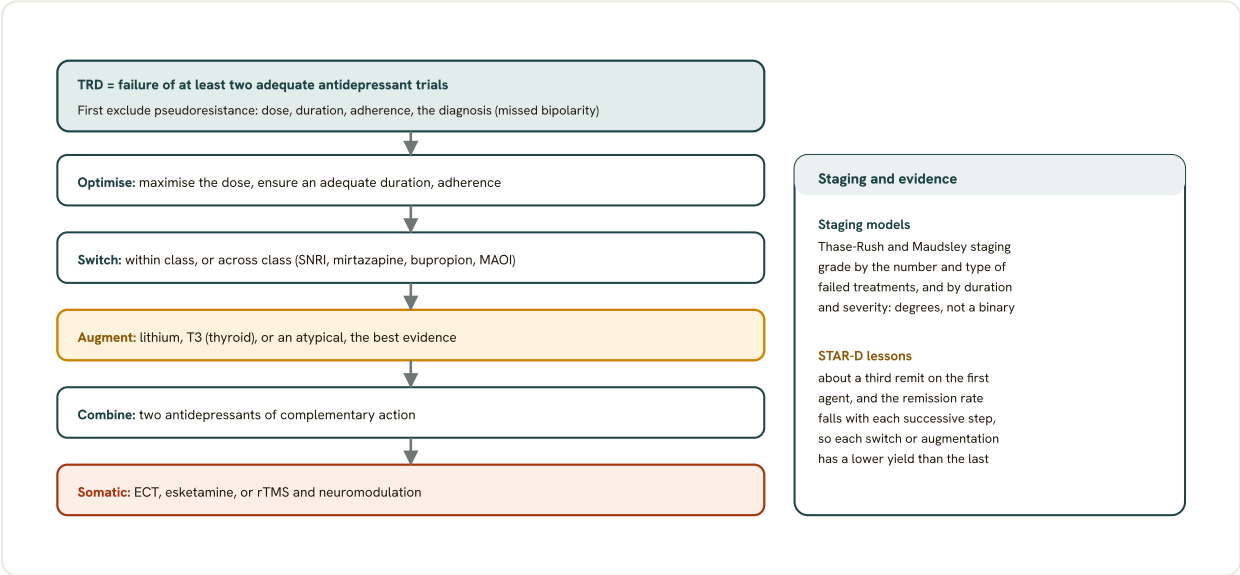

Fig 12.11 Treatment-resistant depression: staging and the augmentation ladder. Resistance means at least two failed adequate antidepressant trials, but pseudoresistance (inadequate dose or duration, non-adherence, missed bipolarity) is excluded first. The sequence then runs optimise, switch, augment (lithium, T3 or an atypical carry the best evidence), combine, and finally the somatic treatments. The STAR-D trial showed remission rates fall with each successive step.

27.1 The definition: two adequate failed trials in the current episode

The working definition. **Treatment-resistant depression** (**trd**) is conventionally defined as a failure to respond to at least **two** adequate antidepressant trials, each at an adequate dose for an adequate duration, in the current depressive episode (Tasman 2015; Maudsley 2021). Failure of a single trial is so common that it does not qualify as resistance; true resistance is better defined as failure to reach remission after two treatments given at adequate dosage and duration (Tasman 2015).

The definition is not settled. There is no universally accepted operational definition of treatment-resistant depression, which is precisely why comparisons across the literature are so difficult (Tasman 2015). Definitions vary in three ways: the *number* of failed trials required (some demand two, some more), the *outcome* threshold that counts as failure (non-response, usually less than a 50 percent symptom reduction, versus failure to reach full remission), and whether the failed trials must be of different pharmacological classes. Remission, not response, is the modern target, because response without remission carries a high relapse risk (Tasman 2015).

RULE **Two adequate antidepressant trials must fail in the current episode before the depression is called resistant.** Each trial must have been at an adequate dose for an adequate duration.

27.2 What "adequate" means: dose and duration

Adequacy is dose plus duration. A trial only counts toward resistance if it was truly adequate, meaning a therapeutic dose sustained for long enough to work. The BAP directs that before declaring a drug to have failed you must increase to a recommended therapeutic dose, and for a tricyclic aim for a dose-equivalence of at least **125 mg** if tolerated (BAP 2015). On duration, the guidelines assess response at **4 weeks** of adequate treatment and again at **6 to 8 weeks**; a marginal or low dose, or a trial cut short before this window, has not adequately tested the drug (BAP 2015; CANMAT 2016).

Optimise before you escalate. The first step in the treatment-resistant depression pathway is therefore not a new drug but optimisation: check the adequacy of the current treatment, and raise a low or marginal dose to a recommended therapeutic dose first (BAP 2015). Only a trial that was adequate in both dose and duration can be counted as a genuine failure.

2	4 to 8	50
ADEQUATE FAILED TRIALS TO DEFINE TRD	WEEKS TO JUDGE ONE ADEQUATE TRIAL	PERCENT SYMPTOM DROP DEFINING RESPONSE

27.3 Staging: resistance is a degree, not a binary

Why stage. Because resistance is a continuum, several **staging** systems quantify *how* resistant a depression is, which predicts outcome and guides how aggressively to treat (Tasman 2015). The two the board tests are the **thase-rush** five-stage model and the **maudsley staging** method; the Massachusetts General Hospital (MGH) staging method is a third. Each grades resistance by the number and type of failed treatments and, for the newer methods, the duration and severity of illness.

The clinical point of any staging system. All of them exist to make one point: neither doctor nor patient should be discouraged by a single failed trial, and good treatment demands persistence through multiple adequate trials (Tasman 2015). Staging turns "resistant or not" into a graded score that tracks the odds of remission.

27.4 The Thase-Rush five-stage model

Staged by class of drug failed. The Thase-Rush five-stage model grades resistance purely by non-response to sequential trials of antidepressants with differing mechanisms, culminating in

electroconvulsive therapy (Tasman 2015). It is the classic, examinable ladder.

STAGE	DEFINITION (CUMULATIVE)
Stage I	Failure of an adequate trial of one antidepressant
Stage II	**Stage I plus failure of a trial of an antidepressant of a different class**
Stage III	Stage II plus failure of a tricyclic antidepressant
Stage IV	Stage III plus failure of a monoamine oxidase inhibitor
Stage V	Stage IV plus failure of a course of electroconvulsive therapy

The Thase-Rush five-stage model, graded by non-response to antidepressants of progressively different mechanism and finally to ECT (Tasman 2015). Its weakness: it assumes a fixed hierarchy of drug classes and does not weigh dose, duration, augmentation or combination.

Its limitation. The Thase-Rush model presumes that a monoamine oxidase inhibitor is intrinsically superior to a tricyclic, and it cannot grade a trial by its dose or duration, nor does it credit augmentation or combination strategies (Tasman 2015). This is why the later staging methods were developed.

27.5 The Maudsley staging method

Multidimensional scoring. The Maudsley staging method (Fekadu et al. 2009) scores resistance across three separate dimensions rather than a single ladder: the *prior treatment* (number of failed antidepressants, plus augmentation and ECT), the *current symptom severity*, and the *duration* of the illness (Tasman 2015; Maudsley 2021). The points sum to a total that places the patient on a mild-to-severe resistance gradient.

Why it is preferred. By incorporating severity and chronicity, and by crediting augmentation and combination, the **maudsley staging** method predicts continuing treatment resistance and longer-term outcome better than the Thase-Rush ladder in inpatient samples (Fekadu et al. 2009; Tasman 2015). The MGH method, for comparison, assigns one point per adequate monotherapy trial of at least 6 weeks, adds 0.5 points for optimising, augmenting or combining, and adds 3 points for ECT (Petersen et al. 2005).

GOOD TO REMEMBER

- **Thase-Rush five-stage model:** grades resistance by failed drug *class* in sequence, ending at ECT (Stage V); ignores dose, duration and augmentation.
- **Maudsley staging method:** scores three dimensions, prior treatment, current symptom severity and duration of illness (Fekadu et al. 2009); better predicts persistence and outcome.
- **MGH staging method:** 1 point per adequate 6-week monotherapy trial, 0.5 for optimise/augment/combine, 3 for ECT (Petersen et al. 2005).
- **The shared message:** resistance is a degree, not a binary; do not be discouraged by one failed trial.

27.6 Before you label it resistant: reconsider the diagnosis

Resistance is often a wrong diagnosis. The first evaluation before calling any depression resistant is to reconsider the diagnosis. The BAP directs a formal diagnostic review, including the possibility of comorbid medical or psychiatric conditions and unrecognised bipolarity, psychosis or atypical features, using screening tools where helpful (BAP 2015). The commonest missed diagnoses are a missed bipolar disorder (the depression is a bipolar depression that will not respond to, and may be worsened by, an antidepressant alone), a missed psychotic depression (which needs an antipsychotic added), and a missed organic or substance cause (hypothyroidism, anaemia, alcohol or substance use) (Tasman 2015; IPS 2017).

And a comorbidity that sustains the depression. A coexisting personality disorder, a chronic medical illness, or an untreated anxiety or substance use disorder can hold a depression down and masquerade as pharmacological resistance. The Indian Psychiatric Society Clinical Practice Guidelines (Gautam et al.) make this explicit: the IPS treatment-resistant depression pathway reassesses the diagnosis to rule out bipolar disorder, substance use and medical contributors before escalating (IPS 2017). Where a finer IPS-specific staging or threshold cannot be confirmed against the guideline rows, it is flagged under gaps rather than invented.

TRAP **Calling a bipolar depression "treatment-resistant" and stacking on antidepressants.** An unrecognised bipolar depression will not respond to an antidepressant alone and can be destabilised by it; screen for bipolarity first.

27.7 Pseudoresistance: adherence, dose and duration

Confirm adherence. Once the diagnosis holds, confirm the patient actually took the drug. Non-adherence, whether from side effects, cost, or belief, is a leading cause of apparent non-response, and a depression that was never adequately dosed in the patient's body cannot be called resistant; the **ips guidelines** and the BAP both make confirming adherence a step before escalation (BAP 2015; IPS 2017). This is the essence of **pseudoresistance**: an apparent treatment resistance that is really an artefact of inadequate treatment.

The three checks that unmask pseudoresistance. Was the *dose* therapeutic? Was the *duration* long enough (at least 4 to 8 weeks at that dose)? Was *adherence* intact? If any answer is no, the depression is not resistant, it is under-treated, and the correct action is to optimise, not to escalate (BAP 2015; CANMAT 2016). A subtherapeutic or non-adherent trial simply does not count toward the two-trial definition.

RULE **Before labelling depression resistant, confirm the dose, the duration, adherence and the diagnosis.** Only then does a failed trial count.

INDIA

Pseudoresistance is disproportionately common in Indian outpatient practice, where largely out-of-pocket payment drives early self-discontinuation once the patient feels a little better or once side effects appear, and where a subtherapeutic dose may have been given to limit cost. Before any escalation, verify that a cheap generic SSRI such as escitalopram (Nexito or S-Citadep) or sertraline (Serta or Daxid) was actually taken at a therapeutic dose for an adequate duration; the commonest "resistant" case is a half-dose, half-taken first trial.

27.8 The STAR-D lessons: remission falls with each step

The landmark effectiveness trial. The STAR-D trial (the Sequenced Treatment Alternatives to Relieve Depression programme, Rush et al. 2006), a large NIH-funded practical trial highly applicable to real-world practice, gave the best available data on what happens across sequential steps (Tasman 2015). Patients who did not remit on the initial citalopram progressed through sequential, randomised steps of switching and augmentation.

Two lessons the examiner rewards. First, about a *third* of patients remit on the first agent: STAR-D reported first-step remission of roughly 28 percent by the Hamilton scale and 33 percent by the QIDS-SR, so lack of remission to a first antidepressant is common rather than exceptional (Tasman 2015). Second, remission rates *decline* with each successive step: the cumulative remission was about 37 percent after one trial, rising to 49 percent after two, but only to 50 percent after three and 51 percent after four (Tasman 2015). The small gains at steps three and four show how an increasingly resistant episode becomes progressively harder to treat.

STAR-D TREATMENT STEP	CUMULATIVE REMISSION (PERCENT)
After step 1 (citalopram)	**37**
After step 2	49
After step 3	50
After step 4	51

STAR-D cumulative remission by treatment step (Rush et al. 2006; Tasman 2015): about a third remit on the first agent, and each further step yields diminishing returns. Patients who need more steps to remit also relapse at a higher rate.

What STAR-D informs. These figures underpin the whole switch-versus-augment logic: because a first agent so often fails, a planned sequence of next steps is essential, and because returns diminish, staging and diagnostic review matter more with each failed step. STAR-D also showed that switching within class was no different in outcome from switching to another class (CANMAT 2016), and that patients needing more steps to remit relapse at a higher rate (Tasman 2015). The augmentation ladder that operationalises these next steps is the next topic.

TRAP **Reading STAR-D as evidence that antidepressants do not work.** A third remit on the first drug and roughly half by the second; the lesson is diminishing returns and the need for a planned sequence, not futility.

27.9 The pre-escalation checklist and where the ladder begins

The work-up before escalation, in order. Put the topic together as the checklist the examiner wants before any next-step drug: (1) reconsider the diagnosis, screening for missed bipolarity, psychosis, an organic or substance cause, and a medical or personality comorbidity; (2) confirm adherence; (3) confirm the dose was therapeutic; (4) confirm the duration was adequate (4 to 8 weeks); and only then (5) stage the resistance and move to the next-step algorithm (BAP 2015; IPS 2017; CANMAT 2016).

Then the ladder. Once genuine resistance is confirmed, the options are to switch antidepressant, augment or combine, or move to neurostimulation. At guideline level the first-line augmentation agents are aripiprazole or brexpiprazole (CANMAT 2016), with quetiapine, aripiprazole or lithium as the BAP first-line augmentation choices (BAP 2015); lithium augmentation has the best evidence in older people (BAP 2015). Electroconvulsive therapy is reserved for those who have not responded to other treatments (BAP 2015). The detail of that ladder, and the ECT and neurostimulation technique, belong to the next topic and to the ECT and neurostimulation notes.

HOLD THIS

Treatment-resistant depression is failure of two adequate antidepressant trials in the current episode, but most apparent resistance is pseudoresistance or a missed bipolar depression, so confirm dose, duration, adherence and diagnosis before you ever escalate.

MNEMONIC

DADD before you ESCALATE

Diagnosis (reconsider, screen for bipolarity), **A**dherence (confirm it), **D**ose (therapeutic?), **D**uration (4 to 8 weeks?). Only when all four are cleared do you stage the resistance and climb the augmentation ladder.

GOOD TO REMEMBER

- **Definition:** treatment-resistant depression is failure of at least two adequate antidepressant trials (adequate dose and duration) in the current episode; no single agreed definition exists.
- **Pseudoresistance:** most apparent resistance is a subtherapeutic dose, an inadequate duration, poor adherence or a wrong diagnosis; exclude it, and exclude missed bipolarity, first.
- **Staging:** Thase-Rush grades by failed drug class to ECT; the Maudsley staging method scores prior treatment, current severity and illness duration and predicts outcome better.
- **STAR-D:** about a third remit on the first agent (28 percent HAM-D, 33 percent QIDS-SR); cumulative remission is roughly 37, 49, 50, 51 percent across steps 1 to 4, so returns diminish.

28 . Augmentation and combination strategies

When an antidepressant has been pushed to an adequate dose for an adequate duration and the depression has still not remitted, the clinician has three moves: **switch** the antidepressant, **augment** it with a second agent of a different pharmacology, or **combine** it with a second antidepressant. This topic teaches how to choose between those moves and, once augmentation is chosen, which agent to add and in what order of evidence. It follows directly from the treatment-

resistant depression topic, which carries the definition, the staging and the pre-escalation work-up; here we climb the ladder itself. It is high-yield because the board tests a discipline, not a drug list: the examiner wants to see that you **augment a partial response** and **switch a non-response**, and that you reach for a proven **augmentation** agent rather than stacking antidepressants irrationally.

The organising principle, repeated across CANMAT (2016), the BAP (2015) and NICE (2014), is that **augmentation** and **combination** are for genuine, confirmed treatment resistance in which the diagnosis, dose, duration and adherence have already been checked. Of the augmentation options, **lithium augmentation** and the atypical antipsychotics carry the strongest and most modern evidence; **thyroid** augmentation with T3 is a real but second-line option; and combining two antidepressants is reserved, evidence-selective and never started from the outset.

28.1 The decision: switch versus augment versus combine

The response guides the move. The single decision that organises the whole ladder is the degree of response to the current antidepressant. If there has been *no* response at all, or the drug is intolerable, **switch** to another agent, because there is nothing to build on and no reason to expose the patient to a second drug. If there has been a *partial* response but not remission, and the current drug is well tolerated, **augment** or combine, because you keep a partly effective treatment and add to it (BAP 2015; CANMAT 2016). The BAP states it directly: consider a second agent for augmentation when there is partial or insufficient response with good tolerability of the current antidepressant, or after an unsuccessful switch (BAP 2015).

Switching first, then building. A rational sequence after one adequate failure is to switch to another first-line agent; switching within class is no different in outcome from switching to another class (CANMAT 2016). After more than one failure within a class, move to a different class (BAP 2015). Only once a partial response emerges, or once switching has been exhausted, does augmentation become the preferred next step.

RULE **Augment a partial response; switch a non-response.** Build on a partly effective, tolerated drug; abandon one that did nothing or cannot be tolerated.

TRAP **Stacking antidepressants irrationally instead of a proven augmentation.** Two antidepressants at the outset is not supported; a proven augmenter (lithium or an atypical) has far better evidence.

28.2 The guideline map of augmentation, at a glance

What the guidelines actually recommend. The lead guideline for this note is CANMAT: for an inadequate antidepressant response, add a first-line adjunct of aripiprazole 2 to 15 mg/day, quetiapine 150 to 300 mg/day, risperidone 1 to 3 mg/day, or brexpiprazole 1 to 3 mg/day; add lithium or triiodothyronine (T3) as a second-line adjunct with drug-level or thyroid monitoring (CANMAT 2016). The BAP ranks the same agents: add quetiapine, aripiprazole or lithium as first-line augmentation, and risperidone, olanzapine, triiodothyronine or mirtazapine as second-line (BAP 2015). NICE, where a combination of medications is chosen, positions adding a

second-generation antipsychotic (aripiprazole, olanzapine, quetiapine or risperidone) or lithium to the antidepressant, in or with advice from a specialist mental health setting (NICE 2022). The Maudsley collapses this to a headline: either lithium or quetiapine is the agent of first choice for augmenting the existing antidepressant (Maudsley 2021).

The Indian position. The Indian Psychiatric Society Clinical Practice Guidelines for depression (Gautam et al.) place augmentation within the treatment-resistant pathway, listing lithium augmentation among the recognised strategies alongside atypical antipsychotic and thyroid augmentation after two adequate trials have failed (IPS 2017). Where a precise IPS-specific ordering of augmenting agents cannot be confirmed against the guideline rows, it is flagged under gaps rather than invented; the IPS guidelines endorse augmentation as a strategy but the exact agent hierarchy is stated less rigidly than in CANMAT.

AUGMENTING AGENT	LINE / EVIDENCE	DOSE (PER DAY)	SIGNATURE CAVEAT
Lithium	First-line; strong, classic evidence; anti-suicidal	to level 0.6 to 1.0 mmol/L	Narrow window; renal, thyroid, level monitoring
Aripiprazole	First-line adjunct (CANMAT); VAST-D positive	2 to 15 mg	Akathisia, some weight gain
Quetiapine	First-line adjunct; agent of first choice (Maudsley)	150 to 300 mg	Sedation, metabolic, QTc
Brexpiprazole	First-line adjunct (CANMAT)	1 to 3 mg	Akathisia, weight gain
Risperidone	First-line adjunct (CANMAT); second-line (BAP)	1 to 3 mg	Prolactin, EPS, metabolic
Olanzapine	Second-line adjunct	2.5 to 10 mg	Highest metabolic burden
Triiodothyronine (T3)	Second-line; older evidence, well tolerated	25 to 50 mcg	Rare thyrotoxic symptoms above 25 mcg; TSH monitoring
Mirtazapine / mianserin	Second-line adjunct antidepressant	30 to 60 mg	A combination, not a true augmentation
Esketamine (intranasal)	Add to SSRI/SNRI after two failed trials	per protocol	Dissociation, blood-pressure rise; supervised dosing

Augmentation agents ranked by guideline evidence for inadequate antidepressant response (CANMAT 2016; BAP 2015; NICE 2022; Maudsley 2021). Lithium and the atypical antipsychotics carry the best modern evidence; T3 is a genuine second-line option. Doses in the header, bare figures in the cells.

28.3 Lithium augmentation: the classic, with anti-suicidal value

The evidence base. **Lithium augmentation** is the oldest and one of the best-evidenced augmentation strategies. Recent meta-analyses show robust efficacy for lithium alongside

quetiapine and the D2 partial agonists, and one meta-analysis found lithium to be the most effective augmenter (Maudsley 2021). The classic evidence derives from older RCTs combining lithium with tricyclics, which is why CANMAT positions it as a second-line adjunct even though it works (CANMAT 2016). It remains widely underused in resistant depression.

Dose to a plasma level, not a milligram target. Lithium augmentation is most effective at a lithium plasma level of **0.6 to 1.0 mmol/L** (Maudsley 2021); the CANMAT adjunctive dose range is **600 to 1200 mg/day** titrated to that therapeutic serum level (CANMAT 2016). As with any lithium prescription, check renal and thyroid function before starting and monitor the level, taking the sample 12 hours post-dose. In India the common carbonate brands are Licab and Intalith; the deeper lithium mechanism, pharmacokinetics and monitoring are carried in the lithium notes of this block.

The anti-suicidal signal. The feature that distinguishes lithium from every other augmenter is its specific effect on suicide. A meta-analysis of clinical trials concluded that lithium reduced the risk of both attempted and completed suicide by about 80 percent in patients with mood disorders, both unipolar and bipolar (Cipriani et al. 2013, BMJ), and the protective effect holds in unipolar depression, though the mechanism is unknown (Maudsley 2021). Clinical predictors of a good augmentation response include more severe depression, psychomotor retardation, weight loss, a family history of major depression, or more than three prior episodes (Maudsley 2021). The full suicide risk assessment and safety planning sit in the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

0.6 to 1.0	600 to 1200	80
LITHIUM AUGMENTATION LEVEL (MMOL/L)	CANMAT ADJUNCTIVE LITHIUM (MG/DAY)	PERCENT LITHIUM SUICIDE-RISK REDUCTION (BIPOLAR)

GOOD TO REMEMBER

- **Lithium augmentation:** add lithium to a partially responding antidepressant; the classic, strong-evidence augmenter, dosed to a plasma level of **0.6 to 1.0 mmol/L** (Maudsley 2021).
- **Signature value:** specific anti-suicidal effect, reducing attempted and completed suicide by about 80 percent in mood disorders, unipolar and bipolar (Cipriani et al. 2013).
- **The one to hold:** check renal and thyroid function before starting; monitor the level 12 hours post-dose. Indian brand Licab or Intalith (lithium carbonate).

28.4 Atypical augmentation: the best modern evidence

The strongest recent evidence. Atypical augmentation, adding a second-generation antipsychotic to an antidepressant, has the best modern evidence base of all the augmentation strategies and is the first-line adjunct in CANMAT (CANMAT 2016). Aripiprazole (Indian brand Arip or Asprito), quetiapine (Qutipin), brexpiprazole, risperidone (Sizodon or Risdone) and olanzapine (Oleanz) are the examinable agents; the D2 partial agonists aripiprazole and brexpiprazole are used at lower doses than in bipolar disorder or schizophrenia because their tolerability at these doses is favourable (CANMAT 2016).

The head-to-head data. Aripiprazole augmentation of an SSRI or venlafaxine is more effective than adding placebo, which won it FDA approval as an adjunct; in the 1,500-patient VAST-D trial aripiprazole augmentation achieved remission somewhat more often than switching to bupropion or augmenting with bupropion (Kaplan and Sadock 2024). Adding quetiapine **150 to 300 mg/day** to a standard antidepressant improved response in registration trials (Kaplan and Sadock 2024), and the Maudsley names quetiapine as an agent of first choice for augmentation (Maudsley 2021). The trade-off is the antipsychotic side-effect burden: akathisia and some weight gain with the partial agonists, sedation and metabolic effects with quetiapine, and the highest metabolic risk with olanzapine, which is why olanzapine is downgraded to second-line (CANMAT 2016).

WORKED EXAMPLE

A patient on escitalopram 20 mg (Nexito or S-Citadep) for eight weeks is 40 percent better but not remitted, and tolerates the drug well. This is a partial response to a tolerated drug: augment rather than switch. A reasonable first-line adjunct is aripiprazole 2 to 5 mg titrated to 10 mg, or quetiapine 150 mg titrated toward 300 mg, warning the patient about akathisia (aripiprazole) or sedation and weight (quetiapine), and monitoring metabolic parameters.

GOOD TO REMEMBER

- **Aripiprazole:** D2/5-HT1A partial agonist; first-line adjunct at **2 to 15 mg/day**; VAST-D beat switching to or augmenting with bupropion; signature effect akathisia (Kaplan and Sadock 2024). Indian brand Arip or Asprito.
- **Quetiapine:** broad antagonist with noradrenergic (norquetiapine) action; first-line adjunct at **150 to 300 mg/day**; the Maudsley agent of first choice; signature effect sedation and metabolic gain (Maudsley 2021). Indian brand Qutipin.
- **Brexpiprazole:** D2 partial agonist, chemically related to aripiprazole; first-line adjunct at **1 to 3 mg/day** (CANMAT 2016; NICE 2014); signature effect akathisia and weight gain.
- **Risperidone / olanzapine:** risperidone **1 to 3 mg/day** (prolactin, EPS); olanzapine **2.5 to 10 mg/day** is second-line, downgraded for the highest metabolic burden. Indian brands Sizodon/Risdone and Oleanz.

28.5 Thyroid augmentation with T3 (liothyronine)

The strategy. **Thyroid** augmentation adds triiodothyronine (T3), the synthetic form liothyronine, to an antidepressant in a nonresponder. It is the most widely studied thyroid strategy for depression; T4 (levothyroxine) has far fewer supporting data in refractory depression and is chiefly reserved as a mood-stabiliser adjunct in rapid-cycling bipolar disorder (Kaplan and Sadock 2024). CANMAT and the BAP both list T3 as a second-line adjunct with thyroid-level monitoring (CANMAT 2016; BAP 2015).

Evidence and dose. Open and controlled studies show that roughly 50 to 60 percent of tricyclic nonresponders respond within 2 to 3 weeks of adding T3, and patients augmented with T3 were about twice as likely to respond as controls (Kaplan and Sadock 2024). In the STAR*D trial, T3 augmentation had remission rates comparable to other augmentation options with a more favourable adverse-event and dropout profile (Kaplan and Sadock 2024). T3 is given as a single

morning dose of **25 to 50 mcg** to avoid insomnia; 25 mcg/day is below the replacement dose so thyrotoxic symptoms are rare, but 50 mcg/day approaches the daily production range and can cause thyroid excess, so doses above 25 mcg are used with caution and TSH is monitored. In responders, taper and stop by 12 weeks; avoid in pregnancy (Kaplan and Sadock 2024).

INDIA

Triiodothyronine (liothyronine) is not freely available in India and is used only occasionally (KDT 2019), so T3 augmentation is a more theoretical than practical option on the ground here; levothyroxine is the freely available thyroid preparation. Know T3 as an examinable second-line augmenter but recognise the supply constraint in Indian practice.

GOOD TO REMEMBER

- **Thyroid (T3, liothyronine):** thyroid hormone receptor agonist added as a second-line augmenter; single morning dose **25 to 50 mcg/day**; about 50 to 60 percent of tricyclic nonresponders respond within 2 to 3 weeks (Kaplan and Sadock 2024).
- **Signature caveat:** 25 mcg is subreplacement and safe; above 25 mcg can cause thyrotoxic symptoms, so monitor TSH and cap short courses; taper and stop by 12 weeks; avoid in pregnancy.
- **India:** liothyronine is not freely available in India; levothyroxine is. T3 is the option to name, not usually the one to reach for locally.

28.6 Combination antidepressant strategies and the polypharmacy caution

What a combination is. A **combination** strategy adds a second antidepressant with a complementary mechanism to the first, most classically an SSRI or SNRI plus mirtazapine (Indian brand Mirtaz), or plus bupropion (Bupron). CANMAT rates adding mirtazapine or mianserin 30 to 60 mg/day as a second-line adjunct and notes this combination is superior to other antidepressant combinations (CANMAT 2016). The rationale is pharmacological: mirtazapine's alpha-2 and 5-HT2/5-HT3 antagonism complements the reuptake block of an SSRI or SNRI, and bupropion's noradrenaline-dopamine action adds a different mechanism.

The evidence is modest and never from the outset. The discipline the board tests is that two antidepressants are never combined at the initiation of treatment (CANMAT 2016). The CO-MED trial found no benefit from starting escitalopram plus bupropion, or venlafaxine plus mirtazapine, over monotherapy from the outset (Kaplan and Sadock 2024). Even as a later strategy the yields are small: in STAR*D the venlafaxine plus mirtazapine combination achieved remission in only about 10 percent, no better statistically than the MAOI tranylcypromine though far better tolerated, and bupropion or buspirone augmentation of citalopram each remitted about 30 percent (Kaplan and Sadock 2024). This is the case against irrational polypharmacy: stacking antidepressants adds interaction and adverse-effect risk for a small, evidence-thin gain, whereas a proven augmenter does better.

COMMON TRAP

Adding a second, then a third antidepressant from different classes and calling it a "combination" when there was never a partial response to build on. This is irrational polypharmacy, not augmentation: it multiplies serotonergic load (raising serotonin syndrome risk, especially near an MAOI, covered in the Perinatal/women's mental health and emergency psychiatry notes) for a remission gain of around 10 percent (Kaplan and Sadock 2024). Use a proven augmenter instead.

GOOD TO REMEMBER

- **Mirtazapine combination:** alpha-2 and 5-HT2/5-HT3 antagonist added to an SSRI/SNRI at **30 to 60 mg/day**; superior to other antidepressant combinations (CANMAT 2016); STAR*D venlafaxine plus mirtazapine remitted only about 10 percent. Indian brand Mirtaz.
- **Bupropion combination:** noradrenaline-dopamine reuptake inhibitor added for a complementary mechanism; STAR*D bupropion augmentation of citalopram remitted about 30 percent (Kaplan and Sadock 2024). Indian brand Bupron.
- **The hold:** never combine two antidepressants at the outset (CO-MED negative); combination is a later, evidence-selective move, weaker than lithium or atypical augmentation.

28.7 When to move to esketamine or ECT

Esketamine and ketamine. For depression that has failed at least two adequate antidepressant trials, intranasal esketamine (Indian brand Spravato) is added to an ongoing SSRI or SNRI, monitoring blood pressure and for dissociative effects (CANMAT 2023). Intravenous racemic ketamine is a second-line adjunct for a rapid antidepressant effect, including rapid reduction of suicidal ideation, again with blood-pressure and dissociation monitoring; both act at the NMDA receptor and work within hours rather than weeks, which is their signature advantage over conventional augmenters. Non-esketamine racemic ketamine given orally, intramuscularly or intranasally is third-line given variable protocols (CANMAT 2023). The deeper esketamine and ketamine pharmacology is carried in its own fragment; here it is the escalation pointer.

ECT. When augmentation and combination have not delivered remission, or where the depression is severe, psychotic, or carries acute suicide risk, electroconvulsive therapy is the next step and remains the most effective acute treatment for severe depression (BAP 2015); the technique sits in the ECT and neurostimulation notes. The escalation logic is that the ladder runs optimise, switch, augment or combine, then esketamine or ECT, matched to the severity, the degree of resistance and the urgency.

PEARL

Two features push you past the augmentation ladder straight toward esketamine or ECT: *urgency* (acute suicide risk, food and fluid refusal, psychotic or catatonic depression) and *rapidity of effect needed*. Conventional augmenters take 2 to 6 weeks; ECT and ketamine/esketamine act far faster, which is precisely why they earn their place when time is the constraint.

GOOD TO REMEMBER

- **Esketamine (intranasal):** NMDA-receptor antagonist added to an SSRI/SNRI after at least two failed antidepressant trials; monitor blood pressure and dissociation (CANMAT 2023). Indian brand Spravato.
- **Ketamine (IV racemic):** second-line adjunct for rapid effect and rapid reduction of suicidal ideation; acts within hours; monitor blood pressure and dissociation.
- **ECT:** the step when augmentation and combination fail or when severity or suicide risk demands the fastest, most effective acute treatment (BAP 2015); technique in the ECT and neurostimulation notes.

HOLD THIS

Augment a partial response and switch a non-response: lithium (to a level of 0.6 to 1.0 mmol/L, and anti-suicidal) and the atypical antipsychotics have the best augmentation evidence, T3 is a second-line option, and two antidepressants are never combined from the outset.

29 . Depression in the elderly

Depression in later life is a high-frequency examinable topic because it looks different from depression in the young, it is dangerous (older men carry the highest completed-suicide rate of any group), and it is under-treated precisely when it is most treatable. **Depression in the elderly** (depression in the elderly, also termed geriatric depression) is tested as a triad: recognise the atypical presentation, exclude the organic mimic, and prescribe with geriatric caution. This fragment teaches the presentation and the assessment, then the pharmacology caveats that make prescribing in the old a different discipline from prescribing in the young (Kaplan & Sadock 2024; Maudsley 2021).

The organising phrase to hold is **start low and go slow**, but the trap it breeds is under-dosing to remission-failure, so the counter-phrase is equally examinable: reach an adequate dose despite starting low. Every dose, serum figure and monitoring interval below is verified against the CANMAT guideline rows, the Maudsley and the parsed textbooks; the wider frailty and cognitive workup cross-refers to the Consultation-liaison, geriatric and transcultural psychiatry notes (CANMAT 2016; Maudsley 2021).

29.1 The presentation: somatic and cognitive, not classically sad

More somatic and cognitive complaints. The older depressed patient frequently does not say they are sad. **Geriatric depression** presents disproportionately with somatic and cognitive complaints: bodily preoccupation, pain, fatigue, weight loss, sleep disturbance, agitation, and a subjective sense of memory failure, often with the affective core masked or denied (Kaplan & Sadock 2024; Shorter Oxford 2018). Anhedonia, psychomotor retardation and loss of drive are common, guilt is often absent, and the picture can be dominated by anxiety or by hypochondriacal fixation rather than low mood.

Why this matters. Because the mood complaint is muted and the somatic and cognitive complaints are loud, **late-life** depression is repeatedly misattributed to physical illness, to normal ageing, or to early dementia, and left untreated. Screening therefore has to be active, not reactive.

RULE **In the old, look for depression behind somatic and cognitive complaints, not behind a complaint of sadness.** The affective core is often masked or denied.

29.2 Pseudodementia: the depression-related cognitive impairment

The cognitive syndrome that mimics dementia. Depression in the old can produce cognitive impairment severe enough that the patient is misclassified as demented, historically termed pseudodementia (depressive pseudodementia), better called depression-related cognitive impairment. This is the most common potentially reversible cause of an apparent dementia, and missing it is catastrophic because a treatable, potentially fatal illness is passed off as an untreatable one (Companion 2010; Tasman 2015).

Discriminating it from true dementia. The examinable discriminators favour depression: a relatively abrupt, datable onset with the patient complaining loudly of memory loss, giving "don't know" answers, showing poor effort but preserved cued recall and orientation, and a personal or family history of mood disorder. True degenerative dementia is insidious, the patient conceals or is unaware of deficits, confabulates or near-misses rather than saying "don't know", and cued recall does not rescue performance (Companion 2010; Kaplan & Sadock 2024).

FEATURE	DEPRESSIVE PSEUDODEMENTIA	DEGENERATIVE DEMENTIA
Onset	**Relatively abrupt, datable**	Insidious, undatable
Complaint of memory loss	**Emphasised by patient**	Concealed or unaware
Typical answer	"Don't know", gives up	Near-miss or confabulation
Cued recall	Improves with cueing	Does not improve
Effort	Poor effort, distressed	Effortful, unconcerned
Mood history	Personal or family mood disorder	Usually absent

The classic discriminators between depression-related cognitive impairment and a degenerative dementia (Companion 2010; Kaplan & Sadock 2024). The picture can overlap, and depression can coexist with or herald a true dementia, so a therapeutic antidepressant trial and follow-up cognition are part of the workup.

TRAP **Writing off a reversible depressive pseudodementia as an untreatable dementia.** It is the commonest reversible cause of apparent dementia; treat the depression and reassess cognition.

29.3 The vascular depression concept

Cerebrovascular disease drives some late-onset depression. The vascular depression hypothesis (Alexopoulos 1997) holds that cerebrovascular disease predisposes to, precipitates or perpetuates some **late-life** depressive syndromes. It rests on the high comorbidity of depression with vascular risk factors, the excess of depression after stroke, and the burden of deep white-matter hyperintensities on MRI in late-onset depression (Kaplan & Sadock 2024).

The recognisable phenotype. Vascular depression tends to present with psychomotor retardation, anhedonia, prominent executive dysfunction, poor insight into the illness and disability, and relatively less guilt, on a background of hypertension and other vascular risk.

White-matter and microstructural disconnection of frontostriatal circuits predicts a poorer and slower response to antidepressants, which is one reason late-life depression is given a longer time to respond (Kaplan & Sadock 2024; Maudsley 2021).

> **PEARL**
>
> Late-onset first-ever depression in an older patient with vascular risk factors, executive slowing and white-matter change on imaging is the vascular-depression picture: expect a slower antidepressant response, treat the vascular risk factors alongside the mood, and do not mistake the executive slowing for early dementia.

29.4 The higher suicide risk in older men

The lethal edge of the topic. Completed suicide rates rise with age and are highest in older men, who use more lethal methods, give fewer warnings, are more often socially isolated and bereaved, and whose depression is more likely to be missed. An older man presenting with depression, physical illness, recent loss and alcohol use is a high-lethality combination that mandates explicit risk assessment at the first contact (Kaplan & Sadock 2024). The full structured suicide risk assessment and safety planning belong to the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

RULE **Ask every depressed older patient, and especially every older man, directly about suicide.** Older men have the highest completed-suicide rate and give the fewest warnings.

29.5 Assessment: screen, exclude an organic cause and drugs, test cognition

Screen. Use a structured instrument because the presentation is atypical: the Geriatric Depression Scale (self-report, yes or no, tolerated by the frail elderly) is the standard screen, with the PHQ-9 or a HAM-D also acceptable; whatever is chosen, repeat it to track response (measurement-based care).

Exclude an organic cause and drugs. Before attributing the picture to primary depression, exclude the medical and iatrogenic mimics that are common in the old. Screen and treat comorbid hypothyroidism and B12 or folate deficiency, look for occult malignancy, anaemia, renal or hepatic failure, Parkinson's disease, and covert cerebrovascular or neurodegenerative disease. Review the drug chart for depressogenic agents (corticosteroids, beta-blockers, some centrally acting antihypertensives, opioids, interferon) and for the anticholinergic and sedative burden that itself impairs cognition and mood.

Test cognition. Perform bedside cognitive testing (for example the MMSE or MoCA) to characterise the deficit, to establish a baseline before starting a drug, and to separate depression-related impairment from an evolving dementia over follow-up. The wider frailty, functional, falls-risk and comprehensive geriatric assessment frame is the Consultation-liaison, geriatric and transcultural psychiatry notes.

29.6 The drug caveats: start low and go slow, prefer an SSRI

The prescribing frame. Ageing changes pharmacokinetics (reduced renal and hepatic clearance, altered volume of distribution, longer half-lives) and pharmacodynamics (greater receptor sensitivity), and the old are on more concurrent drugs, so the **drug caveats** in the elderly all follow from one principle: **start low** and go slow (Maudsley 2021; CANMAT 2016). Begin at about half the usual adult starting dose (for example escitalopram **5 mg/day**, sertraline **25 mg/day**) and titrate slowly, watching tolerability at each step.

Prefer an SSRI. The first-line agent in the old is a well-tolerated SSRI, and the two workhorses are sertraline (Serta or Daxid) and escitalopram (Nexito or S-Citadep), chosen for a clean interaction profile, low anticholinergic load and cardiac safety (CANMAT 2016; Maudsley 2021). The specific geriatric hazards to manage are hyponatraemia, falls, the anticholinergic burden, drug interactions and the citalopram and escitalopram QTc cap.

CAVEAT IN THE ELDERLY	WHAT TO DO	WHY
Start low, go slow	Half the adult start (escitalopram 5, sertraline 25), titrate slowly	Reduced clearance, greater sensitivity, polypharmacy
Prefer an SSRI	Sertraline or escitalopram first-line	Clean interactions, low anticholinergic load, cardiac safety
Hyponatraemia (SIADH)	Check sodium at baseline and 2 to 4 weeks; recheck if drowsy, confused or falling	SSRIs cause SIADH; risk highest in the old, in women, on diuretics
Falls	Review at each visit; minimise sedatives and orthostatic-load drugs	Antidepressants raise fall and fracture risk in the old
Anticholinergic burden	Prefer low-anticholinergic agents; avoid the TCAs	Cumulative anticholinergic load worsens cognition and delirium
Drug interactions	Prefer escitalopram or sertraline over fluoxetine, paroxetine, fluvoxamine	The clean SSRIs are weak CYP inhibitors; the others are potent
Citalopram and escitalopram QTc cap	Citalopram maximum 20, escitalopram maximum 10, in the elderly	Dose-related QTc prolongation; caps are lower in over-65s
Avoid the TCAs	Not first-line; use only where unavoidable	Anticholinergic, orthostatic hypotension, cardiotoxic, lethal in overdose

The verified geriatric drug caveats (Maudsley 2021; CANMAT 2016). The three highlighted rows are the highest-yield: start low and go slow, watch hyponatraemia, and respect the citalopram and escitalopram QTc dose caps in the elderly.

The citalopram and escitalopram QTc cap. Citalopram and escitalopram cause a dose-related QTc prolongation and are the most cardiotoxic of the SSRIs (albeit modestly so), which is why the licensed maximum is reduced in the old: in the elderly, citalopram is capped at **20 mg/day** and escitalopram at **10 mg/day** (Maudsley 2021). Where QTc is a concern, sertraline is the cleaner cardiac choice.

TRAP **Titrating citalopram or escitalopram past the reduced elderly ceiling, or missing an SSRI-induced hyponatraemia.** Respect the QTc caps and check sodium at baseline and 2 to 4 weeks.

5	20	10
ESCITALOPRAM START IN ELDERLY (MG/DAY)	CITALOPRAM ELDERLY MAX (MG/DAY)	ESCITALOPRAM ELDERLY MAX (MG/DAY)

INDIA

In Indian practice the outpatient workhorses are the cheap generic SSRIs, led by sertraline (Serta or Daxid) and escitalopram (Nexito or S-Citadep), which suits a largely out-of-pocket, medically complex elderly population. The TCAs (amitriptyline as Tryptomer, imipramine as Depsonil) remain cheap and available and are still reached for, but their anticholinergic, orthostatic and cardiotoxic load makes them a poor first choice in the old; keep them off first line and prefer the clean SSRI.

29.7 Treatment: adequate dose despite starting low, and a longer wait

Reach an adequate dose. Starting low does not mean staying low. The commonest management error in the old is to under-dose out of caution and leave the patient at a homeopathic, sub-therapeutic dose that never reaches remission. Titrate up to a full adequate antidepressant dose as tolerated (for example sertraline toward **50 to 200 mg/day**, escitalopram toward the elderly ceiling of **10 mg/day**), and judge the trial only once an adequate dose has been given for an adequate time (CANMAT 2016; BAP 2015).

Allow a longer time to respond. In older people the antidepressant response may take longer, so allow more time before declaring failure, and continue treatment after remission because continued antidepressant treatment roughly halves the relapse rate (BAP 2015). For treatment resistance in the old, lithium augmentation has the best evidence, with about half of patients responding to a switch or augmentation (BAP 2015); the deep next-step ladder is the treatment-resistance topic.

The guideline position. At guideline level, CANMAT and the SSRI-first frame apply to the old as to the young, individualised to the patient with a lower start, and the **Indian Psychiatric Society** Clinical Practice Guidelines likewise place the SSRIs first-line for late-life depression with a reduced starting dose and slow titration (CANMAT 2016; IPS 2018). Beyond this SSRI-first-with-caution position, a finer elderly-specific IPS dose could not be confirmed from the parsed source and is flagged rather than invented.

RULE **Start low and go slow, but still reach an adequate dose in the elderly.** Judge the trial only at a full dose given for an adequate (and, in the old, longer) time.

29.8 ECT: a good response in severe or psychotic late-life depression

ECT works well in the old. Severe, psychotic, food-and-fluid-refusing or actively suicidal late-life depression responds well to electroconvulsive therapy, and age is not a contraindication; the elderly, particularly those with psychotic depression, are among the best responders to ECT

(Kaplan & Sadock 2024). It is the treatment of choice where a rapid, definitive response is needed, where the patient is not eating or drinking, or where drug options are exhausted or poorly tolerated. The technique, the anaesthetic considerations and the cognitive-side-effect management belong to the ECT and neurostimulation notes.

GOOD TO REMEMBER

- **Presentation:** somatic and cognitive complaints with the affective core masked; screen actively.
- **Pseudodementia:** depression-related cognitive impairment is the commonest reversible cause of apparent dementia; abrupt onset, "don't know" answers, cued recall improves; treat and reassess.
- **Vascular depression:** late-onset, executive slowing, vascular risk, white-matter change; slower antidepressant response.
- **Suicide:** highest completed-suicide rate is in older men; ask directly at first contact.
- **Sertraline (Serta or Daxid):** SSRI, clean and cardiac-safe, first-line in the old; start **25 mg/day**, target **50 to 200 mg/day**.
- **Escitalopram (Nexito or S-Citadep):** SSRI, clean, dose-related QTc; start **5 mg/day**, elderly maximum **10 mg/day**.
- **Citalopram:** SSRI, dose-related QTc; elderly maximum **20 mg/day**.
- **Drug caveats:** start low and go slow, prefer an SSRI, watch hyponatraemia and falls, mind the anticholinergic burden and interactions, respect the QTc caps, avoid the TCAs.
- **ECT:** a good response in severe or psychotic late-life depression; age is not a contraindication.

MNEMONIC

SAD-SAFE

The elderly prescribing caveats: **S**tart low, **A**dequate dose still reached, **D**rug interactions minimised; **S**odium (hyponatraemia) watched, **A**nticholinergic burden avoided (no TCAs), **F**alls guarded against, **E**CG-aware QTc caps on citalopram and escitalopram.

HOLD THIS

In late-life depression, start low and go slow with a clean SSRI (sertraline or escitalopram) but still reach an adequate dose over a longer trial, watching hyponatraemia, falls, anticholinergic burden and the elderly QTc caps of citalopram 20 mg and escitalopram 10 mg, and remember ECT works well in severe or psychotic late-life depression.

30 . Suicide risk in mood disorders: the pharmacological angle

Why this closes the mood block. Mood disorders carry the highest **suicide risk** in psychiatry, and the drugs a resident chooses either lower that risk, do nothing, or add a lethal means to a suicidal patient's cupboard. This note teaches only the **mood-specific** risk picture and the **pharmacological** angle: which agent has genuine anti-suicidal evidence, which drug not to hand over in bulk, and what to counsel and monitor at the start of treatment. The full clinical **suicide risk** assessment, the stratification interview and the safety-planning method are taught separately in the Somatic-symptom, sexual, impulse-control disorders and suicide notes; the acute serotonin-syndrome and NMS frame sits in the Perinatal/women's mental health and emergency psychiatry notes.

Exam framing is blunt: examiners want the one psychotropic with the strongest mortality evidence (lithium), the psychotic-overlap agent (clozapine), the early-treatment activation caveat, and the overdose-safety principle (never a large tricyclic antidepressant supply to a suicidal patient). Get those four and you have the topic.

30.1 The burden: where the risk concentrates

Highest risk in psychiatry. Lifetime suicide in bipolar disorder is estimated at around 15 percent, among the highest of any psychiatric condition (Maudsley 2021). The risk is not spread evenly across the illness course: it clusters in **severe depression**, in **mixed states**, in the **depressive phase** of bipolar illness, in the **early bipolar illness** (the first years after diagnosis, the first decade), and in the **early recovery phase** as psychomotor retardation lifts before mood and hopelessness do. Recurrent unipolar depression carries a substantial risk too. The mood-specific message: a mixed, agitated or early-course presentation is a higher-risk presentation.

~15	mixed / depressive	first years
LIFETIME SUICIDE IN BIPOLAR (PERCENT)	HIGHEST-RISK MOOD PHASES	EARLY ILLNESS, HIGHEST RISK WINDOW

RULE **Phase drives risk.** Severe depression, mixed states, early bipolar illness and the early recovery phase are the danger windows, screen and act hardest there.

30.2 Lithium: the anti-suicidal drug

The strongest evidence of any psychotropic. The **lithium anti-suicidal** effect is the single most important pharmacological fact in this topic. A meta-analysis of randomised trials concluded that lithium reduced the risk of both attempted and completed suicide by roughly 80 percent in patients with mood disorders, and lithium-treated patients are less likely to complete suicide than patients on other mood stabilisers (Cipriani 2005, Maudsley 2021). This is an effect on suicide and on **all-cause mortality**, not merely on mood-episode counts, and it holds in bipolar illness and appears to protect in unipolar depression too (mechanism unknown). Even naturally occurring lithium in drinking water is inversely related to population suicide rates. No antidepressant, anticonvulsant or antipsychotic has evidence of this strength for reducing suicide in mood disorders.

The clinical consequence. The anti-suicidal effect is a positive reason to weigh lithium in a high-risk bipolar or recurrent depressive patient, over an anticonvulsant stabiliser that lacks the mortality evidence. It runs partly independent of mood-episode prevention, so a patient at high suicide risk gains from lithium even where another agent might control episodes. Note the plasma targets from the mood-stabiliser topic: minimum effective prophylaxis around **0.4 mmol/L**, optimal prophylaxis **0.6 to 0.8 mmol/L**, and the CANMAT maintenance range **0.6 to 1.0 mEq/L** (Maudsley 2021, CANMAT 2018). Full initiation, monitoring and toxicity are taught in the lithium notes; here the point is the anti-suicidal indication.

~80	0.6 to 0.8	0.6 to 1.0
SUICIDE RISK REDUCTION ON LITHIUM (PERCENT)	OPTIMAL PROPHYLAXIS LITHIUM (MMOL/L)	CANMAT MAINTENANCE LITHIUM (MEQ/L)

RULE **Lithium reduces suicide.** In a high-risk bipolar or recurrent depressive patient, weigh lithium specifically for its anti-suicidal and all-cause mortality benefit.

PEARL

The anti-suicidal benefit is why an examiner asks "what would you add for a bipolar patient with repeated attempts" and expects lithium, not a switch to valproate. The evidence base is Cipriani 2005: attempted and completed suicide both cut by about 80 percent.

30.3 Clozapine: the psychotic-overlap anti-suicidal agent

The second drug with real anti-suicidal evidence. Where a mood disorder overlaps with a psychotic illness, or in schizophrenia and schizoaffective disorder, clozapine has a specific anti-suicidal effect. Roughly 5 to 10 percent of patients with schizophrenia eventually complete suicide, and clozapine treatment markedly reduces the suicide rate, demonstrated in the international suicide prevention trial (InterSePT, Meltzer 2003). Clozapine is therefore the antipsychotic to consider for suicidality in the psychotic overlap, remembering its haematological and cardiac monitoring burden (the deep antipsychotic pharmacology sits in the Schizophrenia: management, antipsychotics and adverse effects notes). Lithium remains the answer for the pure mood disorder; clozapine is the answer where a chronic psychotic illness drives the risk.

GOOD TO REMEMBER

- **Lithium:** the strongest anti-suicidal and all-cause mortality evidence of any psychotropic in mood disorders, roughly 80 percent risk reduction (Cipriani 2005); weigh it in high-risk bipolar or recurrent depression, prophylaxis target 0.6 to 0.8 mmol/L.
- **Clozapine:** specific anti-suicidal effect in schizophrenia and the psychotic overlap (InterSePT, Meltzer 2003); the antipsychotic to consider when a chronic psychotic illness drives suicidality, with its neutropenia and cardiac monitoring.

30.4 Early antidepressant activation and the paediatric suicidality signal

Counsel and monitor at the start. Antidepressant treatment has been associated with an increased risk of suicidal thoughts and acts in the early weeks, particularly in children, adolescents and young adults, the basis of the regulatory black-box warning (Maudsley 2021). Two mood-specific mechanisms matter: early **activation** or agitation before mood lifts, and the recovery-phase energising of a still-hopeless patient. The relative risk is raised above placebo in the young, but the **absolute risk stays very small**, and the most effective way to prevent suicide in depression is to treat the depression effectively. The practical rule is to warn the patient (and family for a young person) about early activation, tell them how to seek help, and review early. NICE advises review within 1 week if the person is aged 18 to 25 or there is particular concern about suicide risk, and within 2 weeks otherwise (NICE 2022). Rates also rise when antidepressants are stopped, so apply the same care on discontinuation.

The paediatric point. In children and adolescents the small antidepressant suicidality signal is why guidelines restrict prescribing largely to SSRIs, and why fluoxetine is the best-evidenced first

choice in this age group (BAP 2015). The signal is a reason to counsel and monitor, not a reason to withhold treatment from a depressed adolescent who needs it.

1 week	**first weeks**
REVIEW IF AGE 18 TO 25 OR HIGH SUICIDE CONCERN	PEAK ACTIVATION / SUICIDALITY WINDOW

TRAP **Starting and walking away.** Not counselling about early activation and not reviewing a young patient within a week or two of starting an antidepressant, when the suicidality signal peaks.

WORKED EXAMPLE

A 19-year-old with moderate depression is started on fluoxetine. You counsel him and a parent that the first two weeks can bring restlessness or worsened thoughts before improvement, agree a help-seeking plan, and book review at one week because he is under 25. This is the correct application of the early-activation and paediatric-signal rules: treat, but counsel and monitor early.

GOOD TO REMEMBER

- **Early antidepressant activation:** raised suicidality signal in the first weeks in the young (black-box), absolute risk small; the discriminator is treat-but-counsel, warn on activation and review within 1 week if aged 18 to 25 or high concern (NICE 2022).
- **Paediatric first choice:** restrict to SSRIs, fluoxetine best evidenced; the first management step is family counselling plus early review, not withholding treatment (BAP 2015).

30.5 Overdose safety: never a large TCA supply

The drug is the means. A suicidal mood-disorder patient may take a deliberate overdose of whatever you prescribe, so overdose lethality is a prescribing decision, not an afterthought. Guidelines advise choosing antidepressants that are **better tolerated and safer in overdose**: SSRIs and other newer antidepressants are first-line, partly for this reason (BAP 2015). The tricyclic antidepressant class is the danger. A tricyclic overdose of about 10 times the daily dose can be fatal, death is usually from **cardiac toxicity** (type I antiarrhythmic membrane effect, QRS widening, arrhythmia), and TCA mortality per ingestion runs roughly 25-fold higher than SSRIs (Kaplan and Sadock 2024). Amitriptyline (Tryptomer) is among the leading single-drug causes of death by overdose. Therefore **avoid a large TCA supply** in a suicidal or high-risk patient: if a TCA is genuinely needed, dispense small quantities, and prefer the safer-in-overdose SSRI wherever the choice is open. A pre-existing QTc of 450 ms or more is a contraindication to TCA treatment (Kaplan and Sadock 2024).

AGENT / CLASS	OVERDOSE PROFILE	SUICIDAL-PATIENT IMPLICATION
SSRIs, newer antidepressants	**relatively safe in overdose**	first-line choice on safety grounds (BAP 2015)
Tricyclic antidepressants (amitriptyline, Tryptomer)	**fatal at ~10x daily dose; cardiotoxic; ~25x SSRI mortality**	avoid a large supply; dispense small quantities; QTc >=450 ms contraindicates
Lithium (Licab, Intalith)	narrow therapeutic index, toxic > 1.5 mEq/L	anti-suicidal, but a means in overdose: dispense with care and monitor levels

Overdose lethality as a prescribing lens for the suicidal mood-disorder patient.

TRAP **Handing over a cardiotoxic overdose.** Giving a suicidal patient a large quantity of a cardiotoxic tricyclic when a safer-in-overdose SSRI would do.

INDIA

Amitriptyline (Tryptomer) and imipramine (Depsonil) are cheap, ubiquitous and often the default in general and non-psychiatric Indian practice for depression and pain. That very availability is the hazard in a suicidal patient: lead with an SSRI (escitalopram, Nexito or S-Citadep; sertraline, Serta or Daxid; fluoxetine, Fludac) and, if a TCA is unavoidable, dispense small quantities and enlist family means-restriction. Lithium carbonate (Licab, Intalith) is inexpensive and widely available, so the anti-suicidal option is realistic in Indian practice.

GOOD TO REMEMBER

- **Tricyclic antidepressants (amitriptyline, Tryptomer):** cardiotoxic membrane effect, fatal at roughly 10x the daily dose, about 25-fold the SSRI overdose mortality; never a large supply to a suicidal patient, QTc >=450 ms contraindicates (Kaplan and Sadock 2024).
- **Safer-in-overdose choice:** SSRIs and newer antidepressants are first-line partly because they are safer in overdose (BAP 2015); prefer them wherever the clinical choice is open.

MNEMONIC

LiCK the risk: Lithium, Clozapine, Keep TCAs small

The three pharmacological moves against suicide in mood disorders: Lithium (strongest anti-suicidal, weigh it in high-risk mood disorder), Clozapine (anti-suicidal in the psychotic overlap), and Keep TCA supply small (safer-in-overdose SSRI first, small quantities if a TCA is used).

GOOD TO REMEMBER

- **Where the risk sits:** highest in severe depression, mixed states, early bipolar illness and the early recovery phase; lifetime bipolar suicide around 15 percent.
- **Lithium is anti-suicidal:** the strongest evidence of any psychotropic (roughly 80 percent risk reduction, plus all-cause mortality); weigh it in high-risk bipolar or recurrent depression.
- **Clozapine:** anti-suicidal in the psychotic overlap (InterSePT).
- **Avoid a large TCA supply, counsel early-activation:** lead with a safer-in-overdose SSRI, dispense TCAs in small quantities, warn about early antidepressant activation and review the young patient early.

HOLD THIS

Of every psychotropic, lithium has the strongest evidence for reducing suicide and all-cause mortality in mood disorders, so weigh it in a high-risk patient; and never hand a suicidal patient a large supply of a cardiotoxic tricyclic when a safer-in-overdose SSRI will do.

31 · ECT in mood disorders: indications and place

Why this matters. This topic is about the **place in algorithm**, not the technique. Electroconvulsive therapy (ECT) is the single most effective and most rapid antidepressant treatment available, and the examiner wants to know exactly where it sits: which mood presentations make it a first-line emergency option, where it otherwise slots in behind the drugs, and the one selection trade-off (a powerful, fast response against a transient memory cost). The engineering of the seizure, the electrode placement, the electrical dosing and the anaesthetic all belong to the ECT and neurostimulation notes; what is held here is the selection logic in mood disorder.

Exam framing. The high-yield answer is the list of **indications for ect** in mood disorder and its **place in algorithm**. ECT is a first-line option in the mood emergencies (a life-threatening or immediately dangerous depression or mania) and otherwise sits after adequate pharmacological trials as a treatment for drug-refractory illness. The syndromal criteria and the guideline-anchored drug plan are in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; the full suicide-risk assessment is in the Somatic-symptom, sexual, impulse-control disorders and suicide notes; the acute-emergency and perinatal framing is in the Perinatal/women's mental health and emergency psychiatry notes.

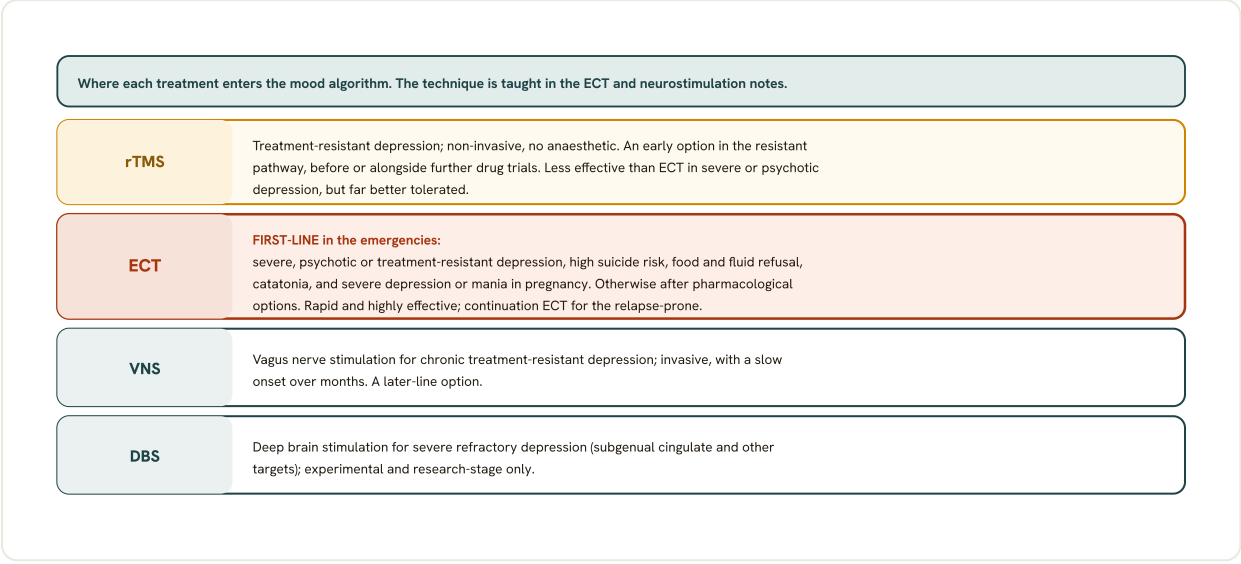

Fig 12.12 Where ECT and neuromodulation enter the mood-disorder algorithm. ECT is first-line in the emergencies (severe, psychotic or treatment-resistant depression, high suicide risk, food refusal, catatonia, pregnancy) and highly effective; rTMS is an early, non-invasive option in the treatment-resistant pathway; VNS is a slow, invasive later-line option; and DBS remains experimental. The technique of each is taught in the ECT and neurostimulation notes.

31.1 ect in mood disorders: strong efficacy and rapid onset

The property that drives every indication is that ECT is both highly effective and fast. In severe depressive illness the response rate is on the order of **70%** for real ECT against roughly **40%** for simulated (sham) treatment, giving a number-needed-to-treat of about **3 to 4** (UK ECT Review Group 2003; Shorter Oxford 2018), and under naturalistic conditions the response rate approaches **80%** (Companion 2010). In head-to-head comparisons ECT is at least as effective as, and works faster than, tricyclic antidepressants and MAOIs in severely depressed inpatients (UK ECT Review Group 2003; Shorter Oxford 2018). This combination of high response and rapid onset is precisely why ECT is reached for early whenever bringing about improvement quickly is essential rather than optional.

RULE **Use ECT mainly when it is essential to improve the patient quickly.** The strongest indications are an immediate high suicide risk, depressive stupor, and danger to physical health from food and fluid refusal (Shorter Oxford 2018).

31.2 The indications for ECT in mood disorder

The examiner wants the indication list held as a set. Combining the standard textbook indications (Shorter Oxford 2018) with the NICE and Royal College criteria, ECT in mood disorder is indicated for:

Severe depression needing a rapid response

severe depressive illness where quick improvement is essential, or when other treatments have failed (NICE 2009)

Psychotic depression

severe depression with mood-congruent delusions or hallucinations, one of the classic and best-responding ECT indications (Maudsley 2021)

Treatment-resistant depression

depression that has not responded to adequate trials of antidepressant drugs, with or without psychotic features (Shorter Oxford 2018)

High suicide risk or food-and-fluid refusal

an immediate high risk of suicide, or life-threatening refusal of food and fluids on the basis of extreme retardation or nihilism (RCPsych 2005)

Catatonia

severe non-organic catatonia, particularly with stupor and poor oral intake or drug non-response (NICE 2003)

Severe or treatment-resistant mania

a prolonged or severe manic episode, or mania unresponsive to pharmacotherapy or with life-threatening exhaustion (NICE 2003; IPS 2017)

Pregnancy where drugs are undesirable

severe depression or mania in pregnancy where medication is undesirable or has failed (CANMAT 2016; IPS 2017)

Across these, the unifying theme is severity plus urgency: the depressive picture that carries marked weight loss, early-morning waking, retardation and delusions is the one that responds best, and delusions and retardation are the features that most distinguish patients who respond to real ECT from those who respond to placebo (UK ECT Review Group 2003; Shorter Oxford 2018). Suicidal risk is named as the first and most important indication in the Indian standard text.

INDICATION IN MOOD DISORDER	CLINICAL TRIGGER	PLACE
Severe depression, rapid response needed	Life-threatening or where speed is essential	**First-line in the emergency**
Psychotic depression	Depression with delusions or hallucinations	**Early; strong ECT indication**
High suicide risk	Immediate, active suicidality	**First-line in the emergency**
Food and fluid refusal	Stupor, retardation, nihilism, dehydration	**First-line in the emergency**
Catatonia	Stupor, mutism, poor intake, drug non-response	**First-line / early**
Treatment-resistant depression	Failed adequate drug trials	After pharmacotherapy
Severe or treatment-resistant mania	Prolonged, exhausting, or drug-refractory mania	Emergency to after-drugs
Pregnancy, drugs undesirable	Severe perinatal depression or mania	**First-line where drugs avoided**

The mood-disorder indications for ECT and where each sits (Shorter Oxford 2018; NICE 2003/2009; IPS 2017; CANMAT 2016).

31.3 Its place in algorithm: first-line in the emergency, otherwise after drugs

The **place in algorithm** has two settings. In the mood emergencies, an immediate high suicide risk, depressive stupor with food and fluid refusal, life-threatening catatonia, and severe or exhausting mania, ECT is a **first-line option** that should be brought in without waiting for drugs to work or fail (Shorter Oxford 2018; IPS 2017). Outside those emergencies, ECT sits **after pharmacological options**: NICE positions it as a treatment for severe depression that is life-threatening or where a rapid response is required, or when other treatments have failed, and it is not used routinely for moderate depression (NICE 2009). For ordinary treatment-resistant depression, BAP places ECT among the next-step options for patients who have not responded to other treatments (BAP 2015). The Indian Psychiatric Society position is explicit that **modified ECT is first-line** for severe mania with food or fluid refusal or exhaustion, psychotic mania unresponsive to pharmacotherapy, severe bipolar depression with suicidality or stupor, mixed states with active suicidality, and catatonia, and that ECT should otherwise be considered for acute mania, mixed episodes or bipolar depression that is severe, refractory, suicidal, catatonic, psychotic, or in pregnancy (IPS 2017).

TRAP **Do not delay ECT through a sequence of failed drug trials in a life-threatening depression.** In a patient who is actively suicidal, in depressive stupor, or refusing food and fluids, ECT is first-line, not a last resort after every drug has failed.

31.4 Continuation and maintenance ECT for the relapse-prone

Response to an acute ECT course is high, but relapse rates after it are also high, especially in patients refractory to drugs (Shorter Oxford 2018). The answer for relapse-prone patients is **continuation and maintenance ECT**: after the acute course brings remission, further ECT sessions are given at spacing intervals (for example weekly, then fortnightly, then monthly) to hold the gain, usually alongside continuation pharmacotherapy. In psychotic depression, one small randomised controlled trial found maintenance ECT plus nortriptyline superior to nortriptyline alone at **2 years**, and ECT may be more protective against relapse in psychotic than in non-psychotic depression (Maudsley 2021). Maintenance ECT is therefore the tool reserved for patients who respond well to acute ECT but relapse rapidly on drugs alone. The dosing and scheduling of the maintenance course itself are in the ECT and neurostimulation notes.

31.5 Practical points relevant to choice: efficacy, memory, consent

Three practical facts drive the decision to use ECT and the conversation with the patient. First, **efficacy**: ECT is the most effective and most rapid treatment for severe mood disorder, and bilateral ECT is moderately more effective than unilateral (Companion 2010). Second, the **transient cognitive adverse effect**: both anterograde and retrograde memory disturbances are common, but they are usually mild and recovery occurs within about **1 to 6 months** of treatment, and unilateral ECT causes much less memory impairment than bilateral. This memory cost is the main reason patients hesitate and the main thing to weigh against ECT's speed and power. Third, **consent or the legal pathway**: ECT is always given after informed consent from the patient, or, where the patient lacks capacity, through the relevant legal pathway and local

statutory procedure. The technique, the electrode placement, the electrical dosing and the anaesthetic detail are all cross-referred to the ECT and neurostimulation notes.

70 vs 40	3 to 4	1 to 6
RESPONSE, REAL VS SHAM ECT (%)	NUMBER-NEEDED-TO-TREAT, ECT IN DEPRESSION	MEMORY RECOVERY AFTER ECT (MONTHS)

The three numbers a resident should hold: efficacy against sham, NNT, and time to memory recovery (UK ECT Review Group 2003).

INDIA

ECT is widely available and heavily used across Indian psychiatry, and the norm in current Indian practice is **modified ECT**, that is, ECT given under general anaesthesia with a muscle relaxant (usually succinylcholine) and oxygenation. Direct (unmodified) ECT, given without anaesthesia or muscle relaxation, is no longer standard and carries a fracture and dislocation risk; the Mental Healthcare Act 2017 restricts unmodified ECT. The Indian Psychiatric Society makes modified ECT first-line for the mania and bipolar-depression emergencies listed above (IPS 2017). The anaesthetic and modified-ECT technique itself is in the ECT and neurostimulation notes.

PEARL

The single feature that best predicts a good ECT response in depression is the presence of **psychotic features (delusions)**, followed by psychomotor retardation; these are the very features that separate real-ECT responders from placebo responders (UK ECT Review Group 2003).

TRAP **Do not quote a permanent memory loss as a reason to withhold ECT from a dying patient.** The memory effect is usually mild and recovers within 1 to 6 months, and unilateral placement minimises it; in a life-threatening depression the balance clearly favours treating.

HOLD THIS

ECT is the fastest and most effective treatment in severe mood disorder and is first-line, not last resort, in the emergencies: severe/psychotic depression, high suicide risk, food and fluid refusal, catatonia, severe or refractory mania, and severe mood illness in pregnancy where drugs are undesirable.

MNEMONIC

SPRINT

Suicide risk high, **P**sychotic depression, **R**esistant (treatment-resistant), **I**ntake refused (food and fluids), **N**ot-eating catatonia, **T**oo-severe mania or pregnancy where drugs are undesirable: the mood indications where ECT is reached for early.

GOOD TO REMEMBER

- **Indications for ect (mood):** severe depression needing rapid response, psychotic depression, treatment-resistant depression, high suicide risk or food-and-fluid refusal, catatonia, severe or treatment-resistant mania, and severe depression or mania in pregnancy where drugs are undesirable.
- **Place in algorithm:** first-line in the emergencies (high suicide risk, stupor, food/fluid refusal, catatonia, exhausting mania); otherwise after adequate pharmacotherapy for drug-refractory illness (NICE 2009; IPS 2017).
- **Efficacy and onset:** the most effective and most rapid treatment for severe mood disorder; about 70% real vs 40% sham response, NNT 3 to 4, roughly 80% naturalistic response (UK ECT Review Group 2003; Companion 2010).
- **Adverse effect to hold:** transient anterograde and retrograde memory disturbance, usually mild, recovering within 1 to 6 months; unilateral placement causes less.
- **Continuation/maintenance ECT:** spaced sessions after the acute course for relapse-prone patients; maintenance ECT plus nortriptyline beat nortriptyline alone at 2 years in psychotic depression (Maudsley 2021).
- **Consent and legality:** given after informed consent or through the legal pathway; the norm in Indian practice is modified ECT under anaesthesia with a muscle relaxant. Technique is elsewhere.

32 · Neuromodulation in depression

Why this matters. This topic is about the **place in algorithm**, not the technique. The examiner wants to know where each device sits in the treatment-resistant depression pathway: which is licensed and offered early, which is invasive and held back, and which is still research only. The engineering of coils, currents and electrodes belongs to the ECT and neurostimulation notes; what is held here is the selection logic. Three devices matter, in descending order of how routinely they are used: rtms (repetitive transcranial magnetic stimulation), vns (vagus nerve stimulation) and dbs (deep brain stimulation).

The frame is neuromodulation as a step in the pathway after antidepressants have underperformed. rTMS is a genuine guideline-supported option that can be brought in early; VNS and DBS are progressively more invasive and progressively less established, so they sit later in the ladder or outside routine practice altogether. The full technique of each device, the coil physics, the stimulation parameters and the surgery, is cross-referred to the ECT and neurostimulation notes; the wider acute-emergency and perinatal framing is in the Perinatal/women's mental health and emergency psychiatry notes.

32.1 rTMS: the licensed, non-invasive, early option in treatment-resistant depression

rtms is a non-invasive brain-stimulation technique delivered awake in an outpatient chair with no anaesthetic and no seizure induction, which is exactly why it earns an early place in the algorithm. CANMAT recommends rTMS as a **first-line** neuromodulation option for major depressive disorder that has not responded to at least one adequate antidepressant trial (CANMAT 2016), so it is a first-line-to-early option in the treatment-resistant pathway and can be offered before or alongside further drug trials rather than being reserved for the very end. The standard protocol is high-frequency stimulation (**at least 5 Hz**) over the left dorsolateral prefrontal cortex, or low-frequency stimulation (**1 Hz or less**) over the right dorsolateral prefrontal cortex, delivered **20 to**

40 min per session, daily on 5 days a week for **4 to 6 weeks** (CANMAT 2016). It is non-invasive, well tolerated, and its commonest adverse effects are scalp discomfort and headache, with a rare seizure risk; this good tolerability, alongside the absence of anaesthetic and cognitive load, is the selling point that puts it ahead of the more invasive options.

RULE **rTMS is an evidence-based option in treatment-resistant depression, offered before or alongside further drug trials.** It is non-invasive, needs no anaesthetic, and is a first-line neuromodulation choice, not a last resort.

32.2 Theta-burst variants shorten the session

The practical evolution of rTMS is **theta-burst stimulation**. Intermittent theta-burst stimulation (iTBS) is offered as a first-line rTMS protocol that is non-inferior to conventional high-frequency rTMS but delivers the treatment in a much shorter session, on the order of **about 3 min** rather than 20 to 40 min (CANMAT 2023). Because each session is so short, accelerated protocols that pack several sessions into each day can compress a whole course into as little as **5 days** (CANMAT 2023). The theta-burst variants therefore make rTMS faster and more scalable without losing efficacy, which further supports its early place in the algorithm.

at least 5	20 to 40	about 3
HIGH-FREQUENCY RTMS, LEFT DLPFC (HZ)	STANDARD RTMS SESSION (MIN)	ITBS SESSION (MIN)

Verified rTMS parameters and the theta-burst session time (CANMAT 2023).

32.3 rTMS relative to ECT: less effective in severe or psychotic depression, better tolerated

The comparison the examiner wants is rTMS against ECT. For treatment-resistant patients the brain-stimulation alternatives to ECT, including rTMS, have **lower efficacy than traditional ECT**, so ECT remains the more powerful treatment for severe, psychotic or highly refractory depression (Kaplan & Sadock 2024). What rTMS offers instead is far better tolerability: it is non-invasive, needs no anaesthetic, and carries none of the anaesthetic and memory burden that makes many patients reluctant to accept ECT (Kaplan & Sadock 2024). The trade-off is the whole point of its place in algorithm, rTMS is the less effective but far better tolerated option, so it is preferred earlier and in less severe treatment-resistant pictures, while ECT is chosen when depth of response matters most, particularly in severe or psychotic depression. The device physics and the ECT technique itself are in the ECT and neurostimulation notes.

GOOD TO REMEMBER

- **rTMS mechanism:** non-invasive focal magnetic stimulation of the dorsolateral prefrontal cortex, awake, no anaesthetic, no induced seizure; signature adverse effects are scalp discomfort and headache with a rare seizure risk.
- **rTMS place:** CANMAT first-line neuromodulation for treatment-resistant depression; the one indication to hold is treatment-resistant depression that has failed at least one adequate antidepressant trial, offered before or alongside further drug trials.
- **rTMS vs ECT:** less effective than ECT in severe or psychotic depression, but better tolerated; the discriminator is tolerability (no anaesthetic, no memory load) traded against ECT's greater efficacy.
- **iTBS:** first-line theta-burst rTMS protocol, non-inferior to high-frequency rTMS, session about 3 min; the number to hold is that accelerated courses can be as short as 5 days.

32.4 VNS and DBS: the later-line and the experimental options

vns is an **invasive, later-line** option. It requires a surgically implanted pulse generator, with an electrode wrapped around the left cervical vagus nerve and the battery placed subcutaneously in the left chest wall (Kaplan & Sadock 2024). Its defining problem for the algorithm is a **slow onset**: only about **15%** of patients respond in the first 3 months, rising to roughly **30%** by 12 months, and response rates are lower than with ECT (Kaplan & Sadock 2024). VNS is approved as a long-term adjunctive treatment for chronic or recurrent treatment-resistant depression and is therefore worth considering only when patients have already failed less invasive treatments, so it sits late in the ladder rather than early (Kaplan & Sadock 2024).

dbs is **experimental** and research-stage for severe refractory depression. It involves surgical implantation of stimulating electrodes into a deep target, most studied at the **subgenual cingulate** cortex, with other targets under investigation (Kaplan & Sadock 2024; New Oxford 2020). The evidence base is still unsettled: small open-label and prospective studies of subgenual DBS were encouraging, but a large industry-supported controlled trial was stopped early on a futility analysis, and DBS for depression is not an approved routine treatment (Kaplan & Sadock 2024). Most of these newer neurostimulation therapies remain in an experimental phase of development (Kaplan & Sadock 2024), so DBS belongs to research protocols and last-resort refractory cases, not the routine algorithm. The neurosurgical technique and target physiology are in the ECT and neurostimulation notes.

DEVICE	INVASIVENESS	PLACE IN ALGORITHM	KEY CAVEAT
rTMS	Non-invasive, no anaesthetic	**First-line-to-early in treatment-resistant depression**	Less effective than ECT in severe/psychotic depression, better tolerated
VNS	Invasive, implanted generator	Later-line, chronic treatment-resistant depression	**Slow onset (about 15% at 3 months, about 30% at 12 months)**
DBS	Invasive, deep electrodes	Experimental, research-stage only	**Subgenual cingulate and other targets; controlled trial stopped for futility**

Place in algorithm of the three neuromodulation options in depression (CANMAT 2016; Kaplan & Sadock 2024; New Oxford 2020).

TRAP **Do not offer DBS or VNS as routine options.** DBS is experimental and research-stage; VNS is an invasive, slow-onset, later-line adjunct, not a mainstream step, and neither substitutes for rTMS or ECT in the ordinary pathway.

Guideline level. CANMAT names rTMS a first-line neuromodulation treatment for treatment-resistant depression and offers iTBS as a first-line rTMS protocol, with ECT reserved for severe, psychotic or refractory illness (CANMAT 2023). NICE similarly supports rTMS for depression as a recognised non-invasive option while positioning ECT for severe or life-threatening depression (NICE 2014). The Indian Psychiatric Society (IPS guidelines, Gautam et al. depression CPG) endorses ECT for severe and treatment-resistant depression, but a specific IPS position on rTMS, VNS and DBS in depression could not be confirmed against the parsed library and is flagged rather than invented; the IPS stance is named here and left as could-not-be-confirmed.

HOLD THIS

rTMS is a first-line, non-invasive, no-anaesthetic option in treatment-resistant depression (less effective than ECT but better tolerated); VNS is invasive, later-line and slow; DBS is experimental only.

GOOD TO REMEMBER

- **rtms:** non-invasive, no anaesthetic, first-line neuromodulation for treatment-resistant depression; hold high-frequency left DLPFC or low-frequency right DLPFC, 20 to 40 min per session, iTBS about 3 min.
- **vns:** invasive implanted generator on the left vagus nerve, later-line adjunct for chronic treatment-resistant depression; signature caveat is slow onset (about 15% respond at 3 months, about 30% at 12 months).
- **dbs:** invasive deep electrodes, experimental and research-stage for severe refractory depression; the target to hold is the subgenual cingulate, and a large controlled trial was stopped for futility.

33 . Psychotherapies for depression: the place

In a drug-focused chapter the drug is not the whole answer, and the board rewards the resident who knows exactly where a talking treatment sits in the depression algorithm. **Psychotherapy for depression** is not a soft alternative offered when medication fails; for mild-to-moderate illness a structured **first-line psychological** treatment is a genuine first-line option in its own right, and for moderate-to-severe illness combined treatment (medication plus psychotherapy) outperforms either alone (CANMAT 2016; Shorter Oxford 2018). This topic teaches the evidence-based *place* of psychotherapy for depression, the guideline-anchored algorithm; the *technique* of each therapy is cross-referred to the Psychotherapies, clinical assessment, MSE and nosology notes.

Ground the place in the guidelines. Lead with **CANMAT**: the Canadian Network for Mood and Anxiety Treatments names cognitive behavioural therapy, interpersonal therapy and behavioural activation as first-line psychological treatments for acute major depression, and directs that where feasible a psychological treatment (CBT or IPT) be combined with an antidepressant

because combined treatment is superior to either alone (CANMAT 2016). The place is then confirmed by the Indian Psychiatric Society, NICE and the BAP. Every first-line status below is verified against the CANMAT guideline rows and the Shorter Oxford (CANMAT 2016; Shorter Oxford 2018).

33.1 The three first-line psychological therapies

CBT, IPT and behavioural activation. The examinable list of **first-line psychological** treatments for acute major depression is three structured, time-limited, evidence-based therapies (CANMAT 2016). **cbt** (cognitive behaviour therapy) targets the depressive cognitive triad and maladaptive behaviour; **ipt** (interpersonal therapy) works on grief, role transitions, role disputes and interpersonal deficits; and **behavioural activation** uses scheduled activity and operant principles to re-engage the patient with rewarding behaviour. Head-to-head, none of the three is convincingly superior to the others, and each is as effective as pharmacotherapy in moderately depressed outpatients (Shorter Oxford 2018).

Each is first-line, alone, in mild-to-moderate depression. For a mild-to-moderate depressive episode, any one of CBT, IPT or behavioural activation may be offered as a stand-alone first-line treatment without medication (CANMAT 2016; Shorter Oxford 2018). Specific psychotherapies are more effective than treatment-as-usual in mild-to-moderate depression, particularly in primary care, and perform as well as drug treatment in the moderately depressed (Shorter Oxford 2018).

CBT

Cognitive behaviour therapy: restructures the depressive cognitive triad and reactivates behaviour; first-line for acute depression.

IPT

Interpersonal therapy: targets grief, role transitions, role disputes and interpersonal deficits; first-line for acute depression.

Behavioural activation

Scheduled, reward-linked activity using operant principles; first-line for acute depression and simple to train.

RULE **Offer an evidence-based psychotherapy first-line in mild-to-moderate depression, and combine it with medication in severe depression.** CBT, IPT and behavioural activation are all first-line for acute major depression.

TRAP **Treating every depression with medication alone when a psychological therapy is indicated.** In mild-to-moderate illness a structured psychotherapy alone is first-line; in severe illness the correct move is to add it, not to omit it.

33.2 The place in the algorithm: alone, combined, or for relapse prevention

Alone in mild-to-moderate; combined in moderate-to-severe. The place is a two-step rule. In a mild-to-moderate episode, offer a first-line psychological therapy (CBT, IPT or behavioural activation) as a first-line option alone, matching the efficacy of an antidepressant (CANMAT

2016; Shorter Oxford 2018). In more severe or recurrent illness, add the psychotherapy to medication rather than relying on either alone, because combined treatment is superior to pharmacotherapy alone for many patients (CANMAT 2016; Shorter Oxford 2018).

And for relapse prevention. After the acute phase, psychotherapy has a maintenance place: CANMAT names CBT and mindfulness-based cognitive therapy (MBCT) as first-line psychological treatments to prevent relapse (CANMAT 2016). Mindfulness-based cognitive therapy is the paradigm example, delivered in remission to patients with recurrent depression to reduce the relapse rate. Add adjunctive CBT to ongoing antidepressant treatment as a recognised next-step option in the patient who has not fully responded (BAP 2015).

ILLNESS SEVERITY / PHASE	THE PLACE OF PSYCHOTHERAPY	EVIDENCE-BASED OPTION
Mild-to-moderate, acute	**First-line, alone (no medication needed)**	CBT or IPT or behavioural activation
Moderate-to-severe, acute	**Add to medication (combined is superior)**	Antidepressant plus CBT or IPT
Partial response to an antidepressant	Add as a next-step to ongoing medication	Adjunctive CBT
Remission, recurrent illness	First-line for relapse prevention	CBT or mindfulness-based cognitive therapy (MBCT)

The place of psychotherapy for depression across severity and phase, verified against CANMAT (CANMAT 2016) and the BAP (BAP 2015): alone in mild-to-moderate illness, added to medication in more severe or recurrent illness, and first-line for relapse prevention.

WORKED EXAMPLE

A 30-year-old teacher presents with a first, mild-to-moderate depressive episode without suicidality, and asks to avoid tablets. Rather than defaulting to an SSRI, offer a first-line psychological therapy alone: a course of CBT, IPT or behavioural activation is a legitimate first-line treatment here and matches antidepressant efficacy in this severity band (CANMAT 2016). Contrast a 45-year-old with a severe, recurrent episode: here the correct move is combined treatment, an antidepressant plus CBT or IPT, because combined treatment is superior to medication alone, followed by CBT or MBCT in remission to prevent the next relapse.

33.3 Where the guidelines agree: CANMAT, the IPS, NICE and the BAP

CANMAT (lead). Offer CBT, interpersonal therapy or behavioural activation as first-line psychological treatments for acute major depression; where feasible combine a psychological treatment (CBT or IPT) with an antidepressant, as combined treatment is superior to either alone; and for maintenance offer CBT or MBCT first-line to prevent relapse (CANMAT 2016).

The Indian Psychiatric Society. The **indian psychiatric society** Clinical Practice Guidelines for depression (Gautam et al.) endorse structured psychotherapy, chiefly CBT and IPT, as a treatment for depression, offered alone in milder illness and combined with pharmacotherapy in moderate-to-severe illness (IPS 2017). The precise severity thresholds and the exact list of first-line psychotherapies in the current **ips guidelines** could not be confirmed from the parsed

library and are flagged under gaps rather than invented; the IPS is named and the position stated only to the level that is verified.

NICE and the BAP. NICE runs a stepped-care model: for less severe depression it prefers the least intrusive psychological options first (guided self-help, group CBT, group behavioural activation) and does not routinely start an antidepressant first-line, reserving combined psychotherapy-plus-antidepressant for more severe depression (NICE 2022). The BAP concurs that adding CBT to ongoing antidepressant treatment is a valid next-step option when response is incomplete (BAP 2015).

INDIA

In Indian practice the access barrier is real: trained CBT and IPT therapists are concentrated in cities and the private sector, so the guideline-ideal of psychotherapy alone for mild-to-moderate depression is often not deliverable, and a low-cost generic SSRI becomes the pragmatic first step. Behavioural activation is the most transportable of the three because, unlike CBT, therapist training in its techniques is claimed to be simple and quickly accomplished (Shorter Oxford 2018), which makes it well suited to task-shifted, non-specialist delivery in resource-limited settings.

33.4 The technique lives elsewhere; what to hold here

Cross-reference, do not duplicate. The actual technique of each therapy, the CBT thought record and cognitive triad, the IPT interpersonal inventory and four problem areas, and the behavioural activation activity schedule, is taught in the Psychotherapies, clinical assessment, MSE and nosology notes. For these notes, hold only the *place*: which therapies are first-line, when they stand alone, when they combine with medication, and where they prevent relapse.

The one line that answers the viva. When the examiner asks "what is the place of psychotherapy in depression?", answer with the two-step rule plus the maintenance rider: first-line alone in mild-to-moderate illness, added to medication in moderate-to-severe illness because combined treatment is superior, and CBT or MBCT for relapse prevention (CANMAT 2016).

3	Combined	MBCT
FIRST-LINE PSYCHOTHERAPIES (CBT, IPT, BA)	SUPERIOR TO MEDICATION ALONE (MODERATE-TO-SEVERE)	FIRST-LINE FOR RELAPSE PREVENTION

MNEMONIC

CIB, then M

CBT, **I**PT, **B**ehavioural activation are the three first-line psychotherapies for acute depression; **M**BCT (with CBT) is first-line for relapse prevention. Alone in mild-to-moderate, combined in severe.

GOOD TO REMEMBER

- **CBT, IPT and behavioural activation:** the three first-line psychological treatments for acute major depression; each may be offered alone in mild-to-moderate illness (CANMAT 2016).
- **Alone vs combined:** first-line alone in mild-to-moderate depression, added to medication in moderate-to-severe or recurrent illness because combined treatment is superior to either alone.
- **Relapse prevention:** CBT or mindfulness-based cognitive therapy (MBCT) is first-line to prevent relapse after remission (CANMAT 2016).
- **The technique:** the technique of each is cross-referred to the Psychotherapies, clinical assessment, MSE and nosology notes; hold only the place here.

HOLD THIS

Offer an evidence-based psychotherapy (CBT, IPT or behavioural activation) first-line and alone in mild-to-moderate depression, add it to medication in moderate-to-severe or recurrent depression because combined treatment is superior to either alone, and use CBT or mindfulness-based cognitive therapy for relapse prevention; the technique is taught elsewhere.

34 . Managing bipolar depression

The depressive pole is where most of the illness burden of bipolar disorder sits, and it is the phase the board most wants you to manage **differently** from unipolar depression. The single organising idea is a warning: the drugs that break a unipolar depression are not the drugs you reach for here, because an **antidepressant** given without anti-manic cover can flip a depressed bipolar patient into mania. This is a management topic, so the marks are in the guideline-anchored selection, the first-line agents, and the recognition and handling of a treatment-emergent switch, not in a recitation of side effects. The deep per-drug pharmacology (lithium, valproate, lamotrigine, quetiapine, the antidepressant classes) is owned by the earlier topics in these notes; this topic carries which agent, which phase, which line, and the manic-switch rule.

Lead the answer with CANMAT (Yatham 2018, the CANMAT/ISBD 2018 guideline), then give the Indian Psychiatric Society position, now carried by the 2025 IPS bipolar update (IPS 2025, Menon et al., which supersedes the 2017 Shah guideline), and the NICE and BAP positions. Every first-line agent, dose, serum level and switch fact below is verified against the CANMAT/ISBD guideline, the Indian Psychiatric Society clinical practice guideline, the Maudsley Prescribing Guidelines, Stahl and Kaplan and Sadock (Yatham 2018; Menon 2025; Shah 2017; Maudsley 2021; Stahl 2021; Kaplan and Sadock 2024). The full syndrome and the wider guideline-anchored management PLAN sit in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; the receptor pharmacology and CYP metabolism behind agent selection sit in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

34.1 Why bipolar depression is managed differently

It is not unipolar depression with a manic history bolted on. Episodes of bipolar depression, compared with unipolar depression, tend to be more rapid in onset, more frequent, shorter, and more likely to carry reverse neurovegetative features such as hypersomnia and hyperphagia and, at times, psychotic features (Maudsley 2021). Two facts drive the whole management plan. First,

the antidepressant response is different: unopposed antidepressants are relatively less effective (perhaps not effective at all) in bipolar than in unipolar depression (Maudsley 2021). Second, and decisively, giving an antidepressant alone risks a **manic switch** and destabilisation of the illness course. So the agents of choice are anti-manic mood stabilisers and specific atypical antipsychotics, not antidepressants.

RULE **Treat bipolar depression with quetiapine, lurasidone, lamotrigine or lithium, not an antidepressant alone.** The first-line agents are anti-manic mood stabilisers and specific atypicals, chosen to cover the depressive pole without flipping the patient into mania (Yatham 2018).

34.2 CANMAT: the first-line agents for bipolar I depression

Lead with CANMAT. For acute bipolar I depression the CANMAT/ISBD guideline names the **first-line** options as: quetiapine (Qutipin) monotherapy; lurasidone monotherapy or adjunctive to lithium or divalproex; lithium (Licab, Intalith) monotherapy; lamotrigine (Lamitor, Lametec) monotherapy or adjunctive; and lurasidone or adjunctive lamotrigine (Yatham 2018). The verified target doses are quetiapine to about **300 mg/day** (the licence and practice range for bipolar depression is **300 to 600 mg/day**), lurasidone **20 to 120 mg/day**, lithium to an acute serum level of **0.8 to 1.2 mEq/L**, and lamotrigine slowly titrated from 25 mg to a minimum of **200 mg/day** (Yatham 2018; Maudsley 2021). One mechanistic pearl the board likes: the antidepressant efficacy of these antipsychotics in bipolar depression is not a dopamine-blocking effect, since aripiprazole and most pure D2 blockers do not work in acute bipolar depression (Maudsley 2021).

The second-line rapid-response pair. When a rapid response is desirable, CANMAT places cariprazine and the **olanzapine-fluoxetine combination** as second-line for acute bipolar I depression (Yatham 2018). The olanzapine-fluoxetine combination (the fixed-dose OFC, olanzapine 6 or 12 mg with fluoxetine 25 or 50 mg) is genuinely effective and is the strongest single piece of evidence for any antidepressant helping in bipolar depression, but note the antidepressant is always paired with an anti-manic partner, never given alone (Maudsley 2021).

TRAP **Naming aripiprazole as a first-line agent for bipolar depression.** Aripiprazole works for mania and manic-relapse prevention but does not have efficacy in acute bipolar depression; the depression antipsychotics are quetiapine, lurasidone, cariprazine and olanzapine (Maudsley 2021).

34.3 NICE and the Indian Psychiatric Society position

NICE. To treat bipolar depression NICE recommends fluoxetine combined with olanzapine, or quetiapine on its own; if the patient prefers, consider olanzapine without fluoxetine, or lamotrigine on its own (NICE 2014; Maudsley 2021). NICE therefore treats lamotrigine as second-line, whereas BAP has lamotrigine and lurasidone as first-line options with the caveat that a mood stabiliser or antipsychotic will still be needed to protect against mania in the longer term (Goodwin 2016).

India. The **Indian Psychiatric Society** clinical practice guideline (IPS 2017, Shah et al.) for acute bipolar depression names quetiapine (**300 to 600 mg**) or the olanzapine-plus-fluoxetine combination as first-line, with lithium and lamotrigine as alternatives, particularly where the antipsychotic burden is undesirable. Crucially the IPS guidelines state that antidepressant monotherapy is contraindicated, and that antidepressants should not be used in rapid cycling or mixed episodes; if an antidepressant is used at all, paroxetine is avoided and bupropion is preferred (Shah 2017). This maps cleanly onto CANMAT, and the indian psychiatric society (IPS) position, as set out in the ips guidelines, is the guideline most likely to be named in an Indian postgraduate examination.

INDIA

The IPS bipolar guideline has been updated: the 2025 IPS bipolar update (IPS 2025, Menon et al., Indian J Psychiatry 2026;68:8-43) supersedes the 2017 Shah guideline and now names the first-line options for acute bipolar depression as the olanzapine-fluoxetine combination (Oleanz plus Fludac), quetiapine (Qutipin), lurasidone and cariprazine, with lithium (Licab, Intalith) and lamotrigine (Lamitor, Lametec) as further options. It keeps the core rule that antidepressant monotherapy or unopposed antidepressant use is not recommended in bipolar depression; where an antidepressant is judged necessary, an SSRI or bupropion (Bupron) is preferred, always under anti-manic cover. All first-line agents are inexpensive Indian brands.

34.4 The first-line bipolar-depression agents at a glance

The first-line and rapid-response agents assemble into one table. Learn the highlighted cell in each row: it is the fact the examiner tests, and it is the line or the caveat, not the side-effect list (which is owned by the per-drug topics).

300 to 600	20 to 120	0.8 to 1.2	200
QUETIAPINE BIPOLAR DEPRESSION (MG/DAY)	LURASIDONE RANGE (MG/DAY)	ACUTE LITHIUM LEVEL (MEQ/L)	LAMOTRIGINE MINIMUM TARGET (MG/DAY)

AGENT (INDIAN BRAND)	CANMAT LINE	DOSE / TARGET	THE BOARD-CRITICAL POINT
Quetiapine (Qutipin)	First-line monotherapy	300 mg/day target (300 to 600 mg/day range)	**Broadest agent: works across mania, bipolar depression and maintenance; not associated with switching to mania (Maudsley 2021)**
Lurasidone	First-line, monotherapy or adjunctive to lithium/divalproex	20 to 120 mg/day	**Metabolically favourable (minimal weight gain); signature adverse effects are nausea and akathisia; take with food (Maudsley 2021)**

AGENT (INDIAN BRAND)	CANMAT LINE	DOSE / TARGET	THE BOARD-CRITICAL POINT
Lithium (Licab, Intalith)	First-line monotherapy	Acute serum level 0.8 to 1.2 mEq/L	**The only agent with specific anti-suicide evidence; acute-depression efficacy is modest but relapse prevention is strong (Maudsley 2021)**
Lamotrigine (Lamitor, Lametec)	First-line, monotherapy or adjunctive	Slow titration 25 to a minimum of 200 mg/day	**Best for the depressive pole and prevention, weak against acute mania; does not induce switching or rapid cycling; slow titration for rash (Yatham 2018)**
Olanzapine-fluoxetine combination (Oleanz + Fludac)	Second-line (for rapid response)	Olanzapine 6 or 12 mg with fluoxetine 25 or 50 mg/day	**Strongest evidence for an antidepressant helping in bipolar depression, but the antidepressant is always paired with olanzapine, never alone (Maudsley 2021)**
Cariprazine	Second-line (for rapid response)	Per licence	**Efficacious in bipolar depression with low weight-gain propensity; smaller effect size than lurasidone (Maudsley 2021)**

First-line and second-line agents for acute bipolar I depression, CANMAT lead (Yatham 2018) with doses verified against the Maudsley Prescribing Guidelines. Indian brands lead each row, this being the chapter where brands belong. Highlighted cells are the examinable line-or-caveat, not the side-effect profile.

WORKED EXAMPLE

A woman with bipolar I disorder, well on maintenance divalproex, presents with a breakthrough depressive episode. The correct next step is not to add an SSRI: add or switch to a first-line bipolar-depression agent, for example lurasidone adjunctive to the divalproex, or quetiapine, or add lamotrigine (titrated at half the usual rate because valproate doubles the lamotrigine level, targeting about 100 mg/day). Reaching for an antidepressant alone here risks a manic switch and rapid cycling, and the antidepressant is relatively less effective in this setting anyway (Yatham 2018; Maudsley 2021).

34.5 The antidepressant-in-bipolar question

The default is: do not. An **antidepressant in bipolar** depression is avoided as monotherapy because of two linked hazards: the risk of a **manic switch** (a flip into hypomania or mania) and the risk of destabilising the illness into rapid cycling (Yatham 2018; Kaplan and Sadock 2024).

Unopposed antidepressants (that is, without mood-stabiliser protection) are generally to be avoided in bipolar depression, especially in bipolar I disorder (Maudsley 2021). If an antidepressant is used at all it is only **with an anti-manic mood stabiliser** as cover, it is **avoided in mixed features and in rapid cycling**, and the adjunctive evidence is weak. Indeed, controlled data suggest a mood stabiliser alone is about as effective as a mood-stabiliser-plus-antidepressant combination (Maudsley 2021).

The nuances the board rewards. Not all antidepressants carry equal switch risk. Venlafaxine (an SNRI) appears more likely than an SSRI or bupropion to induce a switch to mania (Leverich 2006; Maudsley 2021). Tricyclics and MAOIs are usually best avoided. Where an antidepressant is judged necessary, an SSRI (or bupropion) under mood-stabiliser cover is preferred, and the IPS specifically prefers bupropion and avoids paroxetine (Shah 2017). Some guidelines allow a more permissive use of antidepressants in bipolar II depression, where sertraline does not appear to increase switch rates, but bipolar I depression is where the prohibition is firmest (Altshuler 2017; Maudsley 2021).

TRAP **Giving antidepressant monotherapy in a bipolar depression and precipitating a switch or rapid cycling.** An antidepressant is only ever added under anti-manic cover, is avoided in mixed features and rapid cycling, and is never the first-line agent (Yatham 2018; Shah 2017).

34.6 Treatment-emergent mania: recognise it and manage it

What it is. **Treatment-emergent mania** (the treatment-emergent mania of the guidelines) is a switch into hypomania or mania that appears on treatment, classically driven by an antidepressant, sometimes within the first weeks of exposure. In a patient being treated for what looked like a unipolar depression, a treatment-emergent affective switch on antidepressant monotherapy reclassifies the diagnosis as bipolar disorder (Shah 2017; Kaplan and Sadock 2024). Recognise it as the emergence of elevated or irritable mood, reduced need for sleep, increased energy, pressured speech, overactivity or risk-taking against a background of antidepressant use (or a dose increase).

How to manage it. The steps are, in order: **stop (or reduce) the antidepressant**; **optimise the mood stabiliser** (raise lithium or valproate towards the anti-manic range, or add or up-titrate an **atypical antipsychotic**); and reassess the diagnosis and future prophylaxis. In a first-episode manic presentation, discontinue any antidepressant and reassess the diagnosis before starting antimanic agents (Yatham 2018; Shah 2017). One safety point sits alongside this: abruptly adding a serotonergic antidepressant to an existing regimen, or the accidental co-prescription during a switch, can precipitate serotonin syndrome, whose acute management is owned by the Perinatal/women's mental health and emergency psychiatry notes.

RULE **Treatment-emergent switch: stop the antidepressant, optimise the stabiliser, add or up-titrate an atypical.** A switch on antidepressant monotherapy reclassifies the depression as bipolar (Shah 2017).

PEARL

The manic switch is not just an adverse event, it is a diagnostic event. A first manic or hypomanic episode emerging on an antidepressant given for depression converts the working diagnosis from unipolar depression to bipolar disorder and changes the whole prophylaxis plan towards a mood stabiliser, not an antidepressant (Kaplan and Sadock 2024).

MNEMONIC

QuLLL

The four verified CANMAT first-line agents for bipolar depression, in one handle: **Qu**etiapine, **L**urasidone, **L**ithium, **L**amotrigine (Yatham 2018). If you can name only four things in the exam, name these four, and add that an antidepressant is never given alone.

HOLD THIS

Bipolar depression is treated first-line with quetiapine, lurasidone, lithium or lamotrigine (and the olanzapine-fluoxetine combination or cariprazine second-line for rapid response), and never with an antidepressant alone, because unopposed antidepressants risk a manic switch and rapid cycling.

GOOD TO REMEMBER

- **Quetiapine (Qutipin):** multi-acting atypical; the broadest bipolar agent (mania, depression, maintenance); first-line monotherapy for bipolar depression at **300 to 600 mg/day**; not associated with switching (Yatham 2018; Maudsley 2021).
- **Lurasidone:** atypical, metabolically favourable; first-line for bipolar depression, monotherapy or adjunctive to lithium/divalproex, **20 to 120 mg/day**; signature adverse effects nausea and akathisia; take with food (Yatham 2018; Maudsley 2021).
- **Lithium (Licab, Intalith):** first-line monotherapy; acute-depression target serum level **0.8 to 1.2 mEq/L**; the one agent with specific anti-suicide evidence; the full monitoring and toxicity detail is owned by the lithium topics in these notes (Yatham 2018).
- **Lamotrigine (Lamitor, Lametec):** best for the depressive pole and prevention, weak against acute mania; does not induce switching or rapid cycling; slow titration 25 to a minimum of **200 mg/day** for rash; halve the schedule with valproate (Yatham 2018; Stahl 2021).
- **Olanzapine-fluoxetine combination (Oleanz + Fludac):** second-line for rapid response; olanzapine 6 or 12 mg with fluoxetine 25 or 50 mg/day; strongest evidence for an antidepressant helping in bipolar depression, but the antidepressant is always paired, never alone (Yatham 2018; Maudsley 2021).
- **Antidepressant in bipolar:** never monotherapy; only with an anti-manic stabiliser; avoided in mixed features and rapid cycling; venlafaxine carries the higher switch risk, bupropion is preferred over paroxetine (Shah 2017; Leverich 2006).
- **Treatment-emergent mania (the discriminator and first step):** a switch into hypomania or mania on treatment; a switch on antidepressant monotherapy reclassifies the diagnosis as bipolar; first step is to stop the antidepressant, then optimise the stabiliser or add an atypical (Shah 2017; Yatham 2018).

35 . Managing bipolar mixed episodes

A **mixed state** is where depressive and manic or hypomanic symptoms co-occur, and it is the presentation that most often gets the pharmacology wrong. The examiner is testing one insight: a **mixed state does not behave like either pure pole,** it carries the highest suicide risk in the bipolar course, and the drug you reach for a "mixed depression" is not an antidepressant. This is a dedicated management topic. The mixed-episode and mixed-features SYNDROME, its criteria and its neurobiology, is owned by the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; this topic carries the guideline-anchored pharmacotherapy.

Lead the answer with CANMAT (CANMAT 2018, Yatham et al.), then give the Indian Psychiatric Society position, now carried by the 2025 IPS bipolar update (IPS 2025, Menon et al., which supersedes the 2017 Grover and Avasthi guideline and names divalproex first-line and carbamazepine second-line for acute mixed episodes), and the BAP (BAP 2016) and NICE (NICE 2014) positions. The agents with the best mixed-state evidence are the atypicals asenapine, cariprazine, olanzapine and aripiprazole, and valproate (divalproex); lithium is relatively weaker for classic mixed and dysphoric presentations; and antidepressants are avoided.

35.1 The principle: a mixed state responds differently from a pure pole

Define it first. A **mixed state** spans two things the exam wants named distinctly: a full **mixed episode** (co-occurring depressive and manic or hypomanic symptoms meeting threshold, the classic dysphoric mania and agitated mixed depression) and the milder DSM-5 **mixed features** specifier attached to a manic, hypomanic or depressive episode (Kaplan and Sadock 2024). Dysphoric mania is manic overactivity, pressured speech and reduced sleep carried on a dysphorically excited, irritable, anxious mood, often with agitation and suicidal ideation (Kaplan and Sadock 2024). **Why it matters.** The mixed state carries a **high suicide risk**, among the highest of any phase of the illness, because manic-level drive and energy sit on top of depressive despair (IPS 2017). It responds differently from a pure manic or a pure depressive episode, so it is managed as its own entity, not as "the mania" or "the depression" that happens to be present.

RULE **Treat the mixed state as its own high-suicide-risk entity.** It is not a pure pole with extra symptoms, and it does not respond like one.

35.2 Lithium is relatively weaker in classic mixed and dysphoric presentations

The single most tested selection fact: **lithium underperforms in mixed and dysphoric presentations.** Kaplan and Sadock is explicit that patients with concomitant depressive symptoms, that is dysphoric mania, respond more poorly to lithium, as do those with a high cumulative episode burden; and in subtype analyses the irritable manic subtype responded significantly better to divalproex than to lithium, while the classic euphoric manic subtype responded similarly to both (Kaplan and Sadock 2024). Lithium keeps its place as the anti-suicide agent of the illness and a first-line antimanic and maintenance drug, but it is not the drug you build a classic mixed or dysphoric-manic plan around. Its deep pharmacology, dosing and monitoring are owned by the lithium topics in these notes.

TRAP **Reaching first for lithium in a dysphoric mania.** Dysphoric and irritable presentations respond more poorly to lithium and better to divalproex or an atypical (Kaplan and Sadock 2024).

35.3 Valproate (divalproex): the mixed-state mood stabiliser of choice

Mechanism. Valproate broadens GABAergic inhibitory tone, blocks voltage-sensitive sodium channels and modulates T-type calcium currents, damping the excitatory drive that fuels the manic and agitated components of a mixed state (Stahl 2021). **Where it wins.** Valproate and divalproex have specific evidence in dysphoric mania, mixed affective episodes and rapid cycling, and outperform lithium in irritable and dysphoric presentations (Kaplan and Sadock 2024). CANMAT lists divalproex as a first-line monotherapy for acute mania (which includes mixed presentations) at a serum level of **350 to 700 micromol/L** (50 to 100 microg/mL) (CANMAT 2018). **Signature cautions.** Weight gain, tremor, hair loss, thrombocytopenia and hepatotoxicity; and the hard rule that it is **teratogenic** (neural tube defects, neurodevelopmental harm) and is not started in a woman of childbearing potential without a pregnancy-prevention programme (NICE 2014; IPS 2017). The full valproate pharmacology and teratogenicity are owned by the valproate topic in these notes.

GOOD TO REMEMBER

- **Valproate (divalproex; Valprol or Encorate, divalproex Valance or Divaa):** broadens GABA and blocks sodium channels; specific evidence in dysphoric mania, mixed and rapid-cycling states; acute-mania serum target **50 to 100 microg/mL** (CANMAT 2018). Signature: teratogenic, avoid in women of childbearing potential.

35.4 Asenapine: a first-line atypical for mixed states

Mechanism. Asenapine is a high-affinity 5-HT2A and D2 antagonist with a broad serotonergic, dopaminergic and adrenergic binding profile structurally related to mirtazapine (Stahl 2021; Kaplan and Sadock 2024). **Where it wins.** CANMAT names asenapine among the first-line agents for acute mania (alone or in combination), and it has a specific licensed indication for acute manic and mixed episodes of bipolar I disorder, making it one of the go-to atypicals when the presentation is mixed (CANMAT 2018; Stahl 2021). **Dose.** It must be given **sublingually** (about 35 percent bioavailable sublingually, under 2 percent if swallowed), typically **5 to 10 mg twice daily** (10 to 20 mg/day) for mania, with no food or drink for 10 minutes after dosing (Stahl 2021). **Signature effects.** Sublingual oral hypoaesthesia, sedation and a moderate metabolic burden.

GOOD TO REMEMBER

- **Asenapine:** sublingual 5-HT2A/D2 antagonist; first-line for acute manic and mixed episodes of bipolar I; dose **5 to 10 mg twice daily** sublingually, no food or drink for 10 minutes; signature is sublingual oral hypoaesthesia. Indian brand could not be confirmed from the library; prescribe by generic name.

35.5 Cariprazine: the atypical that spans the mixed spectrum

Mechanism. Cariprazine is a D3-preferring D2 and D3 partial agonist with 5-HT1A partial agonism; the D2 blockade in limbic areas treats mania and psychosis while D3 partial agonism in the midbrain enhances prefrontal dopamine to address the depressive and cognitive components, so it works across the bipolar mood spectrum in one agent (Stahl 2021). **Where it wins.** CANMAT names cariprazine among the first-line agents for acute mania, and it carries evidence across manic, mixed and bipolar-depressive presentations, which is exactly the coverage a mixed state needs (CANMAT 2018; Stahl 2021). **Dose.** Acute bipolar mania is **3 to 6 mg/day** once daily, titrated from 1.5 mg; Stahl notes the more manic the features, the higher the dose within range (Stahl 2021). **Signature effect.** Akathisia, which is dose-related and reduced by slower titration.

GOOD TO REMEMBER

- **Cariprazine:** D3-preferring D2/D3 partial agonist that spans the mixed spectrum in one agent; first-line acute mania at **3 to 6 mg/day**; signature is akathisia. Indian brand could not be confirmed from the library; prescribe by generic name.

35.6 Olanzapine and aripiprazole: the other evidenced atypicals

Two further atypicals round out the mixed-state toolkit. Olanzapine (Oleanz) is a first-line antimanic with evidence in mixed episodes, useful where rapid control of agitation is the priority, at the cost of the heaviest metabolic burden of the group, so weight, glucose and lipids are monitored (CANMAT 2018). Aripiprazole is a D2 and D3 partial agonist and 5-HT1A partial agonist, a first-line antimanic with a favourable metabolic profile, again with mixed-episode data (CANMAT 2018; Stahl 2021). CANMAT also endorses combination therapy, an atypical (quetiapine, aripiprazole, risperidone or asenapine) added to lithium or divalproex, as a first-line option for acute mania, especially in severe presentations, and that combination logic carries into severe mixed states (CANMAT 2018). The deep antipsychotic pharmacology and the shared adverse-effect set are owned by the Schizophrenia: management, antipsychotics and adverse effects notes.

GOOD TO REMEMBER

- **Olanzapine (Oleanz):** first-line antimanic with mixed-episode evidence; signature is the heaviest metabolic burden of the group; monitor weight, fasting glucose and lipids (CANMAT 2018).
- **Aripiprazole:** D2/D3 and 5-HT1A partial agonist; first-line antimanic, mixed-episode data, favourable metabolic profile; signature is akathisia (CANMAT 2018).

35.7 The critical caution: antidepressants are avoided in the mixed state

This is the crux of the topic. **Antidepressants are avoided** in a mixed state: they worsen the manic pole and drive the agitation, so a mixed "depression" is not treated with an antidepressant, and any antidepressant already running is discontinued (IPS 2017; CANMAT 2018). The IPS guidelines are unusually direct here: do not use antidepressants as monotherapy in bipolar depression, nor in rapid cycling disorder or mixed episodes; if an antidepressant is unavoidable, avoid paroxetine and prefer bupropion, and never as monotherapy (IPS 2017). CANMAT

reserves antidepressants for pure, non-mixed bipolar depression only, and instructs that antidepressants be discontinued in patients presenting with mania (CANMAT 2018). The mechanistic reason is simple: adding a pro-monoaminergic drug to a state that already contains manic activation pours fuel on the exact symptoms driving the risk.

RULE **Treat a mixed state with valproate or an atypical (asenapine, cariprazine) and stop antidepressants.** The mixed pole is managed from the manic side, not the depressive side.

TRAP **Treating the depressive symptoms of a mixed episode with an antidepressant.** It worsens the manic pole and the agitation and raises the suicide risk; discontinue any antidepressant instead.

35.8 ECT for severe or refractory mixed episodes

When the mixed episode is severe, treatment-refractory, or dominated by active suicidality, catatonia or psychosis, ECT is the answer. The IPS names modified ECT as first-line for mixed states with active suicidality and endorses ECT for a mixed episode that is severe, refractory, associated with suicidality, catatonia or psychosis, or occurring in pregnancy (IPS 2017). It is the fastest route to control when pharmacotherapy is too slow or has failed, and it side-steps the antidepressant problem entirely because it is not pole-specific. The ECT technique, electrode placement and cognitive monitoring are owned by the ECT and neurostimulation notes; the wider acute-emergency and perinatal frame is owned by the Perinatal/women's mental health and emergency psychiatry notes.

GOOD TO REMEMBER

- **ECT in a mixed state:** first-line for severe or refractory mixed episodes and for mixed states with active suicidality, catatonia, psychosis or in pregnancy; not pole-specific, so it avoids the antidepressant problem (IPS 2017).

35.9 The mixed-state options at a glance

The whole selection assembles into one table. Learn the highlighted cell in each row, and learn that antidepressants are the row you do not add.

50 to 100	5 to 10	3 to 6
ACUTE-MANIA VALPROATE (MICROG/ML)	ASENAPINE PER DOSE, TWICE DAILY (MG)	CARIPRAZINE ACUTE MANIA (MG/DAY)

OPTION	LINE AND ROLE	DOSE OR SERUM TARGET	SIGNATURE CAUTION
Valproate (divalproex)	**First-line mood stabiliser for dysphoric mania, mixed and rapid-cycling states; beats lithium here**	Acute-mania serum **50 to 100 microg/mL** (350 to 700 micromol/L)	Teratogenic; avoid in women of childbearing potential
Asenapine	**First-line atypical, licensed for acute manic and mixed episodes of bipolar I**	**5 to 10 mg twice daily** sublingually (10 to 20 mg/day)	Sublingual oral hypoaesthesia; no food or drink for 10 minutes

OPTION	LINE AND ROLE	DOSE OR SERUM TARGET	SIGNATURE CAUTION
Cariprazine	**First-line atypical spanning manic, mixed and depressive poles in one agent**	Acute mania **3 to 6 mg/day**, titrate from 1.5 mg	Akathisia (dose-related; slower titration reduces it)
Olanzapine	First-line antimanic with mixed-episode evidence; rapid agitation control	Standard antimanic dosing	**Heaviest metabolic burden of the group**
Aripiprazole	First-line antimanic, mixed-episode data, metabolically favourable	Standard antimanic dosing	Akathisia
Lithium	Anti-suicide agent and first-line antimanic overall, but relatively weaker for classic mixed and dysphoric presentations	Acute-mania serum 0.8 to 1.2 mEq/L	**Underperforms in dysphoric and irritable mania versus divalproex**
ECT	For severe or refractory mixed episodes, active suicidality, catatonia, psychosis or pregnancy	Acute course per protocol	Not pole-specific; avoids the antidepressant problem
Antidepressant	**Avoided: worsens the manic pole and agitation; discontinue any that is running**	Not indicated in the mixed state	Reserved only for pure, non-mixed bipolar depression, never as monotherapy

The mixed-state pharmacotherapy options, CANMAT-led, with the antidepressant row shown as the one you remove; doses and serum targets verified against CANMAT 2018, Stahl 2021 and Kaplan and Sadock 2024.

INDIA

The IPS bipolar guideline is now the 2025 update (IPS 2025, Menon et al.), which keeps divalproex first-line and carbamazepine second-line for acute mixed episodes; the earlier 2017 guideline (Grover and Avasthi et al.) still gives the sharpest examinable line for the mixed state: antidepressants are not used as monotherapy in bipolar depression, rapid cycling or mixed episodes, and if an antidepressant is unavoidable, avoid paroxetine and prefer bupropion (IPS 2017). The IPS also flags that suicide risk in bipolar disorder is among the highest of any psychiatric condition (lifetime around 15 to 20 percent) and is greatest in mixed states and the depressive phase, and names modified ECT as first-line for mixed states with active suicidality (IPS 2017). Valproate (Valprol or Encorate; divalproex Valance or Divaa) and olanzapine (Oleanz) are widely and cheaply available in India. Asenapine and cariprazine are the newer atypicals here and a confirmed Indian brand could not be verified from the library, so prescribe them by generic name.

WORKED EXAMPLE

A 29-year-old man is brought in agitated, sleepless for four nights, speaking rapidly and irritably, but voicing hopelessness and a plan to end his life; he has been on an SSRI for a presumed depression for three weeks. This is a dysphoric mania, a mixed state, and the suicide risk is high. The SSRI is **stopped**, not increased. He is started on a mixed-state agent, divalproex titrated to an acute-mania serum level of 50 to 100 microg/mL, or an atypical such as asenapine or cariprazine, with lithium a weaker choice for this dysphoric picture. If agitation, suicidality or refusal of oral medication makes control urgent, or the episode is refractory, ECT is first-line. Nobody adds an antidepressant to this presentation.

COMMON TRAP

Labelling the presentation "bipolar depression" because the mood is low and the patient is suicidal, then reaching for an antidepressant. If manic-side symptoms co-exist, agitation, racing thoughts, reduced sleep, pressured speech, irritability, it is a mixed state, and the antidepressant is the wrong drug. Manage it from the manic side with valproate or an atypical and stop any antidepressant.

PEARL

Read the drive, not just the mood. A suicidal patient who is also energised, sleepless and pressured has the lethal combination the mixed state is famous for: the despair supplies the intent and the manic activation supplies the capacity to act. That is why the mixed state is the highest-risk phase and why you treat it from the manic pole.

HOLD THIS

A mixed state is high-suicide-risk and does not respond like a pure pole: treat it with valproate or an atypical such as asenapine or cariprazine (olanzapine or aripiprazole also work, lithium is weaker for dysphoric mania), use ECT for severe or refractory cases, and stop antidepressants rather than treating the depressive symptoms with one.

36 . Maintenance and prophylaxis of bipolar disorder

Bipolar disorder is a lifelong, recurrent illness, so the acute episode is only half the task: the harder, higher-yield half is the **maintenance treatment of bipolar** disorder, the long-term relapse prevention that keeps a patient euthymic between episodes. The examiner wants a guideline-anchored answer built around one anchor drug and one organising idea: **lithium is the backbone of maintenance, and you match the agent to the patient's predominant pole.** A resident who can name the first-line maintenance agents, quote the maintenance lithium level, and justify continuing treatment long-term after multiple episodes has the marks.

This is a selection topic, so it is **guidelines**-first. The lead guideline is CANMAT (Yatham 2018); the **Indian Psychiatric Society** position (the **IPS guidelines**, Shah/Grover et al. IPS 2017), the BAP (Goodwin 2016) and NICE (NICE 2014) are corroborating. The acute-episode drug pharmacology sits in the lithium and valproate topics; the neurobiology of mood and the wider guideline-anchored management PLAN belong to the Mood disorders: classification, depressive

and bipolar syndromes, neurobiology notes; the perinatal and acute-emergency frame to the Perinatal/women's mental health and emergency psychiatry notes.

36.1 The goal of maintenance: prevent both poles, not just the last one

What maintenance is for. Maintenance (also called continuation-plus-prophylaxis) aims to prevent recurrence of both manic and depressive episodes, reduce sub-syndromal symptoms, lower suicide risk, and preserve function (Yatham 2018; Maudsley 2021). Bipolar disorder spends more time in the depressive than the manic pole, so an agent that only blocks mania leaves the commonest source of morbidity untreated.

Prophylaxis as the frame. The word **prophylaxis** captures the core intent: because relapse is the rule, treatment is preventive rather than reactive, and the default assumption is that an effective agent is continued well beyond symptomatic recovery (Maudsley 2021).

RULE **Maintenance protects both poles.** Judge a maintenance agent by whether it prevents the depressive pole as well as mania, since depression dominates the bipolar course.

36.2 CANMAT first-line maintenance: lithium the anchor

The verified first-line set. CANMAT names, as first-line maintenance monotherapy for bipolar I disorder: lithium, quetiapine, divalproex, lamotrigine, asenapine, and aripiprazole, alone or in combination (Yatham 2018). Lithium (Licab, Intalith) is the anchor: it is the single best-evidenced prophylactic agent and the only psychotropic with a dedicated anti-suicidal signal (Maudsley 2021; Yatham 2018). The target **maintenance treatment of bipolar** lithium level is **0.6 to 1.0 mEq/L** (Yatham 2018).

The anti-suicidal evidence. Lithium reduces the risk of suicide and of relapse requiring hospitalisation (relative risk about 0.34 in one analysis), and this mortality benefit is specific to the ion and not shared by valproate (Maudsley 2021). This is why lithium is preferred in a bipolar patient with any suicide-risk history; the full suicide risk assessment belongs to the Somatic-symptom, sexual, impulse-control disorders and suicide notes.

AGENT (INDIAN BRAND)	MECHANISM / CLASS	POLE IT BEST PREVENTS	KEY MAINTENANCE NUMBER	SIGNATURE CAUTION
Lithium (Licab, Intalith)	Monovalent cation; GSK3-beta and inositol effects	Both poles; best anti-manic and anti-suicidal	Level 0.6 to 1.0 mEq/L	Renal, thyroid, calcium; narrow window
Quetiapine (Qutipin)	Atypical antipsychotic; D2 and 5-HT2A, norquetiapine NET	Both poles (broad-spectrum)	Continue effective acute dose	Metabolic gain, sedation
Divalproex (Valance, Divaa)	Anticonvulsant; enhances GABA, blocks Na channels	Manic pole predominantly	Level about 50 to 100 mcg/mL	Teratogen; avoid in childbearing potential

AGENT (INDIAN BRAND)	MECHANISM / CLASS	POLE IT BEST PREVENTS	KEY MAINTENANCE NUMBER	SIGNATURE CAUTION
Lamotrigine (Lamitor, Lametec)	Anticonvulsant; blocks Na channels, cuts glutamate	Depressive pole (weak for mania)	Target about 200 mg/day; slow titration	Rash / Stevens-Johnson; titrate from 25 mg
Asenapine	Atypical antipsychotic; broad D2 and 5-HT2A	Manic pole predominantly	Sublingual; continue effective dose	Oral hypoaesthesia, sedation
Aripiprazole (oral or LAI)	D2 partial agonist	Manic pole (does not prevent depression)	Once-monthly LAI option	Akathisia; poor for depressive pole

CANMAT first-line maintenance monotherapy agents for bipolar I disorder, mapped to predominant pole and the one maintenance number to hold (Yatham 2018; Maudsley 2021). Lithium and lamotrigine highlighted as the two polarity anchors.

TRAP **Using aripiprazole or asenapine alone in a depression-predominant patient.** These prevent mania but not the depressive pole; the patient keeps relapsing into depression on apparently adequate maintenance.

36.3 The polarity index: matching the agent to the predominant pole

The concept. The **polarity index** (Popovic et al. 2012) quantifies whether a maintenance drug is more anti-manic or more anti-depressive: it is the ratio of the number-needed-to-treat to prevent depression over the NNT to prevent mania (New Oxford 2020; Tasman 2015). A polarity index above 1 marks a manic-predominant agent; below 1 marks a depressive-predominant agent. This gives the clinical **match the polarity** heuristic a number.

The values to hold. Lithium sits close to balanced at **1.39** (mildly manic-predominant but effective both ways); lamotrigine is the strongly depressive-predominant agent at **0.40**; quetiapine is near-balanced at 1.14; olanzapine 2.98 and risperidone LAI 12.09 are strongly manic-predominant (Popovic et al. 2012; Tasman 2015). So a patient whose recurrences are mostly depressive is anchored on lithium and lamotrigine; one whose recurrences are mostly manic leans to an antipsychotic or divalproex.

1.39	0.40	12.09
LITHIUM POLARITY INDEX	LAMOTRIGINE POLARITY INDEX	RISPERIDONE LAI POLARITY INDEX

PEARL

Read the polarity index as a compass: above 1 points to mania-prevention (antipsychotics, divalproex), below 1 points to depression-prevention (lamotrigine at 0.40). Lithium near 1.39 is the all-rounder you build around and then add a pole-matched partner if one pole keeps breaking through.

36.4 Lamotrigine for the depressive pole

Its niche. Lamotrigine (Lamitor, Lametec) is the maintenance agent for the depressive pole: it prevents depressive recurrence well but is weak against mania, so it is rarely used as the sole agent in a mania-predominant patient (Yatham 2018; Maudsley 2021). It is added or substituted when depression is the recurring problem.

The titration rule. Because of the risk of rash and Stevens-Johnson syndrome, lamotrigine must be titrated slowly, starting at **25 mg/day** and building over weeks to a target near **200 mg/day** (Yatham 2018; Maudsley 2021). Valproate roughly doubles lamotrigine levels and mandates a halved lamotrigine dose and even slower titration.

TRAP **Titrating lamotrigine too fast, or forgetting the valproate interaction.** Rapid escalation, or full-speed titration alongside valproate, sharply raises the Stevens-Johnson risk.

36.5 The LAI option for non-adherence

When to reach for a depot. Non-adherence is the leading modifiable driver of relapse, so in a repeatedly non-adherent patient CANMAT offers a long-acting injectable antipsychotic to prevent recurrence: risperidone LAI every 2 weeks or aripiprazole once-monthly (Yatham 2018). The BAP concurs, recommending a depot antipsychotic for prophylaxis against manic recurrence when oral adherence is erratic (Goodwin 2016). Mirror-image data show fewer admissions and bed-days after switching to an LAI of aripiprazole or paliperidone (Maudsley 2021).

The polarity caveat. LAI antipsychotics are strongly manic-predominant (risperidone LAI polarity index 12.09), so they protect against mania far more than depression; a depression-prone non-adherent patient still needs a pole-matched agent alongside (Popovic et al. 2012).

36.6 What IPS, BAP and NICE recommend

The Indian Psychiatric Society. The **IPS guidelines** (the **Indian Psychiatric Society** bipolar CPG, Shah/Grover et al. IPS 2017) keep lithium as the first-choice long-term prophylactic agent, valued for its prophylactic and anti-suicidal evidence, with valproate, carbamazepine, lamotrigine and atypical antipsychotics as alternatives, and psychoeducation as the non-pharmacological base (IPS 2017). The IPS agrees the drug that controlled the acute episode is the rational one to continue long-term. Note: the IPS bipolar CPG is not in the guideline database used for this note, so its first-line ranking is stated here as consistent with the parsed sources rather than DB-verified.

BAP. Continue the lithium or valproate that treated the acute manic episode as a rational long-term choice, and consider a depot antipsychotic where adherence is poor (Goodwin 2016).

NICE. NICE positions lithium as the first-line long-term pharmacological treatment for bipolar disorder, with valproate second-line (avoided in women of childbearing potential), and olanzapine or quetiapine as further options (NICE 2014).

INDIA

Lead with the Indian brand: lithium carbonate is Licab or Intalith, divalproex is Valance or Divaa, sodium valproate is Valprol or Encorate, lamotrigine is Lamitor or Lametec, quetiapine is Qutipin, olanzapine is Oleanz. Lithium remains cheap and widely stocked, which matters for a lifelong prophylactic; the IPS and CANMAT positions converge on lithium as the maintenance anchor.

36.7 Choice and duration: how long to continue

The duration rule. This is the **choice and duration** question the examiner presses on. Maintenance is long-term and often indefinite: after multiple episodes, or after even one severe episode (for example with high suicide risk, psychosis, or major functional damage), prophylaxis is continued for years and frequently for life (Maudsley 2021; Yatham 2018). There is no fixed stop point analogous to the 6-to-9-month continuation rule in unipolar depression; the recurrent nature of the illness means treatment is not routinely withdrawn after a good year.

Choosing the agent. Choose by (i) what worked acutely (continue it), (ii) the predominant polarity (lithium or lamotrigine for depressive-predominant; antipsychotic or divalproex for manic-predominant), (iii) suicide risk (favour lithium), and (iv) childbearing potential (avoid valproate) (Yatham 2018; Maudsley 2021).

RULE **Anchor on lithium, match the polarity, continue long-term.** After multiple or severe episodes, maintenance is indefinite, not a one-year course.

TRAP **Stopping maintenance after one good year and inviting relapse.** Withdrawing a prophylactic mood stabiliser after a single well year, especially abruptly, sharply raises recurrence risk (rebound mania is a particular hazard with abrupt lithium withdrawal).

36.8 Relapse prevention: predictors and the psychosocial base

The evidence. The **relapse prevention** evidence is strongest for lithium among pharmacological agents, and adding a structured psychosocial intervention lowers relapse further (Yatham 2018). CANMAT makes adjunctive psychoeducation a first-line relapse-prevention intervention in euthymic patients (for example the Barcelona or Life Goals programmes, at least 5 sessions) (Yatham 2018).

The predictors of relapse. The modifiable and non-modifiable predictors a resident should list: non-adherence (the single biggest modifiable driver), residual or sub-syndromal symptoms, comorbid substance use, sleep and circadian disruption, high expressed emotion in the family, and stressful life events (Yatham 2018; Maudsley 2021). The **psychoeducation** and lifestyle base (regular sleep and routine, mood monitoring, early-warning-sign action plans, substance avoidance) targets exactly these.

WORKED EXAMPLE

A 30-year-old woman with bipolar I, three lifetime episodes (two depressive, one manic) and one past suicide attempt, is euthymic on lithium (Licab) at a level of 0.7 mEq/L. Because her recurrences are depression-predominant and she has a suicide history, lithium is the correct anchor (anti-suicidal, near-balanced polarity index 1.39); lamotrigine (Lamitor) is added for the depressive pole given its polarity index of 0.40. She joins a psychoeducation group, keeps a sleep and mood chart, and treatment is planned as long-term rather than time-limited.

36.9 Flibanserin: a note at the mood-sexual interface

What it is and is not. Flibanserin is included here only to fix its place at the **sexual-interface**: it is a **flibanserin** agent for **hypoactive sexual desire** disorder (HSDD) in premenopausal women, a 5-HT1A agonist and 5-HT2A antagonist that in the prefrontal cortex lowers serotonin and raises noradrenaline and dopamine (Kaplan and Sadock 2024). It was originally trialled as an antidepressant and failed, so it is emphatically not a mood stabiliser and has no maintenance role in bipolar disorder.

The one fact to hold. Flibanserin is FDA-approved (2015), dosed at **100 mg** at night, with dizziness, sedation and fatigue as its common adverse effects and a historical caution about alcohol and hypotension (Kaplan and Sadock 2024). It matters for the exam as a discriminator: a serotonergic mood/sexual-interface drug for female HSDD, distinct from any bipolar prophylactic.

HOLD THIS

Bipolar maintenance is anchored on lithium (level 0.6 to 1.0 mEq/L, anti-suicidal), lamotrigine is added for the depressive pole, you match the agent to the predominant polarity, and you continue long-term after multiple or severe episodes.

MNEMONIC

LQ-DLAA

The six CANMAT first-line maintenance agents: Lithium, Quetiapine, Divalproex, Lamotrigine, Asenapine, Aripiprazole. Lead the list with Lithium (the anchor) and remember Lamotrigine is the one for the depressive pole.

GOOD TO REMEMBER

- **Lithium (Licab, Intalith):** monovalent cation (GSK3-beta and inositol effects); best prophylactic and only anti-suicidal mood stabiliser; maintenance level 0.6 to 1.0 mEq/L, polarity index 1.39. First-line maintenance anchor.
- **Quetiapine (Qutipin):** atypical antipsychotic (D2 and 5-HT2A, norquetiapine NET); broad-spectrum, near-balanced polarity index 1.14; metabolic gain and sedation are the signature caution. First-line maintenance.
- **Divalproex (Valance, Divaa):** anticonvulsant (GABA enhancement, Na-channel block); manic-predominant; teratogen, so avoid in women of childbearing potential. First-line maintenance.
- **Lamotrigine (Lamitor, Lametec):** Na-channel blocker cutting glutamate; the depressive-pole agent (polarity index 0.40), weak for mania; rash / Stevens-Johnson signature, titrate from 25 mg to about 200 mg/day. First-line for depression-predominant maintenance.
- **Asenapine:** sublingual atypical antipsychotic (broad D2 and 5-HT2A); manic-predominant; oral hypoaesthesia is the signature. First-line maintenance.
- **Aripiprazole (oral or once-monthly LAI):** D2 partial agonist; prevents mania but not depression; akathisia signature; the once-monthly LAI is the non-adherence option. First-line maintenance monotherapy.
- **Flibanserin:** 5-HT1A agonist / 5-HT2A antagonist for female hypoactive sexual desire disorder; 100 mg nocte; NOT a mood stabiliser, no bipolar maintenance role. The mood-sexual-interface discriminator.

Apply and consolidate

37 . Apply: four worked pharmacotherapy vignettes

The mood-block pharmacotherapy syllabus is easiest to hold when it is rehearsed as clinical decisions rather than drug lists, and the exam frequently poses exactly that: a short case, a demand for the next drug, and an implied demand for the reasoning behind it. This closing topic runs **four** short worked vignettes that each fuse a scenario, the reasoning and the resolution, so that the antidepressant-selection, lithium-initiation, emergency and treatment-resistance chapters are exercised together as they will be at the bedside.

How to read each vignette. Every vignette below is presented as a worked example: it starts with the case (each opens with the literal marker "case:"), states the reasoning against a named guideline or a verified dose, and ends with the resolution and the trade-off. The class detail behind each is developed in the parent topics; here the skill is **application**. Doses, serum levels and first-line agents are verified against the Maudsley Prescribing Guidelines, Stahl, CANMAT, the BAP and the Indian Psychiatric Society CPGs (Maudsley 2021; Stahl 2021; CANMAT 2016; Malhi 2015; Gautam 2017). Where a brand is named it leads with the Indian brand.

37.1 Vignette 1: an antidepressant choice in comorbid depression with chronic pain and prior SSRI sexual dysfunction

The decision. This vignette is a **selection** problem: two patient-specific factors, a comorbid pain syndrome and an intolerable adverse effect on the previous drug, should steer the choice off the default SSRI. The reasoning turns on matching the drug's secondary pharmacology to the comorbidity, and its adverse-effect profile to what the patient could not tolerate before. Both

candidates below are CANMAT first-line agents, so the choice is a trade-off, not a hierarchy (CANMAT 2016).

WORKED EXAMPLE

Case: a 46-year-old man with a moderate depressive episode and long-standing diabetic neuropathic pain. A prior trial of an SSRI (escitalopram) helped his mood but caused marked sexual dysfunction that he found intolerable, and he stopped it. Reasoning: the SSRI class as a whole causes sexual dysfunction through serotonin-transporter blockade, so simply swapping to another SSRI is likely to reproduce the problem; the comorbid neuropathic pain is a positive reason to choose a drug that treats both targets. The two rational off-SSRI choices are an SNRI, duloxetine (Duzela), which is CANMAT first-line for major depression at 60 mg/day and separately licensed for diabetic neuropathic pain and fibromyalgia because of its noradrenergic action on descending spinal pathways; or bupropion (Bupron), a noradrenaline-dopamine reuptake inhibitor that is CANMAT first-line at 150 to 300 mg/day and carries the lowest sexual-dysfunction rate of the common antidepressants. Resolution: duloxetine is the sharper choice here because it treats the depression and the neuropathic pain with one drug, and it does not aggravate the previous problem the way another SSRI would; the trade-off is that duloxetine, like the SSRIs, can itself cause some sexual dysfunction, whereas bupropion would spare sexual function most fully but does nothing for the pain. If the sexual adverse effect were the single dominant concern and there were no pain, bupropion would be the first pick.

The trade-off stated cleanly. Duloxetine (Duzela) 60 mg/day wins on the pain comorbidity; bupropion (Bupron) 150 to 300 mg/day wins on sexual tolerability. A third option, mirtazapine (Mirtaz) 15 to 45 mg/day, also spares sexual function and aids sleep and appetite but does not treat pain (Stahl 2021; CANMAT 2016). Both duloxetine and bupropion require the standard adequate-trial window before they can be judged: response is assessed at 4 weeks and again at 6 to 8 weeks (BAP 2015; CANMAT 2016). The SSRI-versus-SNRI class detail and the full antidepressant-selection algorithm are set out in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

RULE **Let the comorbidity and the prior intolerance pick the antidepressant.** Comorbid pain points to duloxetine; prior sexual dysfunction points to bupropion or mirtazapine, never to a second SSRI.

TRAP **Swapping one SSRI for another after SSRI-induced sexual dysfunction.** The adverse effect is a serotonin-transporter class effect, so a second SSRI usually reproduces it; switch class, not molecule.

37.2 Vignette 2: lithium initiation, target level, the twelve-hour trough and the no-NSAID counselling

The decision. This vignette is an **initiation and monitoring** problem: the baseline work-up, the target serum level for the phase being treated, the sampling rule, and the interaction counselling that keeps the patient out of toxicity. Every figure below is verified (Maudsley 2021; Yatham 2018; Shah 2017).

WORKED EXAMPLE

Case: a 30-year-old woman with bipolar I disorder, recovering from an acute manic episode, for whom lithium is chosen for maintenance. Reasoning: before the first tablet, establish the two organs lithium threatens and the cardiac baseline. The baseline work-up is renal function (eGFR, creatinine, urea and electrolytes), thyroid function (TSH), serum calcium, weight or BMI, an ECG where there are cardiovascular risk factors, and, because lithium is a human teratogen (Ebstein anomaly), a pregnancy test with contraception counselling in a woman of child-bearing potential (Maudsley 2021; Yatham 2018). Start lithium carbonate (Licab, or the controlled-release Intalith CR) and titrate to a maintenance target of 0.6 to 1.0 mmol/L, drawing the level as a twelve-hour trough: the blood is taken 12 hours (ideally 10 to 14 hours) after the last dose, which for a bedtime dose means the next morning before the day's tablet. Recheck the trough 5 to 7 days after each dose change, then roughly 3-monthly once stable, with renal and thyroid function about 6-monthly. Resolution: counsel the patient that anything reducing renal lithium clearance raises the level and can cause toxicity, so she must avoid NSAIDs (ibuprofen, diclofenac) for pain and tell any doctor she is on lithium before starting a thiazide diuretic or an ACE inhibitor; she should keep well hydrated, and report tremor, ataxia, slurred speech, vomiting or diarrhoea at once as toxicity signs.

The phase sets the target. In acute mania the target trough is higher, 0.8 to 1.2 mmol/L, and it steps down to 0.6 to 1.0 mmol/L for maintenance; toxicity appears reliably above 1.5 mmol/L (Yatham 2018; Maudsley 2021). The twelve-hour trough and the 5-to-7-day recheck after a dose change are the two most-tested sampling facts, developed in full in the lithium-monitoring topic of these mood-block notes.

0.6 to 1.0	0.8 to 1.2	12	1.5
MAINTENANCE LITHIUM (MMOL/L)	ACUTE MANIA TARGET (MMOL/L)	TROUGH SAMPLING (HOURS POST-DOSE)	TOXICITY THRESHOLD (MMOL/L)

RULE **Draw lithium as a twelve-hour trough and counsel against NSAIDs.** The **12-hour** post-dose sample is the only interpretable level; NSAIDs, thiazides and ACE inhibitors raise the level toward toxicity.

TRAP **Checking a lithium level at the wrong time.** A non-trough sample drawn a few hours post-dose reads falsely high and invites a wrong dose cut; standardise to 12 hours every time.

INDIA

Lithium carbonate is cheap and heavily prescribed in India as Licab and the controlled-release Intalith CR, and the serum assay is inexpensive and widely available. The practical failure point is the twelve-hour trough discipline in a busy outpatient department, so counsel the patient to attend fasting in the morning before the day's dose and to note the time of the last tablet. Over-the-counter NSAID use for musculoskeletal pain is common and unsupervised, which makes the no-NSAID counselling a genuine safety instruction, not a formality.

37.3 Vignette 3: suspected serotonin syndrome on an SSRI plus tramadol, reasoned through the Hunter criteria

The decision. This vignette is a **recognition and emergency-management** problem: identify the syndrome from a combination of a serotonergic antidepressant and a serotonergic analgesic, apply the diagnostic rule, take the first management step, and separate it from its dopamine-blocker mimic. The management sequence and the discriminator are verified (Maudsley 2021; Kaplan and Sadock 2024).

WORKED EXAMPLE

Case: a 52-year-old man on sertraline (Serta) for depression is given tramadol for acute back pain and within hours becomes agitated, sweaty and febrile at 39 degrees Celsius, with dilated pupils, a tachycardia of 130, brisk lower-limb reflexes and sustained ankle clonus. Reasoning: sertraline plus tramadol is a two-drug serotonergic combination, and tramadol is itself weakly serotonergic, so this is the classic precipitant of serotonin syndrome. Apply the Hunter Serotonin Toxicity Criteria: in a patient on a serotonergic agent, the diagnosis is met by any one of spontaneous clonus; inducible clonus with agitation or diaphoresis; ocular clonus with agitation or diaphoresis; tremor plus hyperreflexia; or hypertonia plus temperature above 38 degrees Celsius plus ocular or inducible clonus. This patient has spontaneous clonus, which alone satisfies the Hunter criteria. Resolution: the first and most important step is to stop all serotonergic agents at once (both the sertraline and the tramadol); then give supportive care with intravenous fluids and active cooling for the hyperthermia, sedate with a benzodiazepine for agitation and neuromuscular hyperactivity, and in this moderate-to-severe case give cyproheptadine (Ciplactin, or Practin), a 5-HT2A antagonist, orally as the serotonin-antagonist antidote, a common regimen being an initial 12 mg then 2 mg every two hours if symptoms persist, to a ceiling around 32 mg in 24 hours. Most cases resolve within about 24 hours of stopping the trigger.

The NMS differential is the point. Serotonin syndrome and neuroleptic malignant syndrome share hyperthermia, rigidity, autonomic instability and altered consciousness, so the examiner rewards the one discriminator: serotonin syndrome follows a serotonergic drug, comes on rapidly over hours, and shows clonus with hyperreflexia; neuroleptic malignant syndrome follows a dopamine-blocker, comes on slowly over days, and shows lead-pipe rigidity with hyporeflexia and a markedly raised creatine kinase, often above 1000 units per litre (Maudsley 2021). The wider acute-emergency management frame is set out in the Perinatal/women's mental health and emergency psychiatry notes.

clonus	hours	12 then 2
THE HUNTER ANCHOR AND NMS DISCRIMINATOR	SEROTONIN-SYNDROME ONSET AFTER TRIGGER	CYPROHEPTADINE (MG, INITIAL THEN Q2H)

RULE **Stop the serotonergic drugs first, then support, sedate and give cyproheptadine.** Clonus with hyperreflexia in a patient on a serotonergic agent is serotonin syndrome until proven otherwise.

TRAP **Missing serotonin syndrome when an SSRI meets tramadol, or mislabelling it as NMS.** Tramadol is serotonergic; clonus and hyperreflexia (not lead-pipe rigidity) separate serotonin syndrome from its dopamine-blocker mimic.

INDIA

Tramadol is casually co-prescribed for musculoskeletal pain across Indian practice, so the highest-risk everyday scenario is a patient already on an antidepressant who is given tramadol. Cyproheptadine is freely available in India as an oral antihistamine (commonly stocked as Ciplactin or Practin), which makes the specific antidote easy to obtain once moderate-to-severe serotonin syndrome is recognised.

37.4 Vignette 4: treatment-resistant depression up the augmentation ladder

The decision. This vignette is an **escalation-discipline** problem: before augmenting, prove the depression is genuinely resistant and not merely under-treated, then climb the augmentation ladder in the guideline order. Every guideline opens the treatment-resistant depression pathway with a mandatory review of adequacy and diagnosis before any escalation (CANMAT 2016; BAP 2015; Gautam 2017).

WORKED EXAMPLE

Case: a 40-year-old woman with a major depressive episode that has not remitted despite an SSRI (escitalopram) followed by an SNRI (venlafaxine). Reasoning: first confirm this is true resistance, defined as failure of at least two adequate antidepressant trials in the current episode, each at an adequate dose for an adequate duration (response judged at 4 weeks and again at 6 to 8 weeks). Confirm each trial actually reached a therapeutic dose and was taken long enough, and confirm adherence, because most apparent resistance is pseudoresistance from an inadequate dose, an inadequate duration, poor adherence or a wrong diagnosis; review the diagnosis for a missed bipolar disorder, psychotic depression, or an organic or substance cause. Resolution: with two genuinely adequate failures confirmed, augment rather than endlessly switch. The first-line augmentation moves are to add lithium (Licab) 600 to 1200 mg/day titrated to a therapeutic serum level, or to add an atypical antipsychotic such as aripiprazole 2 to 15 mg/day or quetiapine (Qutipin) 150 to 300 mg/day (CANMAT 2016; BAP 2015). If augmentation fails, the next tier is the glutamatergic and neurostimulation options: add intranasal esketamine (Spravato) to an SSRI or SNRI for patients who have failed at least two adequate antidepressant trials, monitoring blood pressure and dissociation, or refer for electroconvulsive therapy, which is considered for patients who have not responded to other treatments and is the treatment of choice in severe, psychotic or high-suicide-risk depression.

The ladder in order. Optimise and confirm adequacy and adherence, review the diagnosis, then augment with lithium or an atypical (first-line augmentation), then move to esketamine or ECT. Lithium augmentation has the best evidence in older people, and CANMAT places aripiprazole, brexpiprazole, quetiapine and lithium among the first-line adjuncts, with esketamine reserved for at least two failed trials (BAP 2015; CANMAT 2016). The staging systems (Thase-Rush, Maudsley staging method) and the full ladder are developed in the treatment-resistant depression topic; the ECT technique itself is in the ECT and neurostimulation notes.

STEP	ACTION	AGENT / DOSE (VERIFIED)
1	**Confirm adequacy and adherence, review diagnosis**	Two adequate trials at therapeutic dose, judged at 4 and 6 to 8 weeks; exclude bipolar, psychotic, organic and substance causes
2	Optimise the current antidepressant	Raise a low or marginal dose to a recommended therapeutic dose first
3	**First-line augmentation: lithium or an atypical**	Lithium 600 to 1200 mg/day (to therapeutic serum level); aripiprazole 2 to 15 mg/day; quetiapine 150 to 300 mg daily
4	Glutamatergic or neurostimulation	Intranasal esketamine added to an SSRI/SNRI after 2 failed adequate trials; or ECT

The treatment-resistant depression ladder as applied in the vignette: confirm resistance and adherence, optimise, augment with lithium or an atypical, then esketamine or ECT (CANMAT 2016; BAP 2015). Highlighted steps are the board-critical moves.

RULE **Prove adequacy and adherence before you augment.** Two adequate trials must fail in the current episode; then augment with lithium or an atypical before moving to esketamine or ECT.

TRAP **Stopping at response instead of remission, or escalating over pseudoresistance.** Response without remission relapses; an inadequate dose, an inadequate duration or a missed bipolar diagnosis is under-treatment, not resistance.

GOOD TO REMEMBER

- **Vignette 1, antidepressant choice:** comorbid pain plus prior SSRI sexual dysfunction reasons to duloxetine (Duzela) 60 mg/day (treats pain and mood, CANMAT first-line SNRI) or bupropion (Bupron) 150 to 300 mg/day (lowest sexual-dysfunction rate); never a second SSRI for a class-effect adverse event.
- **Vignette 2, lithium initiation:** baseline renal (eGFR/creatinine), thyroid (TSH), calcium, weight, ECG where indicated, and pregnancy test; maintenance target 0.6 to 1.0 mmol/L (acute mania 0.8 to 1.2); draw a twelve-hour trough; counsel no NSAIDs, and caution with thiazides and ACE inhibitors.
- **Vignette 3, serotonin syndrome:** SSRI plus tramadol, Hunter criteria met by spontaneous clonus; stop all serotonergic agents first, then support and cool, benzodiazepine, then cyproheptadine (Ciplactin/Practin) 12 mg then 2 mg every 2 hours; clonus and hyperreflexia (not lead-pipe rigidity) distinguish it from NMS.
- **Vignette 4, treatment-resistant depression:** confirm two adequate failed trials and adherence, review the diagnosis, then augment with lithium 600 to 1200 mg/day or an atypical (aripiprazole 2 to 15 mg/day, quetiapine 150 to 300 mg/day), then esketamine (Spravato) or ECT.

HOLD THIS

The four clinical moves: match the antidepressant to the comorbidity and the prior intolerance (duloxetine for pain, bupropion for sexual sparing); start lithium on a full baseline work-up with a twelve-hour trough and no-NSAID counselling; in serotonin syndrome stop the serotonergic drugs first and give cyproheptadine; and in resistant depression prove adequacy and adherence before augmenting with lithium or an atypical and then esketamine or ECT.

38 . Consolidate: mnemonic, retrieval and synthesis

This is the closing topic of the mood pharmacotherapy block, and its job is not to add new drug facts but to **consolidate** the ones already taught into a form you can retrieve cold in an examination. Two evidence-based study moves do the heavy lifting: a single master **mnemonic** that chains the whole chapter into four movements so nothing is dropped, and **active recall** against a map you can redraw from memory. The pharmacology and the algorithms are all upstream; here they are re-indexed for retrieval.

The board does not reward a resident who can recognise a fact when prompted; it rewards one who can **generate** it under time pressure. That is why this topic is built around retrieval, not re-reading: the mnemonic is the retrieval cue, the recall prompts are the practice, and the synthesis map is the whole chapter compressed to one page you rebuild without looking. Everything below points back to a topic taught in full elsewhere in these notes.

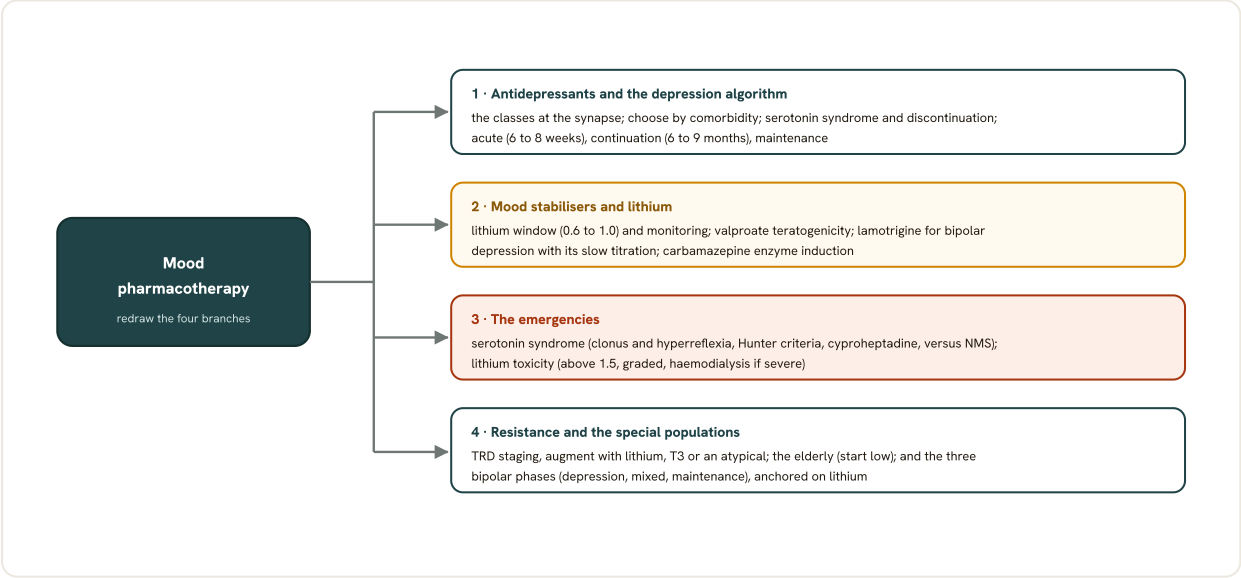

Fig 12.13 The whole chapter at a glance, framed for retrieval: cover the branches and redraw them from memory. The four branches are the antidepressants and the depression algorithm; the mood stabilisers and lithium with their monitoring and teratogenicity; the emergencies (serotonin syndrome and lithium toxicity); and treatment resistance with the special populations and the three bipolar-management phases.

38.1 The master mnemonic: chaining the whole chapter

One handle, four movements. The entire pharmacotherapy block hangs on the Step-2 seed you planted at the outset, and this is its payoff. Hold the whole chapter as **"A SNoM LiVeS, then CALM the STORM, then climb the LADDER"**. The first beat is the antidepressant classes and the depression algorithm; the second is lithium and the mood stabilisers with their monitoring and teratogenicity; the third is the two pharmacological emergencies; the fourth is treatment

resistance, augmentation and the bipolar-phase management. Each capitalised letter is a slot that expands into a full topic, and every fact chained below is verified against the source that owns it (Maudsley 2021; Stahl 2021; CANMAT 2016; CANMAT 2018; Yatham 2018).

MNEMONIC

A SNoM LiVeS, then CALM the STORM, then climb the LADDER

A SNoM is the antidepressant classes and the depression algorithm. **A**ntidepressants classify by synaptic action: SSRIs (SERT block, first-line, escitalopram **10 to 20 mg/day**), **S**NRIs (SERT plus NET, venlafaxine **75 to 225 mg/day** with dose-related blood-pressure rise), **N**aSSA/**N**DRI (mirtazapine, an alpha-2 antagonist that sedates; bupropion, a noradrenaline-dopamine reuptake inhibitor that spares sexual function and lowers the seizure threshold), the **o**lder tricyclics and **M**AOIs (reserved, dangerous, the tyramine and serotonergic hazards), and the **M**ultimodal and glutamatergic agents (vortioxetine, ketamine/esketamine). The depression algorithm is treat by phase to **remission**: acute review every **1 to 2 weeks**, judge by **2 to 4 weeks**, continuation at the same acute dose for **6 to 9 months**, maintenance **2 years or longer** if recurrent (CANMAT 2016). **LiVeS** is the mood stabilisers: **Li**thium (maintenance level **0.6 to 1.0 mmol/L**, twelve-hour trough, specific anti-suicide effect, first-trimester Ebstein signal), **V**alproate (serum **50 to 100 microg/mL**, the highest-risk teratogen: neural-tube defects, major-malformation rate around **10 percent**, dose-related IQ and autism harm, avoided in women of childbearing potential), lamotrigine (the depression pole, titrate **25 to 200 mg/day** slowly for the rash), the Stabiliser antipsychotics and carbamazepine (serum **4 to 12 mg/L**, enzyme induction, HLA-B*1502). **CALM the STORM** is the two emergencies: serotonin syndrome (clonus, hyperreflexia, autonomic instability, altered mental state, rapid over hours; stop the drug and give cyproheptadine) and lithium toxicity (coarse tremor and ataxia, toxic above **1.5 mmol/L**; stop, rehydrate with saline, dialyse if severe). **The LADDER** is treatment resistance and the bipolar phases: prove adequacy first (dose, duration, adherence, diagnosis), then switch, augment (lithium to **0.6 to 1.0 mmol/L**, or an atypical), combine, neuromodulate (ECT); and treat bipolar by phase (mania: lithium/valproate/an atypical, stop the antidepressant; bipolar depression: quetiapine, lurasidone, lithium, lamotrigine, never an antidepressant alone; maintenance: continue what worked, lithium level **0.6 to 1.0 mmol/L**).

RULE **Classify first, then treat by phase and polarity.** A SNoM LiVeS names the drug; CALM the STORM and the LADDER name what to do when it goes wrong or fails.

TRAP **Reciting the mnemonic without the numbers.** The letters are a scaffold; the exam marks fall on the doses, the serum levels and the monitoring intervals hung on each letter, so rehearse the figures, not just the acronym.

38.2 Retrieval practice, cover the answers

Practise generating, not recognising. The single most efficient consolidation move is **active recall**: close the notes and force the fact out, then check. What follows is a set of answer-free prompts spanning the four bands of the chapter. Use them as **retrieval practice**: read a prompt, say or write the full answer aloud from memory, and only then reveal the source topic to mark yourself. The prompts print no answers by design; that is the point of **cover the answers** practice. Space the repetitions across sittings rather than massing them.

RETRIEVAL PRACTICE, COVER THE ANSWERS

1. Name the primary synaptic action of each antidepressant class (SSRI, SNRI, TCA, MAOI, NaSSA, NDRI, multimodal, glutamatergic), and the one signature adverse effect or interaction that belongs to each.
2. State the four phases of the unipolar depression algorithm with the review interval, the response-judging point, the continuation duration and the maintenance duration, and say what defines the end of the acute phase.
3. Give the first-line agents for bipolar depression and state the one thing you never do with an antidepressant in bipolar disorder.
4. Recite the tyramine (cheese-reaction) food list for a patient on an irreversible MAOI, and the two washout intervals when switching to and from an MAOI or fluoxetine.
5. State lithium's molecular target and mechanism, its maintenance and acute serum ranges, the sampling rule (when the level is drawn), and the two anti-suicide claims attached to it.
6. List the lithium monitoring schedule: the trough timing, the recheck interval after a dose change, the ongoing level interval once stable, and the thyroid and renal monitoring intervals.
7. Give the drugs that raise and the drugs that lower the lithium level, and name the teratogenic signal and the trimester it belongs to.
8. State valproate's serum range, its full adverse-effect set, and the complete teratogenicity picture (structural, neurodevelopmental and its dose-dependence) with the prescribing rule that follows.
9. Give the lamotrigine titration and the one drug interaction that forces you to halve the schedule, and name the pole and phase lamotrigine is best for.
10. State carbamazepine's serum range, its three signature hazards, and the effect of its autoinduction on the level.
11. Recite the serotonin syndrome triad, the one sign that discriminates it from neuroleptic malignant syndrome, and the four-step management sequence.
12. Give the lithium toxicity level bands (mild, moderate, severe), the matching clinical features, the classic precipitants, and the four-step management including the dialysis indication.
13. State the definition of treatment-resistant depression, the four adequacy checks you clear before escalating, and the order of the switch-augment-combine-neuromodulate ladder.
14. Name the best-evidenced augmentation agents and the target lithium level for lithium augmentation.
15. Lay out the three bipolar phases (mania, depression, maintenance) with the first-line agents for each and the maintenance lithium level.

TRAP **Re-reading the notes and mistaking familiarity for mastery.** Recognising a fact on the page is not the same as retrieving it under a stem; only cover-the-answers recall trains the generation the board tests.

38.3 The synthesis map: redraw from memory

Rebuild the chapter on one page. The final consolidation move is to draw the whole-chapter **synthesis map** and then **redraw from memory** until it comes out clean. The map is a single

node, the mood pharmacotherapy block, with four branches, each a movement of the master mnemonic. Branch one is the antidepressants and the depression algorithm (the class map keyed to synaptic action, and the acute-continuation-maintenance phases). Branch two is the mood stabilisers and lithium (lithium initiation, monitoring, toxicity and teratogenicity, then valproate, carbamazepine, lamotrigine and the stabiliser antipsychotics). Branch three is the emergencies (serotonin syndrome and lithium toxicity, each with its discriminator and first management step). Branch four is treatment resistance and the special populations (the adequacy work-up and the augmentation ladder, the three bipolar phases, and prescribing in pregnancy and old age). Draw the four branches from the central node, hang the two or three load-bearing numbers on each leaf, and repeat the exercise cold until nothing is missing; the leaves you cannot fill are exactly the topics to revisit.

HOLD THIS

A SNoM LiVeS, then CALM the STORM, then climb the LADDER: four movements, four branches, one page you can redraw from memory.

GOOD TO REMEMBER

- **Branch 1 (antidepressants and the algorithm):** classify by synaptic action, then treat by phase to remission, continuation **6 to 9 months**, maintenance **2 years or longer** if recurrent (CANMAT 2016).
- **Branch 2 (stabilisers and lithium):** lithium maintenance **0.6 to 1.0 mmol/L** at a twelve-hour trough; valproate **50 to 100 microg/mL**, the highest-risk teratogen; lamotrigine for the depressive pole, titrated slowly (CANMAT 2018; Maudsley 2021).
- **Branch 3 (emergencies):** serotonin syndrome is clonus plus hyperreflexia (stop the drug, cyproheptadine); lithium toxicity is coarse tremor and ataxia above **1.5 mmol/L** (stop, saline, dialyse if severe) (Maudsley 2021).
- **Branch 4 (resistance and special populations):** prove adequacy (dose, duration, adherence, diagnosis) before you switch, augment, combine or neuromodulate; treat bipolar by phase and never give an antidepressant alone in bipolar depression (CANMAT 2016; Yatham 2018).
- **The retrieval rule:** generate the fact from a cue and space the repetitions; recognition on re-reading is not the skill the examination tests.

INDIA

For the Indian postgraduate examination, lead every management answer with CANMAT (CANMAT 2016 for depression, CANMAT 2018 and Yatham 2018 for bipolar disorder), then name the Indian Psychiatric Society position (Gautam et al. 2017 for depression, Grover and Avasthi 2017 for bipolar disorder), then note BAP and NICE where they converge (BAP 2015; NICE 2014). The Indian brands are learnt one drug at a time in the individual topics, Indian brand first: for example escitalopram (Nexito or S-Citadep), sertraline (Serta or Daxid), lithium carbonate (Licab or Intalith), sodium valproate (Valprol or Encorate), lamotrigine (Lamitor or Lametec) and quetiapine (Qutipin). Lithium remains a mainstream first-line stabiliser in Indian practice.

Previously asked

Mood pharmacotherapy is examined heavily and at the level of the individual drug: the SSRIs, the SNRIs, lithium, ketamine and the newer antidepressants have each come as standalone short notes, and the management of resistant depression and of refractory bipolar illness recurs as both a short note and the tail of a long essay. The reliable pattern is that every long mood question ends in a guideline-anchored drug plan, and a drug-specific note (a class, an agent, a monitoring rule, an adverse effect) can be asked on its own. The genuine questions on record are grouped by band below. The classification, the clinical syndromes and the neurobiology that these drugs treat are developed in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

HOW THIS TERRITORY IS ACTUALLY TESTED

- **Antidepressant classes and agents.** "SSRI antidepressants", "SNRI antidepressants" and "newer antidepressants" have each been asked as 10-mark notes, and "the recent advances in depression and development of antidepressants" as a longer question, so each class must be ready with its mechanism, its representative agents, its adverse-effect signature and its place. "Antidepressants in epilepsy with depression" tests the drug choice in a comorbidity. Prepare the class map, the individual agents and the comorbidity-driven selection. short note and essay, recurring

- **Serotonin syndrome and drug-induced states.** A case of a patient on an antidepressant and an antipsychotic who develops involuntary movements has been asked as a diagnose-investigate-manage question, and serotonin syndrome sits behind any antidepressant-combination scenario. Prepare serotonin syndrome (the Hunter criteria, the discrimination from NMS, the management) and the drug-induced movement disorders by cross-reference. case question, recurring

- **Rapid-acting and novel agents.** "The use of ketamine in depression" has come as a standalone note, so the NMDA mechanism, the rapid effect, the esketamine indication and the monitoring must be exam-ready, and the glutamatergic and other novel agents are worth a line. short note

- **Lithium and the mood stabilisers.** "Lithium" is a classic 10-mark note (mechanism, indications, the therapeutic range, monitoring, toxicity and the organ effects), and "carbamazepine" recurs across the papers. Prepare lithium in full, and valproate, carbamazepine and lamotrigine with their monitoring and their signature risks (valproate teratogenicity, lamotrigine and Stevens-Johnson). short note, recurring

- **Treatment resistance and bipolar management.** "The management of resistant depression" and "the management of treatment-resistant depression" have both come as standalone questions, and "the conceptual overview of bipolar spectrum disorder with the management of treatment-refractory bipolar II" and "the clinical features, differential diagnosis and management of bipolar depression" as essays. Prepare the TRD staging and augmentation ladder, and the three dedicated bipolar-management topics (bipolar depression, mixed episodes and maintenance), guideline-first. essay and short note, recurring

Prepare this material to be prescribed and monitored, not just recited: the class map, the dose-anchored good-to-remember boxes, the lithium monitoring and toxicity figures, the serotonin-syndrome differential and the guideline-anchored selection and management topics in these notes are built to the way the block is examined. The mood classification, the clinical syndromes and the neurobiology live in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; the ECT and neurostimulation technique lives in the ECT and neurostimulation notes; the full clinical suicide risk assessment lives in the Somatic-symptom, sexual, impulse-control disorders and suicide notes; and the wider perinatal and emergency frames live in the Perinatal/women's mental health and emergency psychiatry notes.

Quick review

The whole subject in one table	
ANTIDEPRESSANT CLASSES	Classify by the primary synaptic action: reuptake inhibitors (SSRI at SERT, SNRI at SERT and NET, TCA at both plus H1/M1/alpha-1 blockade), enzyme inhibitors (irreversible MAOI, reversible moclobemide), receptor-acting (mirtazapine NaSSA, bupropion NDRI), multimodal (vortioxetine, agomelatine, trazodone) and glutamatergic (ketamine, esketamine). The site predicts the tolerability and the dangerous interactions.
SSRIS	First-line, broadly equal in efficacy; differ in half-life, interactions and adverse-effect emphasis. Fluoxetine (long half-life, activating), sertraline (broadest), escitalopram and citalopram (cleanest, dose-dependent QTc, citalopram capped at 40 mg/day), paroxetine (short half-life, anticholinergic, worst discontinuation, avoid in pregnancy), fluvoxamine (OCD, CYP1A2). Class effects: GI upset, sexual dysfunction, hyponatraemia/SIADH in the elderly, bleeding with NSAIDs, early activation.
SNRIS AND TCAS	SNRIs: venlafaxine (dose-dependent noradrenergic effect and blood-pressure rise, marked discontinuation), desvenlafaxine, duloxetine (neuropathic pain). TCAs: reuptake blockade plus off-target H1/M1/alpha-1 (the adverse effects); dangerous in overdose (quinidine-like cardiotoxicity, QRS widening, seizures), so weigh the suicide risk; amitriptyline, imipramine, clomipramine (OCD), nortriptyline (best tolerated).
MAOIS	Irreversible non-selective (phenelzine, tranylcypromine) or reversible RIMA (moclobemide, safer). Tyramine (cheese) reaction gives a hypertensive crisis; never combine with a serotonergic drug (serotonin syndrome). Washout: at least two weeks off an MAOI before a serotonergic drug; about one week off most SSRIs/SNRIs (two off a TCA) before an MAOI; five weeks off fluoxetine before an MAOI.
MIRTAZAPINE, BUPROPION, NEWER	Mirtazapine (NaSSA): sedation and weight gain (more at low dose), minimal sexual dysfunction, for depression with insomnia and poor appetite. Bupropion (NDRI): activating, low sexual dysfunction, smoking cessation, lowers the seizure threshold (avoid in seizure and eating disorders). Newer: vortioxetine and vilazodone (multimodal), agomelatine (melatonergic, needs LFT monitoring), trazodone (SARI, priapism), tianeptine.

The whole subject in one table	
SEROTONIN SYNDROME VS NMS	Serotonin syndrome: rapid onset from a serotonergic combination; clonus, hyperreflexia, tremor, hyperthermia, hyperactive bowel sounds, mydriasis; Hunter criteria; stop the agent, supportive care, cyproheptadine. NMS: slow onset from a dopamine blocker; lead-pipe rigidity, hyporeflexia, marked CK rise; dantrolene, bromocriptine. The pivot is clonus and hyperreflexia (serotonin) versus lead-pipe rigidity (NMS).
KETAMINE, DISCONTINUATION	Ketamine and esketamine (NMDA antagonists): rapid effect within hours via AMPA and synaptogenesis; esketamine (intranasal) for treatment-resistant depression and MDD with acute suicidality, given under observation for dissociation and blood pressure; effect is transient. Discontinuation syndrome (FINISH: flu-like, insomnia, nausea, imbalance, sensory zaps, hyperarousal): worst with paroxetine and venlafaxine, least with fluoxetine; taper slowly, it is not addiction.
CHOOSING AND THE PHASES	First-line agents are equal in efficacy, so choose by comorbidity, adverse-effect profile, past response, safety and cost (CANMAT lead; IPS and NICE agree). Acute phase: treat to remission over 6 to 8 weeks, review by 2 to 4 weeks. Continuation: the SAME acute dose for 6 to 9 months. Maintenance: 2 years or longer for recurrent or high-risk depression. Psychotic depression needs an antidepressant plus an antipsychotic, or ECT.
LITHIUM: DOSE AND MONITORING	Mechanism: inositol depletion and GSK-3 inhibition; renally excreted, sodium-linked, narrow therapeutic index. Range: acute mania 0.8 to 1.0 (up to 1.2), maintenance 0.6 to 0.8 (up to 1.0), elderly 0.4 to 0.6 mmol/L. Sample as a 12-hour trough; recheck 5 to 7 days after a dose change; renal and thyroid function 6-monthly. Baseline: renal, thyroid, calcium, ECG, pregnancy, weight.
LITHIUM: TOXICITY AND ORGANS	Toxicity (dehydration, NSAIDs, thiazides, ACE inhibitors precipitate): mild 1.5 to 2.0 (coarse tremor, GI, lethargy), moderate 2.0 to 2.5 (confusion, ataxia, dysarthria), severe above 2.5 (seizures, coma, renal failure); stop, saline, haemodialysis for severe. Organs: nephrogenic DI and long-term CKD (watch eGFR trend), hypothyroidism and goitre (thyroxine, keep lithium), hypercalcaemia, benign T-wave changes, acne and psoriasis, fine tremor. Ebstein anomaly first-trimester (small but raised). Interactions that RAISE the level: NSAIDs, thiazides, ACE inhibitors and ARBs.
VALPROATE, CARBAMAZEPINE, LAMOTRIGINE	Valproate: anti-manic and maintenance (not bipolar depression alone); hepatotoxicity and PCOS; CRITICAL teratogenicity (neural-tube and neurodevelopmental risk), so avoid in women of childbearing potential without a pregnancy-prevention programme. Carbamazepine: potent CYP3A4 autoinducer (oral-contraceptive failure), hyponatraemia, blood dyscrasias, HLA-B*1502 SJS screen. Lamotrigine: for bipolar depression and

The whole subject in one table	
	maintenance (weak for mania); slow titration, HALVED with valproate; stop for a serious or mucosal rash (Stevens-Johnson).
TRD AND AUGMENTATION	TRD: failure of at least two adequate antidepressant trials, but exclude pseudoresistance first (dose, duration, adherence, missed bipolarity); Thase-Rush and Maudsley staging; STAR-D showed remission falls with each step. Ladder: optimise, switch, augment (lithium the classic and anti-suicidal, T3, an atypical, the best evidence), combine, then ECT, esketamine or neuromodulation.
BIPOLAR MANAGEMENT BY PHASE	Acute mania: stop any antidepressant; first-line lithium, quetiapine, valproate, or an atypical (aripiprazole, asenapine, risperidone, cariprazine), combination for severe. Bipolar depression: quetiapine, lurasidone, lithium, lamotrigine, olanzapine-fluoxetine, cariprazine; never an antidepressant alone (manic switch). Mixed episodes: valproate, asenapine, cariprazine, olanzapine, ECT; antidepressants avoided; lithium relatively weaker. Maintenance: lithium anchors (anti-suicidal), quetiapine, valproate, lamotrigine for the depressive pole, LAI for non-adherence.
ECT, NEUROMODULATION, PSYCHOTHERAPY	ECT: first-line in the emergencies (severe, psychotic or treatment-resistant depression, high suicide risk, food refusal, catatonia, pregnancy), rapid and effective; technique elsewhere. rTMS: non-invasive, for treatment-resistant depression. VNS: later-line, slow. DBS: experimental. Psychotherapy: CBT, IPT and behavioural activation are first-line in mild-to-moderate depression alone and combined with medication in severe depression.
SPECIAL POPULATIONS AND SUICIDE	Elderly: somatic and cognitive presentation, vascular depression; start low and go slow but still reach an adequate dose; prefer an SSRI (watch hyponatraemia, falls, the QTc cap), avoid TCAs; ECT works well in severe late-life depression. Suicide: mood disorders carry the highest risk (severe, mixed, early illness, early recovery); lithium is anti-suicidal; avoid a large TCA supply; counsel early antidepressant activation.

References

The pharmacology is grounded in the standard prescribing and psychopharmacology sources (the source hierarchy below), with the Maudsley Prescribing Guidelines and Stahl as the depth bar for the mechanisms, doses, serum levels and monitoring, and the management is guideline-first (CANMAT leading, with the Indian Psychiatric Society, the British Association for Psychopharmacology and NICE). Every dose, serum level, therapeutic range, monitoring interval, teratogenicity fact, drug interaction and first-line recommendation has been checked against these sources; anything that could not be confirmed was omitted and flagged rather than guessed. Each journal PMID here was verified against PubMed this build, matched on title, first author

and year; identifiers that resolved to the wrong paper were corrected or dropped. The classic sources seeding the field (Cade's 1949 report of lithium in mania, Schou's lithium work) are named in the prose by author and year.

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