WEAVE SPRINT · PAPER II

Antipsychotics

The treatment of schizophrenia in one document. Three bands run from the antipsychotics and the treatment algorithm, through the psychosocial rehabilitation that treatment alone cannot deliver, to the adverse effects and the emergencies of the drugs themselves.

CONTENTS

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Contents

Concept / rule Key number Trap

PAPER II

Schizophrenia: management, antipsychotics and adverse effects

Four sections · one complete notes document

This material gathers the treatment of schizophrenia into one document, the counterpart to the chapter on the illness itself. The first band is **antipsychotic pharmacotherapy and the management plan**: the biopsychosocial plan and the treatment-phase algorithm that orient every case, the receptor pharmacology that explains both the benefit and the harm of these drugs, the first-generation and second-generation and newer agents, the management of the first episode and of maintenance, the depot and long-acting injectables, and then the hard end of the algorithm, treatment resistance and clozapine and the management of the negative symptoms that respond least. The second band is **psychosocial rehabilitation and psychological treatment**: the rehabilitation, family and skills-based work, the psychological therapies, and the community models, including those of Indian practice, that carry the recovery a prescription cannot. The third band is **adverse effects and emergencies**: the extrapyramidal effects and tardive dyskinesia, the metabolic, prolactin and cardiac burden and its monitoring, and the emergencies, neuroleptic malignant syndrome and the differential that separates it from its mimics. The examinable skill is judgement across all three: to build a phase-based plan, to choose the right drug against its adverse-effect cost, to reach for clozapine at the right point, and to recognise and manage the emergencies the drugs create.

HOW TO USE THESE NOTES

Read the three bands as one argument that runs from the plan to its cost. The **pharmacotherapy** band builds the management spine, where the patient is treated, what is targeted in each phase, and every mode of treatment available, then works down the algorithm from the first episode to clozapine; each named drug ends with a **Good to remember** box giving its class and mechanism, its dose range, and the one monitoring parameter to hold. The **rehabilitation** band carries the psychosocial half of recovery, the family, skills, psychological and community work that medication alone cannot deliver. The **adverse-effects** band closes on the harm the drugs create and the emergencies to recognise, each effect ending with a box giving its feature, its discriminator, and the first management step. 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. Four boundaries are worth stating up front: the phenomenology, aetiology, criteria and course of the illness are taught in the Schizophrenia: aetiology, phenomenology, classification and course notes and are not repeated here; the receptor and pathway mechanics and the CYP metabolism belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the technique of electroconvulsive therapy for augmentation and resistance lives in the ECT and neurostimulation notes; and malignant catatonia and the other psychotic disorders as entities live in the Other psychotic disorders, delusional syndromes and catatonia notes, needed here only inside the emergency differential. This is doctor-facing revision, so the full technical vocabulary is used, and every dose, range and monitoring threshold is verified against a source.

Antipsychotic pharmacotherapy and the management plan

1 · Orientation: the biopsychosocial plan and the treatment algorithm

These notes turn from what schizophrenia *is* to what you *do* about it, and the whole of that doing is organised by one schema: the **treatment algorithm**. Schizophrenia is treated, not cured. The realistic aim is symptom control, restored function and recovery over the long run, and the backbone of every phase is an antipsychotic, prescribed inside a wider **biopsychosocial** plan (Maudsley 2021, APA 2020). The examiner on a management question is never testing whether you can name a drug; they are testing whether you can place a given patient on the algorithm, choose a locus of care, target the right symptoms for the phase, and defend the choice against the guideline.

How to use this page. Fix three orienting frames before any drug detail arrives. First, the biopsychosocial **management plan** as a spine with three limbs, the **locus** (where care happens), the **focus** (which symptoms, set by the phase) and the **modus** (every mode of treatment on the table). Second, the treatment algorithm run forward across the **phases of treatment**: acute, stabilisation and maintenance, then the branch to clozapine when two adequate trials fail. Third, the master mnemonic that chains the whole chapter so one cue unpacks the note. The illness itself, its phenomenology, aetiology, criteria and course, is not re-taught here; it belongs to the Schizophrenia: aetiology, phenomenology, classification and course notes, and this chapter

applies management to it. The receptor pharmacology and CYP metabolism behind the drugs belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

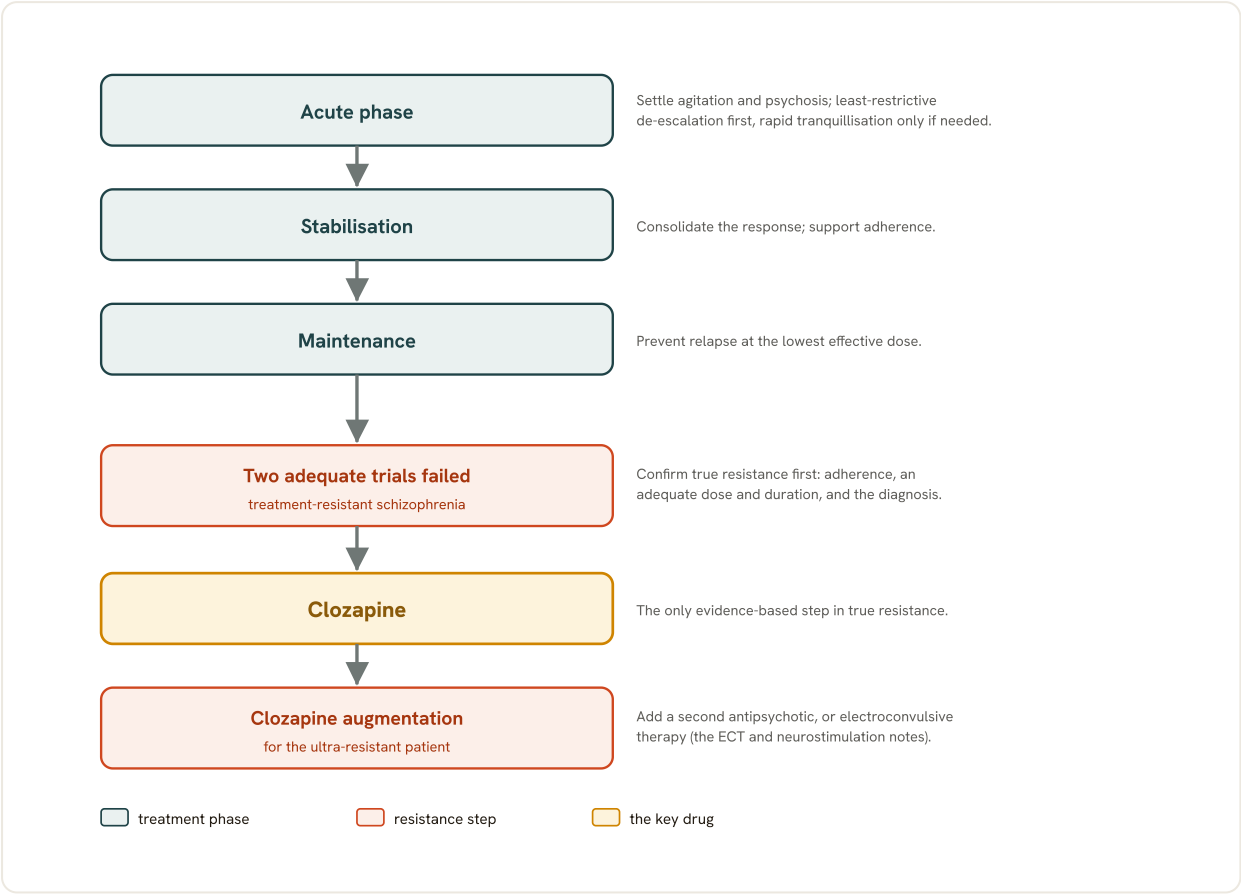

Fig 9.1 The antipsychotic treatment algorithm. Care runs down the phase ladder, acute to stabilisation to maintenance at the lowest effective dose. When two adequate trials have genuinely failed, the illness is treatment-resistant and the evidence-based next step is clozapine, not a third same-class switch; the ultra-resistant patient is then augmented.

1.1 The guidelines-first frame: where the algorithm comes from

Answer from a named guideline, not from memory. Management answers carry more weight when anchored to a source, and three guidelines supply the algorithm used throughout these notes. The Maudsley Prescribing Guidelines (Maudsley 2021) are the practical prescribing backbone: dose ranges, rapid tranquillisation, clozapine initiation and monitoring, and the treatment-resistance pathway. The NICE guideline (NICE CG178/NG, 2014 onward) and the APA Practice Guideline (APA 2020) frame the phase-based structure, the offer of an antipsychotic plus family intervention and CBT, and physical-health monitoring. For the Indian setting the Indian Psychiatric Society (IPS) Clinical Practice Guidelines for schizophrenia, updated in 2025 (IPS 2025, Sahoo et al., Indian J Psychiatry 2026;68:94-121), give the locally calibrated version, including community and resource-aware recommendations. Lead with the guideline the paper names; where unmarked, the phase structure is common to all three, so cite the phase framework and the Maudsley for the numbers.

RULE **Name the source.** Every management recommendation you give should be traceable to the Maudsley, NICE/APA or IPS guidance; a phase-anchored, guideline-cited answer beats an unsourced drug list every time.

1.2 The biopsychosocial management plan: locus, focus, modus

The management spine. A **biopsychosocial management plan** is not a drug prescription with extras bolted on; it is a spine with three limbs that you set for every patient. Hold them as **locus**, **focus** and **modus**. Deciding all three, and revisiting them at each review, is the management task the algorithm then structures.

Locus

Where care is delivered, chosen on the least-restrictive-first principle: outpatient (clinic and community team), day-hospital, inpatient admission, or crisis/community care (home treatment and crisis-resolution teams).

Focus

Which symptoms you are targeting now, set by the **phase of treatment**: agitation and florid psychosis acutely, consolidation and adherence in stabilisation, relapse prevention and function in maintenance.

Modus

Every mode of treatment available: antipsychotics (the pharmacological backbone), psychosocial rehabilitation, family work, and physical-health care, combined rather than chosen between.

Locus, least-restrictive first. The default locus is the least restrictive option that is safe. Most treatment is outpatient. Escalate to day-hospital, then inpatient admission (voluntary where possible, involuntary only where the legal threshold is met), only when risk, non-adherence with deterioration, or the need for supervised initiation demands it. Crisis-resolution and home-treatment teams can hold many acute presentations in the community and are the least-restrictive alternative to admission where they exist.

Focus by phase, modus across all phases. The **focus** is what changes across the phases; the **modus** stays broad throughout. From the first contact the plan runs the antipsychotic alongside psychosocial rehabilitation (social-skills and vocational work), family intervention (psychoeducation and reduction of high expressed emotion), and structured physical-health care (metabolic and cardiovascular monitoring), because the drug alone does not restore function and does not prevent the physical-health mortality gap. The detail of monitoring, family work and rehabilitation is developed in the dedicated topics; the point here is that they are part of the plan from the outset, not an afterthought.

COMMON TRAP

Equating "management" with "which antipsychotic". The drug is one limb of the modus. An answer that names a molecule but never states the locus, the phase-set focus, or the psychosocial and physical-health limbs has missed the biopsychosocial plan the question is testing.

1.3 The treatment algorithm: the orienting schema across the phases

The whole chapter on one decision tree. The **treatment algorithm** is the schema every management topic hangs from. Read it forward as three sequential phases with a resistance branch. In the **acute phase** the target is control of agitation and florid psychosis: secure safety, start (or optimise) a single antipsychotic at an adequate dose, and manage acute agitation by de-escalation, then rapid tranquillisation if needed. In **stabilisation** the target is consolidation: continue the effective drug at the effective dose, allow time for response (an adequate trial is 4 to 6 weeks at optimum dose), treat residual symptoms and adverse effects, and build adherence and the psychosocial plan. In **maintenance** the target is relapse prevention and function: continue the antipsychotic long-term (a long-acting injectable is a key option for adherence), keep physical-health monitoring running, and taper only slowly and with full risk-benefit review. The single most examined branch off this trunk is treatment resistance: where the illness fails to respond to adequate trials of at least two antipsychotics, the pathway turns to clozapine and then to augmentation. That branch, the two-failed-trials definition and the clozapine monitoring detail, is developed in the treatment-resistance and clozapine topics; here it is only the fork in the algorithm.

PHASE	THE ONE TARGET	THE CORE MOVE
Acute phase	Control agitation and psychosis, secure safety	**De-escalate; start/optimise a single antipsychotic; rapid tranquillisation only if needed**
Stabilisation	Consolidate response; adherence; treat residuals	**Continue the effective drug at the effective dose; adequate trial 4 to 6 weeks; add psychosocial limbs**
Maintenance	Prevent relapse; restore function	**Long-term antipsychotic (consider LAI); ongoing monitoring; taper only slowly with review**
Resistance branch	Non-response after two adequate trials	**Turn to clozapine, then augmentation (developed in the treatment-resistance and clozapine topics)**

The treatment algorithm as an orienting schema: three sequential phases, each with a single target, plus the treatment-resistance fork to clozapine. Drawn as Fig 9.1.

TRAP **Switching too early.** Declaring an antipsychotic a failure before an adequate trial (4 to 6 weeks at optimum dose, with adherence confirmed) manufactures pseudo-resistance; much apparent resistance is inadequate dose, duration or covert non-adherence (Maudsley 2021).

1.4 The acute-agitation step: de-escalation, then rapid tranquillisation, then restraint

A staged, least-restrictive escalation. The first move of the acute phase is often managing **acute agitation**, and it is a staged escalation, least-restrictive first. Begin with de-escalation: a calm environment, verbal and non-verbal techniques, addressing needs, and offering oral medication. Only when de-escalation and offered oral treatment fail, and the patient is placing themselves or

others at significant risk, move to rapid tranquillisation with parenteral medication. Physical restraint and seclusion are used only when necessary, for the shortest time, as the least-restrictive means of maintaining safety, and always with monitoring. The drug detail is kept brief here and the wider protocol, including the management of substance-related and undifferentiated agitation, is cross-referenced to the emergency chapter.

The rapid-tranquillisation ladder, in brief. Per the Maudsley (2021), after de-escalation the ladder is: offer *oral* treatment first, for example lorazepam **1 to 2 mg** (with or without promethazine) in a benzodiazepine-naive patient, or an oral antipsychotic such as olanzapine, risperidone or quetiapine; then *intramuscular* treatment if two oral doses fail or sooner if risk is high, with the common IM options being lorazepam **2 mg**, promethazine **50 mg**, or IM olanzapine **10 mg**. Generic names lead in Indian practice; where a brand is needed, haloperidol is marketed as Serenace. Haloperidol IM **5 mg** is the last drug to consider because acute dystonia is common: give it with promethazine, keep procyclidine to hand, and a pretreatment ECG is required. IM olanzapine must not be combined with an IM benzodiazepine, and antipsychotic polypharmacy is avoided in rapid tranquillisation because of the additive QTc risk. After any parenteral dose, monitor level of consciousness, respiratory rate, oxygen saturation, pulse, blood pressure and temperature; keep flumazenil available for benzodiazepine-induced respiratory depression.

1 to 2 mg	10 mg	4 to 6 wk
ORAL LORAZEPAM, RT STEP 2	IM OLANZAPINE, RT STEP 3	ADEQUATE ANTIPSYCHOTIC TRIAL

TRAP **Restraint or rapid tranquillisation before de-escalation.** Reaching for the IM tray or physical restraint before de-escalation and an offered oral dose is both a clinical and a governance error; restraint is a last resort, time-limited and monitored, never the opening move.

INDIA

In Indian practice the antipsychotic backbone is affordable and widely available, and generic prescribing dominates. Where a long-acting injectable is chosen for maintenance adherence, olanzapine pamoate long-acting injection is marketed as Tolaz (Torrent); its binding practical constraint is the post-injection delirium sedation syndrome, which mandates a supervised post-injection observation period after each dose, a service most outpatient setups cannot deliver. Community and resource-aware delivery models sit under the District Mental Health Programme (DMHP) and the IPS guideline; clozapine monitoring in the Indian setting is addressed in the clozapine topic.

1.5 The master mnemonic: chaining the chapter

One hook for the whole management chapter. A single mnemonic chains the management sequence so that one cue unpacks the note. Fix it in reading order and every later topic slots onto its link.

MNEMONIC

"CHOOSE, MAINTAIN, RESIST, REHABILITATE, WATCH THE HARMS"

Unpack it link by link. **Choose** is the acute-phase and stabilisation task: select a single antipsychotic on adverse-effect profile and patient factors, at an adequate dose for an adequate trial. **Maintain** is the maintenance phase: continue long-term for relapse prevention, using a long-acting injectable where adherence is the problem. **Resist** is the treatment-resistance branch: two failed adequate trials turn the algorithm to clozapine and then augmentation. **Rehabilitate** is the psychosocial modus that runs across all phases: family intervention, CBT for psychosis, social-skills and vocational rehabilitation. **Watch the harms** is the safety spine: extrapyramidal side-effects, the metabolic syndrome, QTc and prolactin, and the emergencies of neuroleptic malignant syndrome and clozapine-related neutropenia. One seed, the whole chapter.

WORKED EXAMPLE

A 24-year-old man with a first episode arrives agitated and threatening on the ward. Walk the algorithm. Locus: he needs a safe setting, so admission (least-restrictive that is safe) with the crisis team considered if risk can be held. Focus: this is the acute phase, so the target is agitation and psychosis. Modus, acute step: de-escalate first, offer oral lorazepam 1 to 2 mg or an oral antipsychotic; if he refuses and risk is high, move to IM (olanzapine 10 mg or lorazepam 2 mg), with restraint only if necessary and monitored, and full physical monitoring after any parenteral dose. Then choose a maintenance antipsychotic, run it for an adequate 4 to 6 week trial in stabilisation, add family work and physical-health monitoring, and plan maintenance. If a second adequate trial also fails, the algorithm forks to clozapine. That single case exercises locus, focus, modus and every phase of the algorithm.

HOLD THIS

Schizophrenia is managed, not cured: an antipsychotic backbone across acute, stabilisation and maintenance phases, inside a biopsychosocial plan set by locus, focus and modus, with the algorithm forking to clozapine after two adequate trials fail; acute agitation goes de-escalation, then rapid tranquillisation, then restraint, least-restrictive first.

GOOD TO REMEMBER

- **Antipsychotic (the backbone):** dopamine-D2-blocking agent that is the pharmacological limb across every phase; dose is chosen within the licensed range and titrated (the class and per-drug mechanics belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes); the one caveat to hold is that an adequate trial is 4 to 6 weeks at optimum dose with adherence confirmed before calling it a failure.
- **Lorazepam (rapid tranquillisation):** short-acting benzodiazepine used for acute agitation; oral 1 to 2 mg then IM 2 mg per the Maudsley ladder; the one parameter to hold is respiratory depression, so monitor after parenteral dosing and keep flumazenil available.
- **Olanzapine IM (rapid tranquillisation):** second-generation antipsychotic given IM 10 mg for agitation; the one caveat is that it must never be combined with an IM benzodiazepine, and physical observations are monitored after the dose.
- **Haloperidol (rapid tranquillisation, last-line; brand Serenace):** high-potency first-generation antipsychotic, IM 5 mg; the discriminating caveat is a high rate of acute dystonia and QTc prolongation, so it is the last drug considered, given with promethazine, with procyclidine to hand and a pretreatment ECG.
- **Clozapine (the resistance branch):** the drug for treatment-resistant schizophrenia after two failed adequate trials; the one parameter to hold is mandatory haematological monitoring for neutropenia (developed with the ANC cut-offs in the clozapine topic).
- **Restraint (emergency step):** physical restriction of a dangerously agitated patient; the discriminator from rapid tranquillisation is that it is a last resort after de-escalation fails; the first management principle is least-restrictive, time-limited and continuously monitored, with the wider protocol in the emergency chapter.

Figure. The treatment algorithm, the three-phase decision tree (acute, stabilisation, maintenance) with the acute-agitation ladder and the treatment-resistance fork to clozapine, is drawn as Fig 9.1.

2 · Antipsychotic mechanism and receptor pharmacology

Every antipsychotic earns its place by what it does at the dopamine D2 receptor, and it earns its adverse-effect signature by what else it touches on the way. This topic is the single axis that explains both the benefit and the harm of the whole class, and the examiner rewards a resident who can move from a receptor to a symptom and from a receptor to a side effect without hesitation. The pathway anatomy and the receptor biology themselves are the property of the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; here that biology is applied to predict clinical effect.

Why this is the master key. The **mechanism of action** of every effective agent runs through D2 blockade, and the **receptor pharmacology** of a given drug, its affinities across D2, 5-HT2A, H1, M1 and alpha-1, predicts almost everything a resident is asked in a viva: which symptoms respond, how much extrapyramidal risk there is, whether it sedates, whether it drops blood pressure and whether it raises prolactin (Stahl 2021; Kaplan & Sadock 2024). Learn the receptor profile and the adverse-effect profile falls out of it. The disorder itself, its phenomenology, aetiology and course, belongs to the Schizophrenia: aetiology, phenomenology, classification and course notes and is not re-taught here.

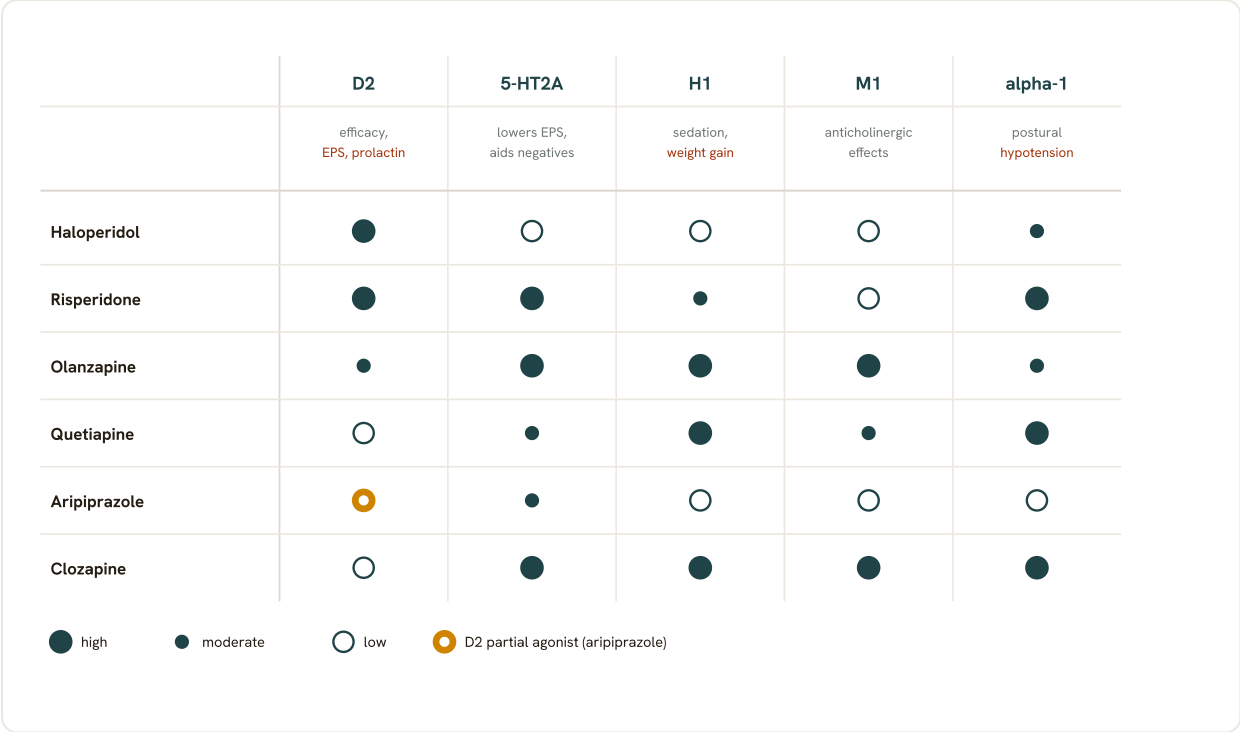

Fig 9.2 The receptor-affinity grid. A drug's receptor profile predicts its adverse-effect signature: D2 blockade buys efficacy but costs extrapyramidal effects and prolactin; 5-HT2A antagonism lowers the extrapyramidal burden; H1 drives sedation and weight gain; M1 the anticholinergic effects; and alpha-1 the postural hypotension. Aripiprazole is a D2 partial agonist, not a full blocker, which is why its profile differs.

2.1 The unifying principle: D2 blockade

One shared action. All clinically effective antipsychotics are antagonists (or partial agonists) at the dopamine D2 receptor, and this d2 blockade is the common final pathway of antipsychotic action (Kaplan & Sadock 2024; Stahl 2021). The classic evidence is that antipsychotic potency across first-generation agents correlates tightly with D2 binding affinity: the tighter a drug binds D2, the lower the milligram dose needed. No agent lacking meaningful D2 activity has proven antipsychotic in schizophrenia, which is why D2 blockade, not any single receptor gimmick, is the definition of the class.

Where the benefit lives. The antipsychotic (antidelusional, antihallucinatory) effect maps onto D2 blockade in the mesolimbic dopamine pathway, where excess dopamine transmission is thought to drive the positive symptoms (Stahl 2021). Blocking D2 here dampens the aberrant signalling behind delusions and hallucinations. The pathway mechanics, the mesolimbic, mesocortical, nigrostriatal and tuberoinfundibular tracts, are owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; this topic uses them only to locate benefit and harm.

RULE **No D2, no antipsychotic.** Every drug that treats schizophrenia blocks or partially agonises D2; potency tracks D2 affinity. The receptor is the definition of the class, not an incidental feature.

2.2 The therapeutic window of striatal D2 occupancy

The occupancy story. Positron-emission-tomography studies define a therapeutic window of striatal D2 occupancy. For at least the first-generation agents, antipsychotic effect requires a striatal D2 receptor occupancy of roughly **65 to 70%**, while occupancy above about **80%**

significantly increases the risk of extrapyramidal side effects (Remington & Kapur 1999; Kapur 2000; Tasman 2024). The practical window a resident holds is therefore roughly **65 to 80%** striatal D2 occupancy: below it the drug underperforms, above about 80 percent the extra occupancy buys extrapyramidal symptoms rather than efficacy. Crucially, response and extrapyramidal risk track occupancy, not dose, and occupancy varies widely between patients on the same dose, which is the pharmacological argument for the lowest effective dose.

65 to 70%	>80%	65 to 80%
STRIATAL D2 FOR ANTIPSYCHOTIC EFFECT	STRIATAL D2 WHERE EPS RISK RISES	THE WORKING THERAPEUTIC WINDOW

An illustration. Olanzapine at its usual clinical dose of 10 to 20 mg/day produces about 71 to 80 percent striatal D2 occupancy, and doses of 30 mg/day and above push occupancy over 80 percent, exactly where extrapyramidal liability climbs (Kapur et al. 1998; Tasman 2024). This is why pushing an antipsychotic ever higher in a non-responder is usually the wrong move: past the window you add extrapyramidal symptoms without adding antipsychotic effect.

TRAP **Assuming more D2 occupancy always means more efficacy.** Above roughly 80 percent striatal occupancy, extra D2 blockade adds extrapyramidal side effects, not response; the non-responder needs a switch or clozapine, not a bigger dose.

2.3 The 5-HT2A/D2 ratio that defines the atypicals

The serotonin-dopamine idea. The second-generation (atypical) antipsychotics are, as a group, characterised by relatively more potent 5-HT2A than D2 receptor antagonism, the high 5-ht2a/d2 ratio (New Oxford Textbook; Stahl 2021). The mechanism is that 5-HT2A antagonism disinhibits dopamine release in selected pathways: serotonin at 5-HT2A normally brakes dopamine neurons, so blocking 5-HT2A lifts that brake and restores dopamine in the nigrostriatal and mesocortical pathways. In the nigrostriatal tract the restored dopamine competes with the drug at D2 and softens extrapyramidal symptoms; in the mesocortical tract the added dopamine is proposed to help the negative and cognitive symptoms, which stem partly from a cortical dopamine deficit. Combined 5-HT2A antagonism with less potent D2 antagonism is the most consistent principle yet found for separating antipsychotic action from motor side effects (New Oxford Textbook).

The instructive exceptions. Aripiprazole works not through the 5-HT2A/D2 ratio but through D2 partial agonism, and amisulpride is a selective D2/D3 antagonist with little 5-HT2A activity, yet both are counted as atypical because they too achieve a low extrapyramidal burden (New Oxford Textbook). The lesson for the exam is that atypicality is a clinical outcome, low extrapyramidal liability, reached by more than one receptor route.

PATHWAY	EFFECT OF 5-HT2A ANTAGONISM	CLINICAL READ-OUT
Nigrostriatal	Disinhibits dopamine, competes with D2 blockade	**Lower extrapyramidal symptoms than a pure D2 blocker**
Mesocortical	Restores dopamine in a dopamine-deficient tract	**Proposed benefit for negative and cognitive symptoms**
Mesolimbic	D2 blockade retained; little dopamine disinhibition where positive symptoms live	**Antipsychotic efficacy preserved**

How a high 5-HT2A/D2 ratio splits antipsychotic action from motor harm: serotonin blockade lifts the dopamine brake selectively in the nigrostriatal and mesocortical tracts while D2 blockade continues to treat mesolimbic positive symptoms.

2.4 The receptor basis of the adverse effects

Read the profile, predict the harm. A drug's off-target receptor affinities generate a predictable adverse-effect signature, and this is the single most examinable idea in antipsychotic pharmacology (Stahl 2021). The D2 receptor produces two of the effects, in the wrong pathways; three other receptors, H1, M1 and alpha-1, produce the rest. Map the receptor to the pathway or organ and the side effect follows.

D2, nigrostriatal

Blockade in the motor pathway produces extrapyramidal side effects: acute dystonia, parkinsonism, akathisia and, with time, tardive dyskinesia.

D2, tuberoinfundibular

Blockade removes dopamine's tonic inhibition of prolactin, producing hyperprolactinaemia (galactorrhoea, amenorrhoea, sexual dysfunction).

H1 (histaminergic)

Blockade causes sedation and, over time, weight gain and increased appetite.

M1 (muscarinic)

Blockade causes the anticholinergic cluster: dry mouth, constipation, blurred vision, urinary retention and cognitive dulling.

Alpha-1 (adrenergic)

Blockade causes postural (orthostatic) hypotension and dizziness, and contributes to sedation.

RECEPTOR BLOCKED	SITE / MECHANISM	ADVERSE EFFECT PREDICTED
D2	Nigrostriatal (motor) pathway	**Extrapyramidal symptoms, tardive dyskinesia**
D2	Tuberoinfundibular pathway (loss of dopamine brake on prolactin)	**Hyperprolactinaemia: galactorrhoea, amenorrhoea, sexual dysfunction**
H1	Histaminergic	**Sedation and weight gain**
M1	Muscarinic (anticholinergic)	**Dry mouth, constipation, blurred vision, urinary retention, cognitive dulling**

RECEPTOR BLOCKED	SITE / MECHANISM	ADVERSE EFFECT PREDICTED
Alpha-1	Adrenergic	**Postural hypotension, dizziness, sedation**

The receptor-to-adverse-effect grid: two effects flow from D2 in the wrong pathways, three from H1, M1 and alpha-1; a drug's receptor-affinity fingerprint predicts which of these it will cause.

RULE **The receptor profile predicts the adverse-effect profile.** Match each receptor a drug blocks to its pathway or organ (D2 motor, D2 prolactin, H1, M1, alpha-1) and its side-effect signature is deducible before you prescribe.

The low-potency phenothiazines (for example chlorpromazine) sit heavily on H1, M1 and alpha-1 and so sedate, dry and drop pressure while causing fewer extrapyramidal symptoms per milligram; the high-potency agents (for example haloperidol, marketed in India as Serenace) are lean on those receptors and so cause prominent extrapyramidal symptoms with little sedation or hypotension. The atypicals redistribute the burden: olanzapine and clozapine load H1 and M1 (sedation, weight gain, metabolic effects), risperidone and amisulpride raise prolactin, and quetiapine and clozapine carry alpha-1 orthostatic effects.

2.5 Partial agonism and the muscarinic mechanism

Partial agonism (dopamine stabilisers). Aripiprazole and its relatives are D2 *partial* agonists rather than full antagonists: they occupy D2 and deliver an intermediate, tuned signal, dampening dopamine where transmission is excessive (mesolimbic) yet providing some tone where it is deficient (Stahl 2021). The consequence is a low extrapyramidal and low prolactin profile, because the receptor is never driven to the near-total blockade that produces those effects. The detailed clinical handling of aripiprazole, cariprazine and brexpiprazole is developed in the atypical-agents topic; here the point is only that partial agonism is a distinct mechanistic route to antipsychotic effect.

The muscarinic mechanism (a newer route). Beyond dopamine and serotonin, direct agonism at central muscarinic M1 and M4 cholinergic receptors is an emerging antipsychotic mechanism that reduces dopaminergic overactivity indirectly, without any D2 blockade, and so without the classical extrapyramidal and prolactin liabilities (Stahl 2021). This muscarinic-agonist strategy is the basis of the newest agents and is developed further in the atypical-agents topic; it is flagged here as the exception that proves the rule that dopamine blockade, while universal among the older drugs, is not the only path to an antipsychotic effect.

INDIA

The olanzapine pamoate long-acting injectable is marketed in India as Tolaz LA (Torrent Pharmaceuticals), the local counterpart of the depot whose pharmacology raises the post-injection syndrome, an inadvertent intravascular release causing sedation and delirium that mandates a supervised observation period after each injection. Verify current strengths, the observation protocol and availability against the product information before prescribing.

HOLD THIS

Antipsychotic effect = D2 blockade in the mesolimbic pathway at roughly 65 to 80 percent striatal D2 occupancy; above about 80 percent you buy extrapyramidal symptoms, not efficacy, and every off-target receptor (D2-motor, D2-prolactin, H1, M1, alpha-1) predicts its own adverse effect.

GOOD TO REMEMBER

- **D2 blockade:** the shared mechanism of action of every effective antipsychotic; potency tracks D2 affinity; the antipsychotic effect maps to mesolimbic D2 occupancy. Hold: striatal D2 occupancy of 65 to 70 percent for effect, above about 80 percent for rising extrapyramidal risk (Remington & Kapur 1999; Kapur 2000).
- **5-HT2A/D2 ratio:** the high 5-HT2A over D2 antagonism that defines most atypicals; 5-HT2A blockade disinhibits dopamine in the nigrostriatal and mesocortical pathways, giving lower extrapyramidal symptoms and a proposed effect on negative symptoms. Caveat: aripiprazole (partial agonism) and amisulpride (selective D2/D3) are atypical by other routes.
- **Extrapyramidal symptoms:** from D2 blockade in the nigrostriatal pathway; discriminator is the motor picture (dystonia, parkinsonism, akathisia, tardive dyskinesia); first step is to reduce dose or switch to a lower-extrapyramidal agent.
- **Hyperprolactinaemia:** from D2 blockade in the tuberoinfundibular pathway; discriminator is galactorrhoea, amenorrhoea, sexual dysfunction; first step is to check prolactin and consider a prolactin-sparing agent.
- **H1 blockade:** sedation and weight gain; the read-out that flags olanzapine and clozapine; first step is to weigh the sedative and metabolic cost against the benefit.
- **M1 (muscarinic) blockade:** the anticholinergic cluster (dry mouth, constipation, blurred vision, urinary retention, cognitive dulling); first step is dose review, especially in the elderly.
- **Alpha-1 blockade:** postural hypotension and dizziness; first step is slow titration and a lying-standing blood pressure check.
- **Partial agonism:** aripiprazole as a D2 partial agonist (dopamine stabiliser); the read-out is low extrapyramidal and low prolactin liability; the muscarinic-agonist route achieves antipsychotic effect with no D2 blockade at all.

3 · Typical (first-generation) antipsychotics

Why this matters. The **typical antipsychotic** agents, the **first-generation** drugs, are the substrate on which all antipsychotic pharmacology is built, and the examiner uses them to test one idea above all others: that a single axis, **potency**, predicts the whole adverse-effect profile. These drugs remain in daily Indian practice because they are effective against positive symptoms, cheap and widely available, so their doses and trade-offs are high-yield rather than historical. This topic teaches the classes, the potency axis, the receptor profile and the practical place today; it does not re-teach the illness (that phenomenology, aetiology, criteria and course belong to the Schizophrenia: aetiology, phenomenology, classification and course notes), nor does it re-derive the dopamine pathways and receptor mechanics (those are owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes and are only applied here).

The governing sentence is one line: for a first-generation drug, where it sits on the high-potency to low-potency scale tells you, before you know anything else, whether the patient will suffer more extrapyramidal and prolactin effects or more sedation, anticholinergic and cardiometabolic

effects (Stahl 2021, Kaplan & Sadock 2024). Efficacy against positive symptoms is broadly comparable across the class at adequate dose; what differs is which side effects the patient pays for that efficacy with.

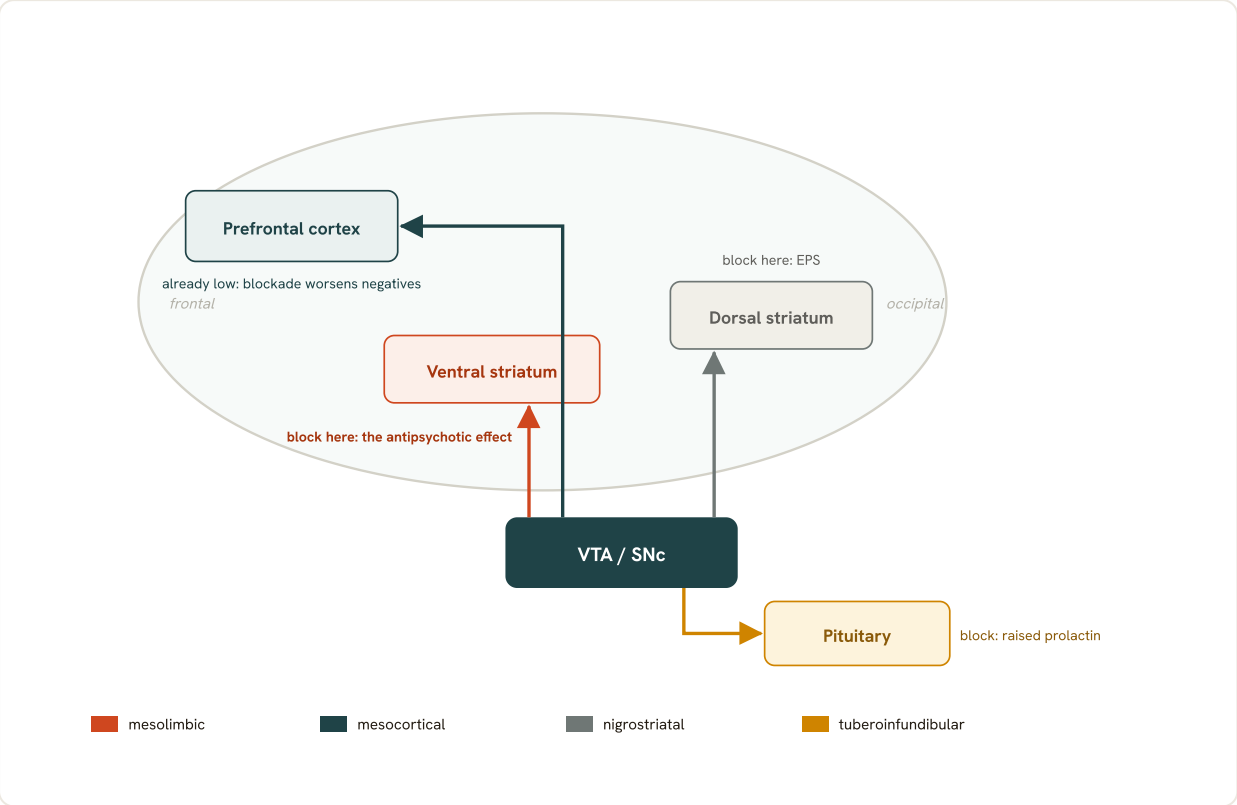

Fig 9.3 What D2 blockade does in each dopamine pathway. Blocking the overactive mesolimbic tract to the ventral striatum produces the antipsychotic effect. The same blockade in the nigrostriatal tract causes extrapyramidal effects, in the tuberoinfundibular tract raises prolactin, and in the already-underactive mesocortical tract can worsen the negative and cognitive symptoms. The pathway mechanics are developed in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

3.1 What "first-generation" means and how the class is defined

The first-generation antipsychotics, also called typical or conventional antipsychotics or neuroleptics, are the drugs introduced from chlorpromazine (1952) onward whose antipsychotic action rests predominantly on blockade of the dopamine D2 receptor (Stahl 2021). They are grouped chemically into the phenothiazines (chlorpromazine, thioridazine, trifluoperazine, fluphenazine), the butyrophenones (haloperidol), the diphenylbutylpiperidines (pimozide) and the thioxanthenes (flupentixol, zuclopenthixol). For the examination the chemical class matters less than the functional axis that cuts across it, potency, which is what the rest of this topic is built around. The term first-generation and the term first generation are used interchangeably in the literature and refer to the same set of drugs.

RULE **A first-generation antipsychotic is defined by predominant D2 blockade.** The antipsychotic effect tracks D2 occupancy in the mesolimbic pathway; almost everything else about the drug follows from how much of that D2 blockade, and how much off-target receptor blockade, it delivers.

3.2 The potency axis: what "potency" actually measures

In this context potency does not mean efficacy or how "strong" the drug is. It means the milligram dose required to achieve a given degree of D2 blockade, expressed by convention against chlorpromazine as the reference (Kaplan & Sadock 2024). A **high-potency** agent achieves antipsychotic D2 occupancy at a few milligrams (haloperidol); a **low-potency** agent needs hundreds of milligrams (chlorpromazine). Because the high-potency drug is given at a low milligram dose, it carries relatively little of the off-target histamine, muscarinic and alpha-1 blockade, so its D2-driven effects (extrapyramidal symptoms and hyperprolactinaemia) dominate. Because the low-potency drug is given at a high milligram dose, it brings substantial H1, M1 and alpha-1 blockade, so sedation, anticholinergic load and postural hypotension dominate while its relative extrapyramidal burden is lower. This inverse relationship is the single most tested idea in the topic.

> **PEARL**
>
> High potency and low potency describe the milligram dose needed for D2 blockade, not the clinical effectiveness. Haloperidol and chlorpromazine are comparably effective antipsychotics; haloperidol is simply "high-potency" because a few milligrams do what several hundred milligrams of chlorpromazine do.

3.3 Receptor profile: D2 plus the off-target three

Every first-generation antipsychotic blocks the dopamine D2 receptor, and that blockade is responsible for both the therapeutic action (in the mesolimbic pathway) and the signature adverse effects (extrapyramidal symptoms from the nigrostriatal pathway, hyperprolactinaemia from the tuberoinfundibular pathway). The low-potency agents add clinically important blockade of three further receptors: histamine H1 (sedation, weight gain), muscarinic M1 (dry mouth, constipation, blurred vision, urinary retention, cognitive dulling) and alpha-1 adrenergic (postural hypotension, dizziness). The high-potency agents, given at low milligram doses, are relatively "clean" of H1, M1 and alpha-1 activity, which is precisely why they are less sedating and less hypotensive but far more likely to cause extrapyramidal reactions (Stahl 2021). The detailed mechanics of each pathway and receptor sit in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; here we simply read the adverse-effect profile off the receptor list.

D2 (dopamine) blockade

Shared by all; mesolimbic blockade gives the antipsychotic effect, nigrostriatal gives extrapyramidal symptoms, tuberoinfundibular gives raised prolactin.

H1 (histamine) blockade

Prominent in low-potency agents; causes sedation and weight gain.

M1 (muscarinic) blockade

Prominent in low-potency agents; causes dry mouth, constipation, blurred vision, urinary retention and cognitive slowing.

Alpha-1 (adrenergic) blockade

Prominent in low-potency agents; causes postural (orthostatic) hypotension, dizziness and reflex tachycardia.

3.4 High-potency versus low-potency: the comparison

The table sets the two poles side by side. Read every row as the same trade being paid in a different currency: the high-potency end pays in movement disorder and prolactin, the low-potency end pays in sedation, anticholinergic burden, weight and blood pressure. Mid-potency agents (for example trifluoperazine and perphenazine) sit between the poles.

FEATURE	HIGH-POTENCY (HALOPERIDOL, TRIFLUOPERAZINE, FLUPHENAZINE, PIMOZIDE)	LOW-POTENCY (CHLORPROMAZINE, THIORIDAZINE)
Milligram dose for D2 blockade	**Low (few mg)**	High (hundreds of mg)
Extrapyramidal symptoms	**More (prominent)**	Fewer
Hyperprolactinaemia	**More**	Less
Sedation (H1)	Less	**More**
Anticholinergic effects (M1)	Less	**More**
Postural hypotension (alpha-1)	Less	**More**
Weight gain and cardiometabolic load	Less	**More**
Seizure threshold lowering	Less	**More**

The potency axis as an adverse-effect trade-off: extrapyramidal-and-prolactin burden at the high-potency end, sedation-and-metabolic burden at the low-potency end.

RULE **Potency predicts the adverse-effect trade-off.** Extrapyramidal symptoms and prolactin cluster at the high-potency end; sedation, anticholinergic effects, postural hypotension and metabolic load cluster at the low-potency end.

3.5 Indications and the practical place today

First-generation antipsychotics are effective against the positive symptoms of psychosis (delusions, hallucinations, thought disorder) and are used for acute and maintenance treatment of schizophrenia, acute psychotic agitation, mania (as adjuncts) and, for individual agents, for tics (pimozide, haloperidol), nausea and intractable hiccups (chlorpromazine). Their enduring place rests on being cheap and widely available, which matters greatly in resource-limited and public-sector settings; against that stands a higher burden of extrapyramidal symptoms and, over time, tardive dyskinesia compared with the second-generation drugs (Kaplan & Sadock 2024). A key limitation is that they do relatively little for negative and cognitive symptoms, and at high doses the high-potency agents can actually worsen negative and cognitive symptoms through excessive mesocortical D2 blockade (the neuroleptic-induced deficit syndrome) (Stahl 2021). They are not without a place in modern practice, but that place is defined by cost, availability and positive-symptom control, not by breadth of benefit.

INDIA

First-generation antipsychotics remain workhorse drugs in Indian public and private practice on grounds of cost and availability. Verified Indian trade names include haloperidol as Serenace and chlorpromazine, which is marketed generically and under multiple local names; both are on the essential-medicines footing that keeps them in wide use. Where an oral atypical is unaffordable, a low-dose high-potency first-generation agent is a legitimate and guideline-consistent choice for positive symptoms.

3.6 High-potency agents in detail

Haloperidol. The prototype high-potency butyrophenone, near-pure D2 antagonist, still one of the most-used conventional antipsychotics worldwide and effective at low doses; the recurring clinical error is dosing it too high, which buys extrapyramidal symptoms without extra antipsychotic benefit and may worsen negative symptoms (Stahl 2021). **Trifluoperazine and fluphenazine** are high-potency phenothiazines with a similar extrapyramidal-and-prolactin profile; fluphenazine is also available as a long-acting depot. **Pimozide** is a diphenylbutylpiperidine reserved as a second-line agent, notable for dose-dependent QTc prolongation and its use in Tourette's syndrome (Stahl 2021).

GOOD TO REMEMBER

- **Haloperidol:** high-potency butyrophenone, predominant D2 blockade; oral **1 to 40 mg/day** (Stahl), typically effective low, around 2 to 15 mg/day; watch for extrapyramidal symptoms and do not over-dose, as it is frequently dosed too high.
- **Trifluoperazine:** high-potency phenothiazine, D2 blockade; oral psychosis **15 to 20 mg/day** (Stahl); watch for extrapyramidal symptoms.
- **Fluphenazine:** high-potency phenothiazine, D2 blockade; oral **1 to 20 mg/day** maintenance, decanoate depot **12.5 to 100 mg** every 2 weeks (Stahl); watch for extrapyramidal symptoms and raised prolactin.
- **Pimozide:** high-potency diphenylbutylpiperidine, D2 blockade; oral usually **less than 10 mg/day** (maximum 10 mg/day, Stahl); monitor QTc, as prolongation is dose-dependent.

3.7 Low-potency agents in detail

Chlorpromazine is the original low-potency phenothiazine (D2 plus substantial H1, M1 and alpha-1 blockade), broad-spectrum but carrying sedation, anticholinergic load, postural hypotension, photosensitivity and, cumulatively, tardive dyskinesia risk (Stahl 2021). **Thioridazine** is a low-potency phenothiazine now largely restricted because of dose-dependent QTc prolongation with risk of ventricular arrhythmia and sudden death, and pigmentary retinopathy at high doses; it is effectively a last-line agent (Stahl 2021).

GOOD TO REMEMBER

- **Chlorpromazine:** low-potency phenothiazine, D2 plus H1, M1 and alpha-1 blockade; oral **200 to 800 mg/day** (Stahl); watch for sedation, postural hypotension and anticholinergic effects, and counsel on photosensitivity.
- **Thioridazine:** low-potency phenothiazine, D2 plus anticholinergic and alpha-1 blockade; oral **200 to 800 mg/day** in divided doses (Stahl); monitor QTc (dose-dependent prolongation, arrhythmia and sudden-death risk) and beware pigmentary retinopathy at high doses.

3.8 The depot (long-acting injectable) question

Several first-generation agents exist as long-acting depot injections (haloperidol decanoate, fluphenazine decanoate, flupentixol and zuclopenthixol decanoate), given every 2 to 4 weeks to secure adherence in maintenance treatment. A depot changes the route and the pharmacokinetics; it does not change the pharmacology. A first-generation depot is still a predominant D2 blocker, so it treats positive symptoms and covenants the same extrapyramidal-and-prolactin trade-off as its oral form. It does not acquire any new action against negative or cognitive symptoms by being injected. Expecting a depot to lift negative symptoms is a category error about what the molecule does.

TRAP **Expecting a first-generation depot to treat negative symptoms.** A depot only changes the route and dosing interval; the drug is still a D2 blocker that treats positive symptoms and, at high doses, can worsen negative symptoms, not relieve them.

3.9 Chlorpromazine equivalents and dosing across the class

Because the agents differ so widely in milligram potency, doses are compared using the chlorpromazine equivalent, the dose of a drug judged equipotent to a defined amount of chlorpromazine. This lets a clinician convert across agents and gauge total antipsychotic load, and it underpins the maintenance-dose evidence: for first-generation drugs, continuous low-dose maintenance (roughly 50 to 100 mg/day chlorpromazine equivalents) is less effective at preventing relapse than standard dosing (roughly 200 to 500 mg/day chlorpromazine equivalents) (Tasman 2015, Barbui et al. 1996). The practical lesson is to dose adequately for maintenance but no higher than needed, since above the therapeutic window the high-potency agents add extrapyramidal symptoms without added antipsychotic benefit.

1 to 40	200 to 800	200 to 500
HALOPERIDOL ORAL MG/DAY (STAHL)	CHLORPROMAZINE ORAL MG/DAY (STAHL)	STANDARD MAINTENANCE, CPZ-EQUIV MG/DAY

HOLD THIS

For a first-generation antipsychotic, potency predicts the poison: high-potency agents (haloperidol) pay in extrapyramidal symptoms and prolactin, low-potency agents (chlorpromazine) pay in sedation, anticholinergic effects, hypotension and metabolic load, and no first-generation drug, oral or depot, treats negative symptoms.

4 · Atypical, partial-agonist and newer agents, and choosing the antipsychotic

Why this matters. The **atypical antipsychotic** agents, the **second-generation** drugs, are what a psychiatrist reaches for first in most schizophrenia today, and the examiner tests two ideas above all: that they buy a lower extrapyramidal burden at the price of a metabolic one, and that choosing between them is an **adverse-effect** decision, not a search for a large efficacy gap. This topic teaches the atypical mechanism, the individual agents, the dopamine partial agonists, the newer and competitor-delta drugs, and the choice logic. It does not re-teach the illness (phenomenology, aetiology, criteria and course belong to the Schizophrenia: aetiology, phenomenology, classification and course notes), nor does it re-derive the receptor pharmacology and dopamine pathways (owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes and only applied here); clozapine and treatment resistance, and the adverse effects, are handled in their own topics.

The governing sentence: apart from clozapine, the landmark effectiveness trials found the second-generation drugs are not dramatically more effective than the first-generation ones, so the drug you pick is decided by which adverse-effect profile fits the patient in front of you (Lieberman 2005, Jones 2006). Second generation does not mean better across the board; it means a different and, for movement disorder, usually gentler trade, and the terms second-generation and second generation are used interchangeably in the literature.

4.1 What "atypical" means: the 5-HT2A/D2 balance

An atypical antipsychotic is defined, at least for the classic agents, by combining dopamine D2 antagonism with potent serotonin 5-HT2A antagonism, the **5-HT2A**/D2 balance (Stahl 2021, Kaplan & Sadock 2024). The "pines" (clozapine, olanzapine, quetiapine, asenapine, zotepine) and the "dones" (risperidone, paliperidone, ziprasidone, lurasidone) bind more potently to the **5-ht2a** receptor than to D2. The functional consequence, worked out mechanistically in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes, is that 5-HT2A blockade disinhibits dopamine release in the nigrostriatal and tuberoinfundibular pathways, which is why these drugs, at therapeutic doses, cause fewer extrapyramidal symptoms and less hyperprolactinaemia than a comparably effective first-generation agent, while retaining mesolimbic D2 blockade for the antipsychotic effect.

Two cautions the examiner likes. First, "atypical" is a loose class: the definition holds well for the 5-HT2A/D2 agents but breaks down for the newer entrants (a dopamine partial agonist, a pure muscarinic agonist), which achieve low extrapyramidal liability by entirely different routes. Second, low extrapyramidal load is not free: most atypicals, and olanzapine and clozapine above all, carry a substantial metabolic burden (weight gain, dyslipidaemia, impaired glucose tolerance).

RULE **The classic atypical trades extrapyramidal burden for metabolic burden.** Potent 5-HT2A antagonism on top of D2 antagonism lowers extrapyramidal and prolactin liability; the price, unevenly across agents, is weight, lipids and glucose.

4.2 The advantages, honestly weighed

Against the first-generation drugs, the atypicals offer three claimed advantages, each real but bounded. **Lower extrapyramidal symptoms and tardive dyskinesia** at therapeutic dose is the most robust, and the reason many guidelines prefer them, though it narrows if a first-generation agent is dosed low (in CATIE, mid-potency perphenazine performed comparably) (Lieberman 2005). **Some negative-symptom benefit** is modest and agent-specific (amisulpride at low dose, cariprazine), not a class property. **Some mood benefit** is genuine for several agents licensed in bipolar disorder (olanzapine, quetiapine, aripiprazole, cariprazine, lurasidone). The honest summary: the advantage is chiefly tolerability of movement, not a leap in antipsychotic efficacy.

4.3 Risperidone

Risperidone is a "done", a potent D2 and 5-HT2A antagonist, effective and widely used and, in India, cheap. Its two signature caveats are both dose-dependent. Extrapyramidal symptoms and, distinctively among atypicals, prolactin elevation rise steeply with dose, so that above roughly 6 mg/day orally it behaves increasingly like a high-potency first-generation drug and the risk of drug-induced parkinsonism climbs (Stahl 2021, Maudsley 2021). It is metabolically intermediate. Paliperidone, its active metabolite, is treated below.

GOOD TO REMEMBER

- **Risperidone:** atypical (D2 and 5-HT2A antagonist); oral **2 to 8 mg/day** for acute psychosis (Stahl), EMA maximum **16 mg/day** (Maudsley); dose-dependent extrapyramidal symptoms and hyperprolactinaemia, watch prolactin and movement above 6 mg/day. Indian brand Sizodon (also Risdone).

4.4 Olanzapine

Olanzapine is a "pine", a broad multi-receptor antagonist (D2, 5-HT2A, plus H1, M1 and others), highly effective and, after clozapine, one of the drugs to trial before clozapine (Maudsley 2021). Its defining problem is metabolic: alongside clozapine it has the worst metabolic profile of the class, with prominent weight gain, dyslipidaemia and impaired glucose tolerance, so it demands the fullest metabolic monitoring. Its low-EPS, sedating, appetite-driving profile is exactly the trade the CATIE data crystallised: longest time to discontinuation, bought with the heaviest metabolic cost (Lieberman 2005).

GOOD TO REMEMBER

- **Olanzapine:** atypical multi-receptor antagonist (D2, 5-HT2A, H1, M1); oral **10 to 20 mg/day** (Stahl); worst metabolic profile of the class with clozapine, so monitor weight, lipids and glucose closely. Indian brand Oleanz.

4.5 Quetiapine

Quetiapine is a "pine" with relatively weak, transient D2 occupancy and strong H1 antagonism. The clinical signature follows: it is markedly **sedating** (H1) and has the **lowest extrapyramidal liability** of the group, effectively no more than placebo, which makes it the atypical of choice where movement disorder must be avoided (for example in Parkinson's disease psychosis) (Stahl

2021). The costs are sedation, postural hypotension and weight gain; efficacy for schizophrenia sits at the upper end of its range.

GOOD TO REMEMBER

- **Quetiapine:** atypical (D2 and 5-HT2A antagonist, strong H1); schizophrenia **400 to 800 mg/day** in 2 doses (Stahl), EMA maximum **750 mg/day** (800 mg/day modified-release, Maudsley); very sedating, very low EPS, watch sedation and postural drop. Indian brand Qutipin.

4.6 Amisulpride, ziprasidone and paliperidone

Amisulpride is a substituted benzamide that is a fairly selective D2 and D3 antagonist (not a 5-HT2A blocker), with a distinctive dose split: low doses preferentially block presynaptic autoreceptors and help negative symptoms, higher doses block postsynaptic receptors for positive symptoms. It raises prolactin and prolongs QTc dose-dependently, and accumulates in renal impairment (Stahl 2021). **Ziprasidone** is a "done" that is metabolically favourable (little weight gain) but must be **taken with food**, which roughly doubles its bioavailability, and it prolongs QTc; it is often underdosed in practice (Stahl 2021). **Paliperidone** is the active metabolite of risperidone (9-hydroxyrisperidone), largely renally cleared, prolactin-raising, and available as long-acting palmitate injections.

GOOD TO REMEMBER

- **Amisulpride:** selective D2/D3 antagonist (benzamide); schizophrenia **400 to 800 mg/day**, negative symptoms only **50 to 300 mg/day** (Stahl), EMA maximum 1200 mg/day; dose-dependent QTc and prolactin, accumulates in renal impairment. Indian brand Amazeo (also Soltus).
- **Ziprasidone:** atypical (D2 and 5-HT2A antagonist); schizophrenia **40 to 200 mg/day** in divided doses, best above 120 mg/day (Stahl); metabolically light but must be taken with food (doubles absorption) and prolongs QTc.
- **Paliperidone:** active metabolite of risperidone; oral **3 to 12 mg/day** (usually 6 mg, Stahl), EMA maximum 12 mg/day; raises prolactin, largely renally cleared; palmitate depot available. Indian brand Paliris.

4.7 The partial agonists: aripiprazole, cariprazine, brexpiprazole

The dopamine **partial agonist** class works differently from every drug above. Aripiprazole is a **dopamine partial** agonist, a dopamine D2 **partial agonist** (with 5-HT1A partial agonism and 5-HT2A antagonism). Its **partial agonism** means it stabilises dopamine transmission: where synaptic dopamine is high (mesolimbic, positive symptoms) it acts as a functional antagonist and dampens it, and where dopamine is low it provides modest tone, which gives it a distinct profile, low metabolic burden, low prolactin (it can even lower prolactin), but a propensity to **akathisia** and activation (Stahl 2021). **Cariprazine** is a D3-preferring D2/D3 partial agonist with 5-HT1A partial agonism, marketed with a claim for negative symptoms; it has a long half-life and can cause akathisia. **Brexpiprazole** is a D2 partial agonist closely related to aripiprazole but with a somewhat less activating profile and lower reported akathisia.

RULE **The partial agonists stabilise rather than block dopamine.** Aripiprazole, cariprazine and brexpiprazole buy a low-metabolic, low-prolactin profile at the price of akathisia and activation, not sedation and weight.

GOOD TO REMEMBER

- **Aripiprazole:** dopamine D2 partial agonist (plus 5-HT1A partial agonist, 5-HT2A antagonist); schizophrenia and mania **15 to 30 mg/day** (Stahl), EMA maximum 30 mg/day; low metabolic burden, low or reduced prolactin, watch for akathisia and activation. Indian brand Arip (also Arip MT).
- **Cariprazine:** D3-preferring D2/D3 partial agonist (5-HT1A partial agonist); schizophrenia **1.5 to 6 mg/day** once daily (Stahl); long half-life, negative-symptom claim, watch for akathisia.
- **Brexpiprazole:** dopamine D2 partial agonist (5-HT1A partial agonist, 5-HT2A antagonist); schizophrenia typically **2 to 4 mg/day** (maximum 4 mg/day, Stahl); low-metabolic profile, less activating than aripiprazole.

4.8 The newer agents: asenapine, lurasidone, zotepine

Asenapine is a "pine" atypical distinguished by its route: it is a **sublingual** agent (oral tablets are not absorbed due to very low oral bioavailability), so it must be placed under the tongue with no eating or drinking for 10 minutes after; it causes oral hypoaesthesia and dysgeusia (Stahl 2021). Lurasidone is a "done" whose selling points are a genuine **metabolic advantage** (weight-, lipid- and glucose-neutral, and one of the few atypicals without a QTc warning) and a pharmacokinetic rule: it must be taken **with food** (a meal of at least 350 calories), because absorption falls by up to 50% on an empty stomach; its common adverse effects are akathisia and somnolence (Stahl 2021). Zotepine is a "pine" atypical of chiefly historical and exam interest, notable for a dose-dependent **seizure risk** (an established dose-related pro-convulsive effect), which limits its use (Maudsley 2021).

GOOD TO REMEMBER

- **Asenapine:** atypical (D2 and 5-HT2A antagonist), sublingual only; **10 to 20 mg/day** in 2 divided doses (Stahl), EMA maximum 20 mg/day sublingual; no food or drink for 10 minutes after dosing, causes oral hypoaesthesia.
- **Lurasidone:** atypical (D2, 5-HT2A, 5-HT7 antagonist, 5-HT1A partial agonist); schizophrenia **40 to 160 mg/day** (Stahl), EMA maximum 148 mg base/day; metabolically friendly with no QTc warning, must be taken with food (350-calorie meal) or absorption drops by half; watch for akathisia.
- **Zotepine:** atypical "pine" (D2 and 5-HT2A antagonist); dose-dependent, established pro-convulsive effect, so seizure risk is the caveat to hold (Maudsley); dose figures not confirmed here, see gaps.

4.9 Xanomeline-trospium (KarXT): a non-D2 route

Xanomeline combined with trospium, marketed as **KarXT** (the combination brand karxt), is the drug that fulfils the forward reference from the illness notes: an antipsychotic that does **not** act by D2 blockade at all. **Xanomeline** is an M1/M4 muscarinic receptor agonist; by stimulating M4 (and M1) receptors it indirectly reduces dopamine release in relevant circuits and increases prefrontal dopamine, producing an antipsychotic effect with essentially no extrapyramidal or

prolactin liability because it never blocks the dopamine receptor (Stahl 2021, Maudsley 2021). Because xanomeline alone causes cholinergic side effects (nausea, vomiting, sweating, salivation), it is co-formulated with **trospium**, a peripherally-restricted anticholinergic that does not cross the blood-brain barrier and so blocks the peripheral muscarinic effects while leaving the central antipsychotic action intact (Stahl 2021). It was studied in the EMERGENT phase-3 programme (Kaul 2024). Licensing status is evolving and jurisdiction-dependent (a US approval for schizophrenia was granted for KarXT; not established for India here), so verify the current licence before quoting it, and see gaps.

TRAP **Treating xanomeline-trospium as a D2 blocker.** It is a muscarinic (M1/M4) agonist that indirectly modulates dopamine; trospium is only there to block peripheral cholinergic side effects. There is no D2 antagonism, which is exactly why it has no extrapyramidal or prolactin signature.

GOOD TO REMEMBER

- **Xanomeline-trospium (KarXT):** xanomeline is an M1/M4 muscarinic agonist (not a D2 blocker), co-formulated with trospium, a peripherally-acting anticholinergic that curbs cholinergic side effects; no extrapyramidal or prolactin liability; dose and India licence not confirmed here, see gaps.

4.10 Step 5a: choosing the antipsychotic

With clozapine reserved for treatment resistance (its own topic), the arc's Step 5a is to **choose** the right antipsychotic by weighing **efficacy** against the adverse-effect **trade-off** for the individual patient. The evidence base for this is the pair of landmark effectiveness trials: CATIE (**catie**, Clinical Antipsychotic Trials of Intervention Effectiveness, USA), where olanzapine had the longest time to all-cause discontinuation but at a heavy metabolic cost and the first-generation comparator perphenazine performed broadly comparably to the other second-generation drugs (Lieberman 2005); and CUtLASS (**cutlass**, Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study, UK), which found no significant advantage of the second-generation drugs over the first-generation ones in quality of life, symptoms or satisfaction (Jones 2006). The lesson both trials teach is the same: apart from clozapine, no antipsychotic is dramatically more effective than another, so the choice is driven by the adverse-effect fit.

Practically, you read the patient's vulnerabilities and pick the agent whose adverse-effect profile least collides with them, avoiding the agent that would hit hardest. The table below is the working tool.

PATIENT FACTOR	PREFERRED AGENT(S)	WHAT TO AVOID
Metabolic risk (obese, diabetic, dyslipidaemic, young at first episode)	**Aripiprazole, lurasidone, ziprasidone, brexpiprazole**	Olanzapine, clozapine (and quetiapine)
Extrapyramidal vulnerability (elderly, Parkinson's, prior severe EPS)	**Quetiapine, clozapine, aripiprazole**	High-dose risperidone, first-generation high-potency agents

PATIENT FACTOR	PREFERRED AGENT(S)	WHAT TO AVOID
Prolactin-sensitive (young woman, sexual or menstrual concern, fertility)	**Aripiprazole (prolactin-sparing/lowering)**	Risperidone, paliperidone, amisulpride, first-generation high-potency
Prominent insomnia, agitation, need for sedation	**Quetiapine, olanzapine**	Aripiprazole, cariprazine (activating, akathisia)
Cardiac risk or QTc concern	**Aripiprazole, lurasidone (no QTc warning)**	Ziprasidone, amisulpride, high-dose quetiapine, thioridazine, pimozide
Prominent negative symptoms	**Amisulpride (low dose), cariprazine**	Relying on high-dose first-generation agents
Adherence problem	**Long-acting injectable (paliperidone palmitate, aripiprazole, risperidone)**	Sole reliance on unsupervised oral dosing
Seizure history or low threshold	**Higher-threshold agents (e.g. aripiprazole, risperidone)**	Zotepine, clozapine, chlorpromazine (dose-dependent seizure risk)

Step 5a in practice: match the agent to the patient's dominant vulnerability, because apart from clozapine the choice is an adverse-effect decision, not an efficacy one.

2	2 to 8	10 to 20
LANDMARK TRIALS DRIVING THE CHOICE (CATIE, CUTLASS)	RISPERIDONE ORAL MG/DAY (STAHL)	OLANZAPINE ORAL MG/DAY (STAHL)

INDIA

Olanzapine is available as a long-acting injectable, marketed in India as Tolaz (olanzapine pamoate); it carries the drug-specific risk of post-injection syndrome (an inadvertent partial intravascular delivery causing sedation and delirium), so it requires a post-dose observation period. The Indian Psychiatric Society (IPS) schizophrenia guideline supports second-generation agents as reasonable first-line choices while recognising cost and availability, and verified Indian trade names for common atypicals include risperidone as Sizodon (also Risdone), olanzapine as Oleanz, quetiapine as Qutipin, aripiprazole as Arip (also Arip MT), amisulpride as Amazeo (also Soltus) and paliperidone as Paliris; where affordability dominates, a well-chosen atypical or a low-dose high-potency first-generation agent are both defensible.

MNEMONIC

MEPS-C

The five axes to weigh when you choose: **M**etabolic, **E**xtrapyramidal, **P**rolactin, **S**edation, **C**ardiac (QTc). Read the patient against each axis and pick the agent that collides least with the dominant one.

HOLD THIS
Apart from clozapine, CATIE and CUtLASS showed no dramatic efficacy gap between antipsychotics, so you choose by matching the adverse-effect profile (metabolic vs EPS vs prolactin vs sedation vs cardiac) to the individual patient.

5 · First-episode management and early intervention

The **first-episode** is the single most consequential moment in the whole treatment algorithm, and the examiner treats it as a management principle in its own right, not a footnote to acute prescribing. Two ideas carry the topic: the first episode is the *best therapeutic window*, because a drug-naive brain responds at lower doses and the treated trajectory of the illness can still be altered; and the **duration of untreated psychosis** is the one prognostic variable the clinician can actually change. Around these two ideas sits a service model, **early intervention**, built specifically to shorten that untreated interval and to deliver low-dose medication, family work and vocational support during the years when the illness is most malleable (New Oxford 2020, Maudsley 2021).

How to use this page. Fix the first-episode principle (start a single antipsychotic at the lowest effective dose after a full baseline), then the modifiable predictor (**duration of untreated psychosis**), then the service that operationalises both (**early intervention** services, the **eis**). The disorder itself, its prodrome, at-risk mental state, criteria and course, is not re-taught here; it belongs to the Schizophrenia: aetiology, phenomenology, classification and course notes, and this topic cross-references the prodrome and at-risk state to it. The receptor pharmacology and CYP metabolism behind the drugs belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

5.1 Why the first episode is the best window

The malleable moment. The first episode of psychosis is the point at which the illness is most responsive to treatment and most open to having its course changed. A first-episode patient is antipsychotic-naive, so response occurs at doses well below those needed in multi-episode illness, and the accumulated disability, adverse-effect burden and treatment-resistance of chronic illness have not yet set in. The realistic aim of intervening well here is not merely to abort the acute episode but to protect the longer trajectory: functional recovery, return to study or work, and prevention of the step-wise decline that follows each subsequent relapse (Maudsley 2021, New Oxford 2020). This is why the management of the first episode is examined as a distinct principle and not simply as "acute treatment in a young patient".

RULE **Start low and go slow in the first episode.** These patients are dose-sensitive: begin a single antipsychotic at the lowest effective dose and titrate against response and tolerability, because they respond at lower doses and are more adverse-effect sensitive than multi-episode patients.

5.2 One drug, lowest effective dose, drug-naive sensitivity

Monotherapy at the minimum effective dose. The prescribing rule for a first episode is a single antipsychotic, chosen on adverse-effect profile and patient preference (there is no clear efficacy

winner among non-clozapine agents, with only minor individual advantages for olanzapine and amisulpride), started at the lowest effective dose and titrated slowly (Maudsley 2021). The first-episode minimum effective dose is lower than the multi-episode dose for essentially every agent, and holding a few of these numbers lets you defend a starting dose in a viva. Clozapine has no place at first presentation; it belongs to the treatment-resistance branch after two adequate trials fail, developed in the treatment-resistance and clozapine topics.

ANTIPSYCHOTIC	FIRST-EPISODE MINIMUM EFFECTIVE DOSE (MG/DAY)	MULTI-EPISODE DOSE, MG/DAY (CONTRAST)
Haloperidol (FGA)	2	4
Olanzapine (SGA)	5	7.5
Risperidone (SGA)	2	4
Aripiprazole (SGA)	10	10
Amisulpride (SGA)	300	400 (estimate)

First-episode minimum effective doses run below multi-episode doses, the numeric expression of drug-naive dose sensitivity (Maudsley 2021, Table 1.1). Generic names lead; verify local formulations.

Why lower doses matter beyond tolerability. There is a signal that first-episode patients who receive lower doses have better long-term functional outcomes, and the possibility of dopamine-receptor super-sensitivity on withdrawal reinforces using the lowest possible dose in all patients (Maudsley 2021). Very low or sub-therapeutic doses, however, lose prophylactic efficacy, so "lowest" means lowest *effective*, not homeopathic.

5.3 The full baseline before the first dose

Baseline everything, then start. Before the first antipsychotic dose the first-episode patient needs a full physical and metabolic baseline, both to detect an organic or co-occurring cause and to serve as the reference point for all later monitoring (APA 2020). This baseline is done once, at the front door, and cannot be reconstructed later. The relevant panel is the initial-assessment column of the standard monitoring schedule.

Physical and vitals

History and physical examination, pulse and blood pressure, weight, height and body-mass index.

Metabolic

Fasting blood glucose (or HbA1c) and a fasting lipid panel, with metabolic-syndrome criteria assessed, because the antipsychotic will move all of these.

Cardiac

Baseline ECG where a QTc-prolonging agent is planned or cardiac risk factors are present; full-blood-count, renal, liver and thyroid function and prolactin as clinically indicated.

The detail of the ongoing monitoring intervals (weight, glucose and lipids at defined follow-up points) is developed in the metabolic-monitoring topic; the first-episode point is that the pre-treatment reading is captured before the drug is given.

5.4 Duration of untreated psychosis: the modifiable predictor

The one variable you can change. The duration of untreated psychosis is the interval from the onset of frank psychotic symptoms to the start of adequate treatment. It matters because longer **duration of untreated psychosis** is associated with poorer prognosis: slower and less complete symptomatic response, poorer functional recovery and greater accumulation of secondary harms (substance misuse, self-harm and suicide, interpersonal and family breakdown) (Addington 2004, New Oxford 2020). Unlike age at onset, sex or family history, it is potentially *modifiable*, which is precisely why it is the rational target of early detection and the theoretical engine of the whole early-intervention movement.

The rationale for early detection. If a long untreated interval worsens outcome, then shortening it should improve outcome, so early-intervention services are built to reduce the duration of untreated psychosis by lowering the barriers to help-seeking, running assertive outreach, and providing rapid, low-threshold access to assessment and treatment. The prodrome and at-risk mental state that precede the first frank episode, and the transition risk from those states, are owned by the Schizophrenia: aetiology, phenomenology, classification and course notes; here they matter only as the window during which detection can begin before psychosis is fully manifest.

TRAP **Delaying treatment.** A long duration of untreated psychosis worsens outcome, so do not delay effective treatment; watchful waiting past the point of frank psychosis squanders the modifiable predictor and the best window the illness will offer.

5.5 Early intervention services: the specialist team

What an EIS is. Early intervention services (the **eis**) are specialist, multidisciplinary teams that deliver phase-specific care to first-episode and early-psychosis patients for the first years of illness, rather than folding them into a generic community team. The characteristic package combines low-dose antipsychotic medication, structured family work and psychoeducation, and vocational and educational support, delivered through intensive case management with low caseloads, assertive outreach and easy access to staff (New Oxford 2020, Maudsley 2021). The model targets the "critical period" of the early illness, on the logic that intervening intensively while the illness is malleable buys durable gains.

The three deliverables. Hold the EIS as three limbs delivered together during the early years: *low-dose medication* (a single antipsychotic at first-episode doses, per 5.2); *family work* (psychoeducation and reduction of high expressed emotion, which lowers relapse risk); and *vocational and educational support* (getting the young person back into study or work, the outcome that matters most to them). Individual-placement-and-support style supported employment embedded in early-psychosis services has achieved employment or return-to-study outcomes at rates well above generic vocational rehabilitation (Killackey 2008).

5.6 The evidence: better engagement and outcome

Specialist early care beats treatment as usual. Randomised trials show that specialist early-intervention teams outperform standard community care during the intervention period on

engagement, relapse, admission and functional outcomes. The Danish OPUS trial randomised first-episode patients to two years of integrated specialist early treatment versus standard treatment and found benefits on psychotic and negative symptoms and service use during the intervention (Bertelsen 2008). The US RAISE Early Treatment Program showed that coordinated specialty care (the American term for the EIS package) improved quality of life and symptom outcomes over usual community care at two-year follow-up (Kane 2016). The important caveat, also examinable, is durability: the two-year OPUS gains largely eroded once patients stepped down to standard care by five-year follow-up, whereas prolonged early intervention (extending the specialist package by one to three years) produced more sustained benefit (Bertelsen 2008, New Oxford 2020). Integrated early care is also broadly cost-effective, because the added treatment cost is offset by fewer inpatient days.

PEARL

The EIS evidence is a "use it or lose it" story. Specialist early intervention reliably beats standard care *while it runs*; the two-year OPUS advantage faded after step-down, and only prolonged early intervention held the gains. In a viva, name OPUS and RAISE, then add the durability caveat, that is the discriminating detail.

5.7 Response timeline, adherence and shared decision-making

The expected response timeline. Set expectations against the algorithm: an adequate antipsychotic trial in the first episode is an adequate dose for an adequate duration, and much apparent non-response is inadequate dose, inadequate duration or covert non-adherence rather than true resistance (Maudsley 2021). Improvement in agitation and sleep can be early; the fuller antipsychotic response accrues over weeks, and positive symptoms respond better and faster than negative and cognitive symptoms. Do not declare failure and switch before an adequate trial has run with adherence confirmed. After remission of a first episode, current consensus is to continue the antipsychotic for one to two years before considering a very gradual, closely monitored dose reduction, because abrupt discontinuation carries a high relapse rate (Maudsley 2021, APA 2020).

26% vs 61%	**1 to 2 yr**	**55% vs 28%**
1ST-EPISODE RELAPSE AT 6 TO 12 MO: MAINTAINED VS PLACEBO	CONTINUE ANTIPSYCHOTIC AFTER 1ST-EPISODE REMISSION	ANY WORK OVER 18 MONTHS, SUPPORTED EMPLOYMENT VS STANDARD (EQOLISE)

Adherence support and shared decision-making. The first episode is where the therapeutic alliance is made or lost, and non-adherence is the commonest driver of relapse. Build adherence deliberately: psychoeducation for patient and family, addressing insight and beliefs about medication, minimising adverse-effect burden (a major reason young people stop), and considering a long-acting injectable early rather than only after a relapse, since guaranteed delivery reduces relapse and rehospitalisation. Frame every choice as **shared decision-making**: present the realistic response timeline, the adverse-effect trade-offs and the maintenance rationale, and decide the drug and route with the patient, because a plan the young person owns is the plan they will actually take.

INDIA

Where a long-acting injectable is chosen to secure early adherence, olanzapine pamoate long-acting injection is marketed in India as Tolaz (Torrent); its binding constraint is the post-injection syndrome (a delirium/excessive-sedation reaction), which mandates a supervised post-injection observation period after every dose, a service most Indian outpatient settings cannot deliver, so it is chosen deliberately, not by default. Community delivery of early psychosis care in India sits under the District Mental Health Programme (DMHP), and the Indian Psychiatric Society (IPS) schizophrenia guideline gives the locally calibrated, resource-aware version of this pathway. Generic prescribing dominates and is affordable; verify the local brand before naming one.

HOLD THIS

The first episode is the best window: one antipsychotic at the lowest effective dose after a full baseline, in a drug-naive dose-sensitive patient, delivered by an early-intervention service that shortens the duration of untreated psychosis (the one modifiable predictor) and combines low-dose medication, family work and vocational support, for one to two years of continued treatment and better engagement and outcome while the specialist team runs.

GOOD TO REMEMBER

- **Antipsychotic in the first episode (the backbone):** a single dopamine-D2-blocking agent (class and per-drug mechanics owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes); first-episode minimum effective doses run low (haloperidol 2 mg/day, olanzapine 5 mg/day, risperidone 2 mg/day, aripiprazole 10 mg/day, amisulpride 300 mg/day); the one caveat is drug-naive dose sensitivity, so start low, go slow, and run an adequate trial before calling it a failure.
- **Duration of untreated psychosis (the modifiable predictor):** the interval from onset of frank psychosis to adequate treatment; the discriminator from fixed predictors (age, sex, family history) is that it is changeable; the first management step is early detection and rapid low-threshold access to treatment, because a longer interval worsens outcome.
- **Early intervention service / EIS (the specialist model):** a multidisciplinary team delivering low-dose medication, family work and vocational support for the first years; the discriminator from a generic community team is intensive low-caseload case management and assertive outreach; the first step is early engagement, with the durability caveat that gains fade after step-down unless intervention is prolonged.
- **Baseline panel (before the first dose):** physical examination and vitals, weight/height/BMI, fasting glucose and lipids, ECG where indicated; the discriminator is that it is captured once, pre-treatment, as the reference for later monitoring; the first step is to complete it before giving the antipsychotic (APA 2020).

Figure. The first-episode pathway, early detection reducing the duration of untreated psychosis, then EIS delivery of low-dose medication plus family and vocational work across the critical early years, is flagged for a concept figure.

6 · Maintenance treatment, relapse prevention and discontinuation

Why this matters. Acute treatment gets the patient well; **maintenance treatment** keeps them well, and it is the single most consequential decision in the long-term care of schizophrenia. The examiner tests one idea above all: that continuing an antipsychotic after remission is not optional

polish but the core intervention that prevents relapse. Off medication, the natural history of the illness reasserts itself and most patients relapse within one to two years; on medication, that risk falls sharply. Maintenance treatment is therefore **relapse prevention** by another name, and the practical questions the examiner asks are three: at what dose, for how long, and how to stop if stopping at all.

The illness itself, its phenomenology, aetiology, criteria and course, is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes and is not re-taught here; the receptor pharmacology and dopamine-pathway mechanics behind why continued blockade prevents relapse belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes and are applied, not re-derived. What this topic teaches is the maintenance decision: the evidence that maintenance prevents relapse (Leucht et al. 2012, Maudsley 2021), the duration of treatment guidelines recommend, the maintenance dose that works, and the safe conduct of discontinuation when it is attempted.

6.1 The rationale: continued treatment markedly reduces relapse

The evidence for maintenance treatment is among the most robust in psychiatry. A landmark systematic review and meta-analysis of antipsychotic drug versus placebo for relapse prevention pooled 65 trials and found that continuing an antipsychotic roughly halved the relapse rate against placebo (Leucht et al. 2012). In that analysis relapse at seven to twelve months occurred in **27 percent** of patients on an antipsychotic versus **64 percent** on placebo, a number needed to treat of **3**, and re-admission fell from 26 percent to 10 percent, a number needed to treat of **5** (Leucht et al. 2012, tabulated in Maudsley 2021). Read against off-medication figures that commonly reach 60 to 80 percent relapse over one to two years, this is a large, reproducible effect. Continued antipsychotic treatment does not cure the illness, but it substantially and reliably reduces the probability that positive symptoms return.

The corollary is that **relapse prevention** is the explicit goal of maintenance, and relapse is costly: each episode risks hospitalisation, carries a suicide and aggression risk, erodes the baseline level of functioning, and the majority of that functional decline occurs in the first decade of illness (Maudsley 2021). Preventing relapse is therefore not merely symptom-suppression, it is protection of the patient's long-term trajectory.

RULE **Maintenance treatment is relapse prevention.** Continuing an antipsychotic after remission roughly halves the relapse rate versus stopping (27 versus 64 percent at 7 to 12 months, NNT 3), and each prevented relapse protects hospitalisation-free functioning.

PEARL

The Leucht et al. 2012 figures (relapse 27 versus 64 percent, NNT 3; re-admission 10 versus 26 percent, NNT 5) are the single most quotable relapse-prevention numbers in the antipsychotic literature. If you memorise one maintenance statistic, memorise the NNT of 3 for relapse.

6.2 The natural history off medication: why relapse is the default

Discontinuation studies make the argument for maintenance from the other direction. When antipsychotics are withdrawn after remission, relapse becomes the expected outcome rather than the exception. A meta-analysis of placebo-controlled first-episode trials found that 26 percent of patients on maintenance antipsychotic relapsed at six to twelve months compared with 61 percent on placebo (Leucht et al. 2012, cited in Maudsley 2021). Longer follow-up is starker: one study of withdrawal after a first episode reported a relapse rate of almost **80 percent** after one year medication-free and **98 percent** after two years (Maudsley 2021), and only a small minority of patients who discontinue remain well one to two years later. A more optimistic 2018 meta-analysis still found relapse rates averaging 35 percent (treated) versus 61 percent (discontinued) at eighteen to twenty-four months (Maudsley 2021). Across every dataset the direction is the same: off medication, the illness returns for most patients within one to two years.

WORKED EXAMPLE

A young man has fully remitted six months after a first episode and asks to stop his olanzapine. The honest framing is not "you are cured" but "the medication is why you are well; stopping in the first year or two carries a relapse risk that studies put anywhere from around 60 percent up to 80 percent, against roughly a quarter if you continue." That risk-benefit framing, not a bare yes or no, is what the guidelines ask you to deliver (Maudsley 2021).

6.3 Duration of treatment: how long guidelines advise continuing

The **duration of treatment** is titrated to the illness stage and prior course. The current consensus, and the figure to hold, is that antipsychotics should be continued for at least **1 to 2 years** after a first episode of schizophrenia before any attempt at withdrawal is considered (Maudsley 2021). After a relapse, and after each subsequent episode, a longer duration is advised because the relapse risk on withdrawal is higher and the functional cost of a further episode is greater. For patients with a history of serious aggression or serious suicide attempts, and those with residual psychotic symptoms, guidelines advise considering **life-long (indefinite) treatment** (Maudsley 2021). The New Oxford Textbook and APA positions are concordant: duration scales with the number of episodes and the severity and dangerousness of the illness.

The reason duration is not simply "forever for everyone" is the trade-off against long-term adverse effects. Continued antipsychotic exposure carries cumulative risks, tardive dyskinesia, metabolic burden and weight gain, hyperprolactinaemia, that must be weighed against the relapse risk of stopping. The individual adverse-effect syndromes are taught in the adverse-effect topics; here the point is that the duration decision is an explicit risk-benefit calculation, revisited over time, not a fixed rule.

CLINICAL SITUATION	GUIDELINE DURATION OF TREATMENT
After a first episode, fully remitted	**At least 1 to 2 years before considering withdrawal**
After a relapse / multi-episode illness	Longer maintenance (several years, individualised)
Severe illness, residual symptoms	Longer, often indefinite
History of serious aggression or serious suicide attempts	**Consider life-long (indefinite) treatment**

Duration of treatment scales with episode number and the danger the illness poses; withdrawal is only considered after the minimum first-episode period of 1 to 2 years (Maudsley 2021).

RULE **Continue at least 1 to 2 years after a first episode, longer after relapses.** Indefinite treatment is advised where the illness is severe, symptoms are residual, or there is a history of serious aggression or serious suicide attempts.

6.4 The maintenance dose: the lowest effective dose that prevents relapse

The governing principle of the **maintenance dose** is the lowest dose that reliably prevents relapse, no lower. The evidence sets a floor. In a meta-analysis of randomised trials, continuous low-dose treatment with first-generation drugs (defined as 50 to 100 mg/day chlorpromazine equivalents) was less effective than standard dosage (200 to 500 mg/day chlorpromazine equivalents) at preventing relapse (Barbui et al. 1996, in Tasman 2015). Older dose-response work found that lowering the acute dose by about 80 percent may be relatively safe in the maintenance phase, but that relapse rates become excessively high when the dose is reduced further (Kane et al. 1983, Marder et al. 1987, in Tasman 2015). Guideline-level dosing for first-generation maintenance is commonly cited as **300 to 600 mg/day** chlorpromazine equivalents (Buchanan et al. 2010 PORT, in Tasman 2015), with no good evidence that doses above 600 mg/day chlorpromazine equivalents add benefit. For the newer drugs there are no data to support routinely using lower-than-standard doses as prophylaxis; the dose that was acutely effective is generally continued, the one supportable exception being very careful dose reduction after a first episode (Maudsley 2021).

The practical rule that emerges is directional: dose adequately for maintenance but no higher than needed. High maintenance doses buy adverse effects, extrapyramidal symptoms and metabolic load, without added antipsychotic benefit once the efficacy threshold is passed, while **very low doses raise relapse risk**. Where dose reduction is undertaken, an international consensus recommended a gradual reduction of about 20 percent every six months until a minimum maintenance dose is reached (Kissling 1991, in Tasman 2015).

27 vs 64	3	10 vs 26
RELAPSE % DRUG VS PLACEBO, 7 TO 12 MO (LEUCHT 2012)	NNT FOR RELAPSE PREVENTION (LEUCHT 2012)	RE-ADMISSION % DRUG VS PLACEBO (LEUCHT 2012)

TRAP **Pushing the maintenance dose too low to spare side effects.** Very-low-dose maintenance (roughly 50 to 100 mg/day chlorpromazine equivalents for the older drugs) raises relapse; the target is the lowest dose that still prevents relapse, not the lowest tolerated dose.

6.5 Intermittent and targeted dosing: why they are not recommended

An intuitively attractive strategy is to stop the antipsychotic once the patient is well and restart it only when prodromal symptoms of relapse appear, so-called intermittent dosing or **targeted** (prodrome-based) dosing, sparing the patient continuous exposure. The evidence is clear and negative. Targeted or intermittent pharmacotherapy is associated with increased risks of symptom exacerbation, relapse and rehospitalisation, and guideline reviews conclude that intermittent strategies should be avoided (Hasan et al. 2013, in Tasman 2015). The Maudsley states the same point directly: targeted relapse treatment is much less effective than continuous prophylaxis (Maudsley 2021). The strategy fails because the prodrome is an unreliable early-warning system; by the time symptoms are detectable, relapse is often already under way, and reinstating the drug does not fully reverse it. Continuous maintenance at the lowest effective dose, not intermittent treatment, is the recommended approach.

TRAP **Intermittent or targeted (prodrome-based) dosing to spare exposure.** It raises relapse, exacerbation and rehospitalisation and is not recommended; continuous maintenance at the lowest effective dose is the standard of care.

6.6 Discontinuation: taper slowly and monitor for early relapse

When **discontinuation** is agreed after a full risk-benefit discussion, how it is done matters as much as whether it is done. Withdrawal of antipsychotic drugs after long-term treatment should be gradual and closely monitored (Maudsley 2021). Abrupt discontinuation carries a distinctly higher relapse risk: the relapse rate in the first six months after abrupt withdrawal is roughly **double** that seen after gradual withdrawal, with gradual defined as a slow taper over at least **3 weeks** for oral antipsychotics (Maudsley 2021). Abrupt cessation of oral treatment may also provoke discontinuation symptoms such as headache, nausea and insomnia. Part of the excess relapse on abrupt withdrawal is thought to reflect a dopamine supersensitivity rebound rather than pure re-emergence of the underlying illness, which is a further argument for tapering slowly (Maudsley 2021).

Throughout discontinuation the patient, carers and key workers must be educated in the early signs of relapse (sleep disturbance, return of suspiciousness, social withdrawal, subtle thought changes) and how to access help quickly, so that treatment can be reinstated at the first sign of deterioration. The factors to weigh before stopping include how long the patient has been symptom-free, the severity of adverse effects driving the wish to stop, the previous pattern and dangerousness of illness, the outcome of any prior dose-reduction attempts, current social stability and the social cost of relapse (Maudsley 2021). Where the concern is adherence rather than the decision to treat, a long-acting injectable secures guaranteed drug delivery and is associated with a reduced risk of relapse and rehospitalisation, discussed in the depot topic on long-acting injectable antipsychotics.

RULE **If stopping, taper slowly and monitor for early relapse.** Abrupt withdrawal roughly doubles the six-month relapse rate versus a gradual taper (at least 3 weeks for an oral antipsychotic); educate the patient and carers on early relapse signs before you start.

INDIA

Where medication adherence is the limiting factor, long-acting injectables that support maintenance in Indian practice include haloperidol decanoate, fluphenazine decanoate and the second-generation injectables; among the latter is the olanzapine long-acting injectable marketed in India as Tolaz, which carries the specific caveat of post-injection delirium/sedation syndrome and mandates a post-dose observation period. Detailed handling of the injectables sits in the depot topic on long-acting injectable antipsychotics; the maintenance point is that a depot converts a maintenance-dose decision into a guaranteed-delivery one and lowers relapse risk in poorly adherent patients (Maudsley 2021).

6.7 Non-adherence: the commonest driver of avoidable relapse

Non-adherence undermines maintenance more than any pharmacological subtlety. Among people with schizophrenia, non-adherence is high and rises steeply: up to 25 percent are partially or non-adherent by just ten days after discharge, rising to about 50 percent at one year and 75 percent at two years (Maudsley 2021). Non-adherence not only increases the risk of relapse, it may increase the severity of relapse and the duration of hospitalisation, and is associated with a roughly four-fold increase in suicide attempts (Maudsley 2021). This is why a maintenance plan that looks adequate on paper can fail in practice, and why identifying covert non-adherence, and offering a long-acting injectable where appropriate, is part of relapse prevention rather than separate from it. The depot topic on long-acting injectable antipsychotics develops the adherence solution.

GOOD TO REMEMBER

- **Maintenance treatment (the intervention):** continued antipsychotic after remission; roughly halves relapse (27 versus 64 percent at 7 to 12 months, NNT 3; re-admission 10 versus 26 percent, NNT 5, Leucht et al. 2012); the one thing to hold is that maintenance equals relapse prevention.
- **Duration of treatment:** at least **1 to 2 years** after a first episode, longer after relapses, indefinite if severe, residual symptoms, or serious aggression or suicide-attempt history; the caveat is the trade-off against cumulative long-term adverse effects (Maudsley 2021).
- **Maintenance dose:** the lowest effective dose that prevents relapse (first-generation guideline dosing about **300 to 600 mg/day** chlorpromazine equivalents, Buchanan et al. 2010); the caveat is that very-low-dose maintenance raises relapse and high doses add only side effects.
- **Intermittent / targeted dosing:** stopping and restarting on prodrome; the discriminator is that it raises relapse, exacerbation and rehospitalisation; the first step is not to use it, prefer continuous maintenance (Hasan et al. 2013).
- **Discontinuation:** gradual, monitored withdrawal; the discriminator is that abrupt stopping roughly doubles the six-month relapse rate; the first step is a slow taper (at least 3 weeks oral) with patient and carer education on early relapse signs (Maudsley 2021).
- **Non-adherence:** commonest cause of avoidable relapse; the discriminator is the steep rise (25 percent by 10 days, 50 percent at 1 year, 75 percent at 2 years); the first step is to detect it and offer a long-acting injectable (Maudsley 2021).

HOLD THIS

Maintenance treatment is relapse prevention: continue at least 1 to 2 years after a first episode (longer, up to indefinitely, after relapses or severe illness) at the lowest dose that still prevents relapse, never use intermittent or targeted dosing, and if you ever stop, taper slowly over weeks with monitoring for early relapse because abrupt withdrawal roughly doubles the relapse rate.

7 · Depot and long-acting injectable antipsychotics

A **depot** or long-acting injectable antipsychotic delivers a slow-release intramuscular formulation every few weeks, so the patient does not have to take a tablet every day. The old image of the depot as a punishment for the non-adherent is wrong: an **lai** gives assured medication delivery, steadier plasma levels and fewer relapses, and it is worth offering early to any patient for whom continuous cover matters, not only after adherence has failed (Maudsley 2021).

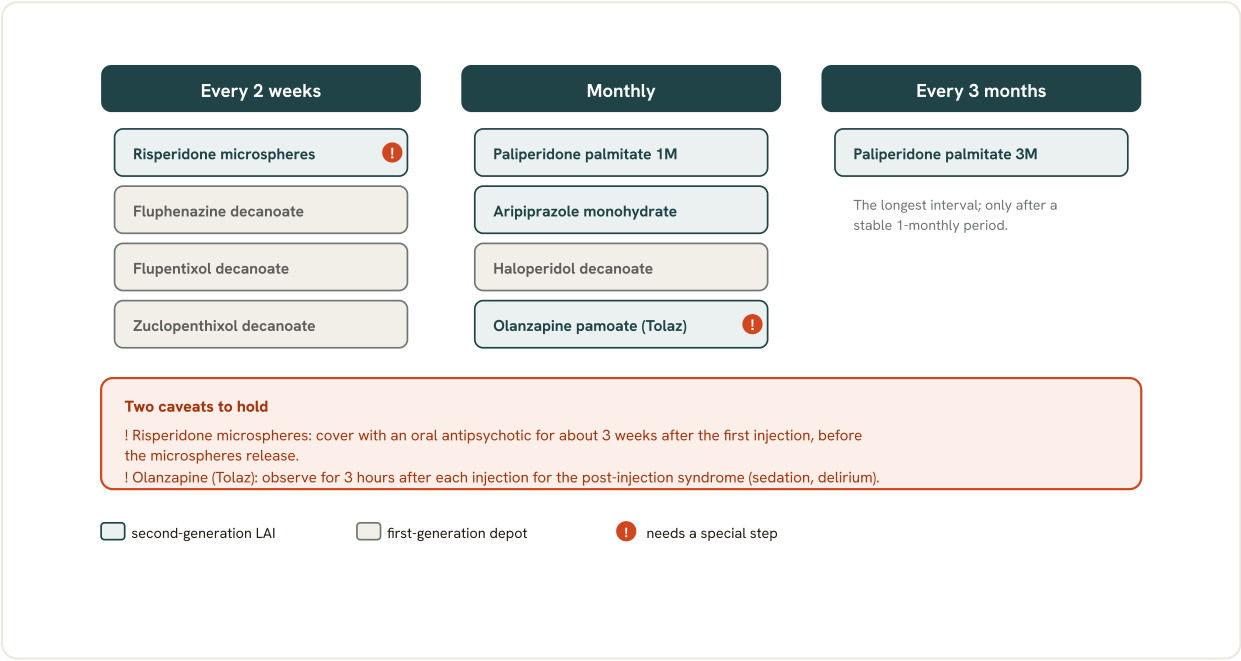

Fig 9.4 Depot and long-acting injectable antipsychotics, grouped by dosing interval. An assured-adherence tool that cuts relapse, worth considering early rather than only after failure. Two caveats matter: risperidone microspheres need oral cover for about three weeks after the first dose, and the olanzapine injectable (marketed in India as Tolaz) needs a three-hour observation for the post-injection syndrome.

7.1 Why use a long-acting injectable

Assured adherence and fewer relapses. Covert non-adherence is common and is a leading cause of relapse, and it is invisible with oral drugs. A depot removes that uncertainty: the clinician knows exactly what has been given. In comparison with oral antipsychotics there is strong evidence that depots reduce relapse and rehospitalisation (Leucht 2012; Tiihonen 2017), and a nationwide cohort found the risk of rehospitalisation roughly **20 to 30 percent** lower on a long-acting injectable than on the same drug by mouth (Tiihonen 2017).

Steadier levels, a clearer dose. The **lai** avoids first-pass metabolism and the peaks and troughs of daily dosing, and because the therapeutic dose range of most injectables is well defined the optimal dose is more likely to be prescribed. Consider it early, and offer it as a positive choice rather than a last resort.

RULE **Offer a long-acting injectable early.** It guarantees delivery and cuts relapse; it is not only for the patient who has already defaulted.

7.2 The first-generation depots

The first-generation depot agents are esterified in an oil vehicle and given every two to four weeks.

Haloperidol decanoate
a high-potency butyrophenone, given every 4 weeks; the most widely used first-generation depot.

Fluphenazine decanoate
a high-potency phenothiazine, every 2 to 4 weeks; a small test dose is given first because of the risk of early extrapyramidal effects.

Zuclopenthixol decanoate
every 2 to 4 weeks; the separate short-acting acetate (acuphase) is for acute disturbance and must not be confused with the depot.

Flupentixol decanoate
every 2 to 4 weeks; the optimal dose is around 40 mg every 2 weeks, only a small fraction of the licensed maximum.

Their trade-off is the first-generation profile: effective against positive symptoms and inexpensive, but with more extrapyramidal effects and prolactin elevation and no advantage against negative symptoms.

TRAP **Zuclopenthixol acetate is not the depot.** The acetate (acuphase) is a short-acting agent for acute disturbance; the decanoate is the long-acting maintenance depot.

7.3 The second-generation long-acting injectables

The second-generation long-acting injectable agents carry the lower extrapyramidal burden of the atypicals into an injectable form.

Risperidone microspheres
given every 2 weeks; because the microspheres do not release drug for about three weeks, oral cover is needed after the first injection.

Paliperidone palmitate
the active metabolite of risperidone, as a 1-monthly and a 3-monthly injection (and now a 6-monthly), which can be initiated without oral supplementation using a loading regimen.

Aripiprazole monohydrate
a monthly injection; overlap with oral aripiprazole for 14 days after the first dose while levels build.

Olanzapine pamoate
every 2 or 4 weeks; carries the post-injection syndrome (see below).

7.4 Olanzapine long-acting injectable and the post-injection syndrome

The olanzapine long-acting injectable, marketed in India as **Tolaz** (olanzapine pamoate), carries a distinctive hazard. Inadvertent entry of the depot into a blood vessel produces the post-injection

syndrome: a delirium and excessive sedation, sometimes with dysarthria, ataxia and agitation, coming on within minutes to a few hours of the injection as a bolus of olanzapine reaches the circulation. Because of this the patient must be observed for **3 hours** after every injection in a facility with resuscitation access, and must not drive home the same day.

INDIA

The olanzapine long-acting injectable is available in India as Tolaz. The mandatory 3-hour post-injection observation applies to every dose, which shapes how and where it can be given.

3 hours	2 or 4 weeks	~3 weeks
POST-INJECTION OBSERVATION	OLANZAPINE LAI INTERVAL	ORAL COVER AFTER RISPERIDONE LAI

7.5 Initiation and oral-to-depot conversion

Establish the oral drug first. The safest conversion is to establish efficacy and tolerability on the oral form of the same drug, then give the equivalent dose as the long-acting injectable, using the manufacturer's conversion table. A small test dose is prudent for the first-generation depots to check for a hypersensitivity or early extrapyramidal reaction.

Do not judge the dose too early. With regular injections the plasma level continues to rise for at least **6 to 12 weeks** after starting, even with no change in dose, so a dose increase during this window is difficult to evaluate and often unnecessary. Continue the oral overlap that each agent requires while the depot level builds.

AGENT	INTERVAL	THE ONE CAVEAT
Haloperidol decanoate	every 4 weeks	first-generation extrapyramidal and prolactin burden
Fluphenazine or flupentixol decanoate	every 2 to 4 weeks	give a test dose first
Risperidone microspheres	every 2 weeks	**oral cover for about 3 weeks after the first dose**
Paliperidone palmitate	1-monthly or 3-monthly	loading regimen, no oral cover needed
Aripiprazole monohydrate	monthly	14-day oral overlap
Olanzapine pamoate (Tolaz)	every 2 or 4 weeks	**3-hour post-injection observation**

The long-acting injectable agents, their dosing interval and the single practical caveat for each.

HOLD THIS

A long-acting injectable guarantees delivery and cuts relapse; the two things to remember are that risperidone microspheres need about three weeks of oral cover and the olanzapine injectable (Tolaz) needs a three-hour post-injection observation.

GOOD TO REMEMBER

- **Long-acting injectable:** assured-adherence maintenance treatment; reduces relapse and rehospitalisation by roughly 20 to 30 percent versus the same oral drug; offer early.
- **Risperidone microspheres:** every 2 weeks; needs oral antipsychotic cover for about 3 weeks after the first injection because the microspheres release late.
- **Paliperidone palmitate:** 1-monthly and 3-monthly; a loading regimen means no oral cover is needed.
- **Aripiprazole monohydrate:** monthly; overlap with oral aripiprazole for 14 days.
- **Olanzapine pamoate (Tolaz):** every 2 or 4 weeks; observe 3 hours after each injection for the post-injection syndrome (delirium and sedation from inadvertent vascular uptake).

8 · Treatment-resistant schizophrenia

Treatment-resistant schizophrenia, the **trs**, is a defined clinical endpoint, not a vague impression that a patient is "difficult". It is one of the highest-yield management topics because it hangs on a single operational definition and a single correct next step: once a patient truly meets criteria for treatment resistance, the evidence-based move is **clozapine**, and everything before that point is about proving that the resistance is real. Around 20 to 30% of patients with schizophrenia fail to respond adequately to non-clozapine antipsychotics and fall into this group (Stahl Clozapine Handbook 2019, Kane 2016), yet clozapine remains badly underused, with mean delays to initiation measured in years after criteria are met.

How to use this page. Learn the definition first (the **failed trials** criterion, two adequate antipsychotic trials), then learn to exclude pseudo-resistance before you accept it, then hold the management algorithm that ends in clozapine, not a third same-class switch. The illness itself, its phenomenology, aetiology, criteria and course, is not re-taught here; it belongs to the Schizophrenia: aetiology, phenomenology, classification and course notes. The receptor pharmacology and CYP metabolism behind the drugs belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. Clozapine's own dosing, titration, ANC monitoring and adverse effects are developed in the clozapine topic; here it is only the destination of the algorithm. Electroconvulsive therapy for augmentation of clozapine and for resistant illness points to the ECT and neurostimulation notes.

8.1 The definition: two failed adequate trials

The operational definition. Treatment resistance is a failure to respond to **two adequate** antipsychotic trials, each of adequate dose and duration, in a patient with confirmed adherence. In the consensus wording, roughly 20 to 30% of patients "fail to adequately respond to two or more documented antipsychotic trials of sufficient dosage and duration" (Stahl Clozapine Handbook 2019). The APA states the same clinical threshold: persistent symptoms of at least moderate severity despite two adequate antipsychotic trials, and where a trial has not produced more than a 20% reduction in symptoms this provides additional evidence of treatment resistance (APA 2020). The two elements a resident must be able to defend are the **failed trials** count (two, not one, since single-trial non-response is far too common to qualify) and the word *adequate*, which is where most of the exam marks and most of the clinical errors live.

Adequate dose

A therapeutic dose, conventionally equivalent to at least **600 mg** chlorpromazine per day, sustained long enough to act (Stahl Clozapine Handbook 2019, TRRIP 2017).

Adequate duration

At least **6 weeks** at that therapeutic dose for each trial (TRRIP 2017); a shorter exposure is an inadequate trial, not a failed one.

Adequate number

At least two past adequate treatment episodes with two different antipsychotics; commonly at least one is a second-generation agent (TRRIP 2017, Maudsley 2021).

Confirmed adherence

At least 80% of prescribed doses taken, established by more than one method (pill counts or dispensing review, patient and carer report, and at least one antipsychotic plasma level) (TRRIP 2017).

RULE **True treatment-resistant schizophrenia is two failed adequate trials, and the answer is clozapine.** Not a third me-too switch to another non-clozapine antipsychotic of the same class.

8.2 The TRRIP consensus criteria for an adequate trial

Why the criteria were formalised. The Treatment Response and Resistance in Psychosis working group published consensus criteria in 2017 to let clinicians decide reliably when a patient is treatment resistant, and recommended that the older term "refractory" be dropped (Stahl Clozapine Handbook 2019). The value of the criteria for the exam is that they turn the loose phrase "didn't respond to a couple of drugs" into four checkable minimum requirements, so a trial that fails any one of them is inadequate rather than failed.

DOMAIN	MINIMUM REQUIREMENT (ADEQUATE TRIAL)	THE DISCRIMINATOR
Duration	At least **6 weeks** at a therapeutic dose, per treatment episode	**Under 6 weeks = inadequate trial, not failure**
Dosage	Equivalent to at least **600 mg** chlorpromazine per day	**Sub-therapeutic dose = pseudo-resistance**
Number of antipsychotics	At least two past adequate episodes with two *different* antipsychotics	**Two of the same, or only one, does not count**
Current adherence	At least **80%** of prescribed doses taken, verified by two or more sources plus one plasma level	**Covert non-adherence is the commonest cause of false resistance**

TRRIP consensus criteria for an adequate antipsychotic trial: all four domains must be met before the trial counts as a genuine failure (TRRIP 2017, as tabulated in Stahl Clozapine Handbook 2019).

The optimum (research-grade) criteria. The optimum version tightens two domains: at least one of the two adequate episodes should use a long-acting injectable for at least 4 months (to guarantee exposure), and trough antipsychotic serum levels should be measured on at least two occasions at least 2 weeks apart, without prior warning to the patient (TRRIP 2017). These are the belt-and-braces version of "we are certain the drug was actually in the patient".

8.3 Staging: exclude pseudo-resistance first

Pseudo-resistance versus true resistance. The **staging** logic of resistance is that apparent non-response must be triaged into pseudo-resistance and true resistance before the label is applied, because the two demand opposite actions. Pseudo-resistance is apparent non-response driven by a fixable reason, and "apparent treatment resistance may simply be a result of inadequate treatment" (Maudsley 2021). True resistance is non-response that persists after every fixable reason has been excluded and two genuinely adequate trials have failed. The examiner wants you to name the four classic drivers of pseudo-resistance and check them before ever writing "resistant".

GOOD TO REMEMBER

- **Non-adherence:** the single commonest cause of false resistance; most non-adherence is undetected in practice (Maudsley 2021). Discriminator: a plasma level below the expected range, or missed refills. First step: confirm exposure with a long-acting injectable or plasma-level monitoring before relabelling.
- **Inadequate dose or duration:** a sub-therapeutic dose or a trial shorter than 6 weeks. Discriminator: the trial fails a TRRIP domain. First step: optimise to a therapeutic dose for an adequate period, then reassess.
- **Substance use:** ongoing cannabis, stimulants or alcohol sustaining symptoms. Discriminator: history and urine drug screen. First step: address the substance use as a treatment target in its own right.
- **Wrong diagnosis:** an organic, mood or other psychotic disorder mislabelled as schizophrenia. Discriminator: atypical course, features or investigations. First step: re-examine the diagnosis before escalating pharmacology.

TRAP **Calling covert non-adherence or an inadequate trial "resistance".** An unswallowed or under-dosed drug has not failed; verify adherence, dose and duration before you ever write "treatment-resistant".

8.4 The TRS work-up before you commit

The confirm-resistance checklist. Before the label is committed and clozapine is offered, the patient is worked up against a fixed set of questions that operationalise the exclusion of pseudo-resistance. This is the checklist a viva expects you to run through out loud.

WORK-UP STEP	WHAT TO CONFIRM	IF IT FAILS, THIS IS PSEUDO-RESISTANCE
Adherence	At least 80% of doses actually taken, verified by two sources and a plasma level; consider a long-acting injectable to guarantee exposure	**Covert non-adherence, not resistance**
Dose	Each of the two trials reached a therapeutic dose (about **600 mg** chlorpromazine equivalent per day)	**Under-dosing, not resistance**
Duration	Each trial ran at least **6 weeks** at that dose	**Inadequate trial, not resistance**
Comorbidity	No active substance use, and no untreated depression, anxiety or physical illness sustaining symptoms; diagnosis re-checked	**Comorbid or misdiagnosed, not resistance**

The TRS work-up: confirm adherence, dose, duration and comorbidity before accepting true resistance and moving to clozapine (Maudsley 2021, TRRIP 2017).

8.5 The management algorithm: confirm, then clozapine

Where the algorithm goes. The **management algorithm** is short and its endpoint is not negotiable. Step one: try two different antipsychotics in sequence, each at an adequate dose for an adequate duration, at least one commonly a second-generation agent. Step two: if response is inadequate, run the work-up above and confirm the resistance is true, not pseudo-resistance. Step three: once resistance is confirmed, move to clozapine. The Maudsley states it flatly: "where there is confirmed treatment resistance (failure to respond to adequate trials of at least two antipsychotic medications), evidence supporting the use of clozapine (and only clozapine) is overwhelming" (Maudsley 2021). Clozapine is the only antipsychotic with proven superiority in this population, established by the landmark double-blind comparison against chlorpromazine in resistant patients (Kane 1988).

What the algorithm is not. The wrong branch, and the classic exam distractor, is a third switch to yet another non-clozapine antipsychotic of the same broad class. Switching among non-clozapine agents in a confirmed-resistant patient yields little: increasing the dose of olanzapine or risperidone in non-responders gave only about a 4% absolute gain in response, whereas switching to clozapine was considerably more successful (Maudsley 2021). Neither high-dose monotherapy nor antipsychotic polypharmacy is a substitute for clozapine in true resistance; delaying clozapine to try them wastes the window, and longer delay independently predicts poorer clozapine response (Stahl Clozapine Handbook 2019). ECT is an augmentation option in clozapine-resistant illness rather than a replacement for clozapine, and its technique belongs to the ECT and neurostimulation notes.

20 to 30%	2	6 weeks	600 mg
OF PATIENTS MEET TRS CRITERIA	ADEQUATE FAILED TRIALS TO DEFINE TRS	MINIMUM ADEQUATE TRIAL DURATION	CPZ-EQUIVALENT ADEQUATE DAILY DOSE

COMMON TRAP

Reaching for a third non-clozapine antipsychotic, high-dose monotherapy or polypharmacy in a confirmed-resistant patient. Increasing the dose of a non-clozapine agent in non-responders gave roughly a 4% absolute response gain; switching to clozapine was far more effective (Maudsley 2021). Every month of me-too switching is a month clozapine is withheld, and delay independently lowers the odds of clozapine response.

8.6 Clozapine as the evidence-based next step

Why clozapine and only clozapine. Clozapine is the single agent with robust, replicated superiority in treatment-resistant schizophrenia, first shown in Kane's double-blind trial against chlorpromazine (Kane 1988) and confirmed in network meta-analysis, which ranks clozapine best for both negative symptoms and overall symptom improvement (Maudsley 2021, Samara 2016). Real-world cohort studies of tens of thousands of patients show clozapine outperforming other antipsychotics for the resistant population and lowering all-cause mortality while the patient stays on it (Stahl Clozapine Handbook 2019). This is why the algorithm converges on clozapine the moment resistance is confirmed, and why unnecessary delay is treated as a quality failure.

GOOD TO REMEMBER

- **Clozapine (dibenzodiazepine second-generation antipsychotic; weak, transient D2 plus 5-HT2A and multi-receptor action):** the only agent proven superior in true TRS. Indian brand: Sizopin (also Lozapin). Dose range and full ANC monitoring are developed in the clozapine topic; the one caveat to hold here is that it is reserved for confirmed resistance and started promptly once criteria are met, because delay lowers response (Kane 1988, Stahl Clozapine Handbook 2019).

INDIA

The Indian Psychiatric Society schizophrenia guideline endorses the same core pathway: confirm resistance across two adequate antipsychotic trials, then move to clozapine as the treatment of choice, with adherence and comorbidity excluded first (IPS CPG). Clozapine is widely available in India as Sizopin (and Lozapin), and its use is governed by the same blood-count monitoring discipline; the practical Indian barrier is the monitoring logistics rather than drug cost. Verify the exact IPS monitoring schedule against the current guideline before quoting frequencies.

MNEMONIC

ADAM: Adherence, Dose, Adequate duration, Misdiagnosis or comorbidity

Run ADAM before you ever write "resistant": confirm *Adherence* (was the drug taken), an adequate *Dose* (about 600 mg CPZ-equivalent), an *Adequate duration* (at least 6 weeks each), and exclude *Misdiagnosis or comorbidity* (substance use, wrong diagnosis). Only when ADAM is clean and two adequate trials have failed is it true TRS, and the answer is clozapine.

HOLD THIS

Treatment-resistant schizophrenia is failure of two adequate antipsychotic trials (each at least 6 weeks at about 600 mg chlorpromazine-equivalent per day, adherence confirmed at 80% or more), and once that is proven the answer is clozapine, never a third same-class switch.

9 · Clozapine: indications, monitoring and the haematological emergencies

Clozapine is the single most effective antipsychotic and the only one with proven superiority in treatment-resistant schizophrenia, yet it is reserved because of a small risk of a fatal blood dyscrasia. The whole of its use is a trade of that superior efficacy against a monitoring discipline: no drug in psychiatry rewards knowing the numbers more, and none punishes guessing them more. Every threshold below is worth committing to memory and confirming against the local monitoring service.

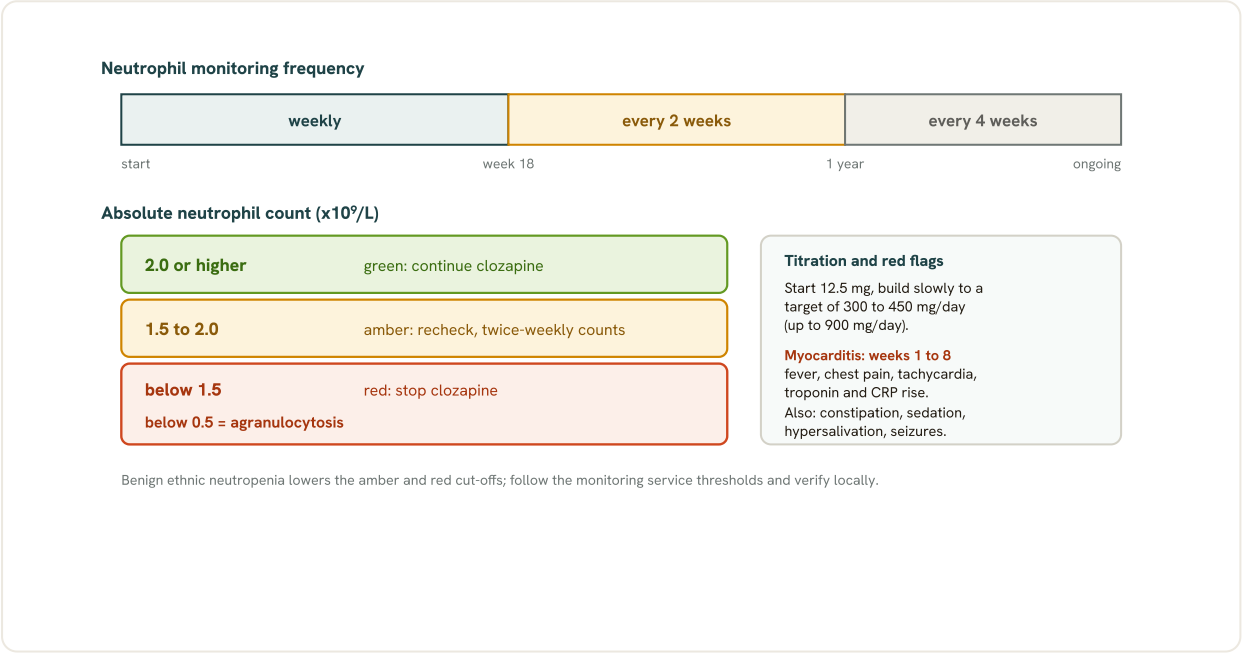

Fig 9.5 Clozapine titration and neutrophil monitoring. Counts run weekly for the first 18 weeks, then every 2 weeks to a year, then every 4 weeks. The traffic-light rule on the absolute neutrophil count decides continuation: green at 2.0 or above, amber at 1.5 to 2.0, red below 1.5 (stop), with agranulocytosis below 0.5. Myocarditis is the other early emergency, in the first one to eight weeks. Verify every threshold against the local monitoring service.

9.1 Indications

Treatment resistance is the main indication. The evidence for clozapine in treatment-resistant schizophrenia is unmatched: the landmark trial found **30 percent** of resistant patients responded to clozapine against **4 percent** to chlorpromazine (Kane 1988), and meta-analysis confirms its superiority over other agents in true resistance with a number needed to treat of about **9** (Siskind 2016). It is the right next step once two adequate trials have failed, not a third me-too switch.

Two further indications. Persistent suicidality in schizophrenia (clozapine reduced suicidal behaviour more than olanzapine in the International Suicide Prevention Trial, Meltzer 2003), and persistent aggression or hostility that has not responded to other antipsychotics.

RULE **Clozapine is the answer to true resistance.** Do not delay it, and do not reach for a third ordinary antipsychotic in its place.

9.2 Initiation and titration

Start low, build slowly. Titration begins at **12.5 mg** on day one, and each dose is roughly doubled if the previous one was tolerated (12.5, then 25, then 50, and so on), so that a target of **300 to 450 mg/day** is reached over about two to three weeks, up to a maximum of **900 mg/day** (Maudsley 2021). Slower titration is used in the community, in the elderly and where cardiac risk is a concern, because it lowers the risk of myocarditis, seizures, hypotension and tachycardia.

Gaps reset the clock. If more than 48 hours of clozapine have been missed, the dose must be re-titrated from a low start; if more than a week has been missed, restart as if it were a first initiation, because tolerance to the cardiovascular and sedative effects is lost within days.

Plasma levels guide the dose in non-response. Where response is inadequate, a trough plasma level (a target around **350 to 600 micrograms/L**) confirms whether the trial is truly adequate before the illness is called clozapine-resistant.

12.5 mg	300 to 450	900 mg
STARTING DOSE	TARGET DOSE (MG/DAY)	DAILY MAXIMUM

9.3 The neutrophil monitoring schedule

Every patient must be registered with a monitoring service before the first dose: no valid blood count, no clozapine. The absolute neutrophil count is the number that decides continuation. The full blood count is taken weekly for the first **18 weeks**, then every 2 weeks to one year, then every 4 weeks thereafter (Maudsley 2021), because the agranulocytosis risk is concentrated in the first months and falls to a low level after the first year.

The result is read as a traffic light on the absolute neutrophil count, in units of 10^9/L:

ABSOLUTE NEUTROPHIL COUNT	SIGNAL	ACTION
2.0 or higher	green	continue clozapine
1.5 to 2.0	amber	**continue but recheck, twice-weekly counts**
below 1.5	red	**stop clozapine, daily counts, haematology**
below 0.5	agranulocytosis	**stop, reverse-barrier nurse, treat as a medical emergency**

The absolute neutrophil count traffic light. Benign ethnic neutropenia, common in patients of African and Middle Eastern descent, lowers these cut-offs, so a low baseline count is worked up before it is called a red result.

9.4 Agranulocytosis and neutropenia

The feared complication. Agranulocytosis (an absolute neutrophil count below 0.5) occurs in roughly **0.8 percent** of patients, with the risk highest in the first 18 weeks and receding after the first year. Managed by the monitoring system the death rate is now low, but an untreated

agranulocytosis carries a serious risk of fatal sepsis, which is why the monitoring is mandatory and non-negotiable.

Neutropenia short of agranulocytosis. A fall to the amber or red range without reaching agranulocytosis (neutropenia) prompts more frequent counts or stopping; a transient benign neutropenia, or one due to benign ethnic neutropenia or a concurrent infection, is distinguished from a true clozapine effect before the drug is abandoned.

TRAP **Do not stop clozapine for a benign transient neutropenia.** A dip in the amber range from an infection or benign ethnic neutropenia is not an agranulocytosis; work it up before throwing away the one drug that works.

9.5 Myocarditis and the cardiac risks

The early cardiac emergency. Myocarditis is the other serious early complication, typically in the first month of treatment. It presents with persistent tachycardia, chest pain, fever, breathlessness and unexplained features of heart failure, with a rise in troponin, C-reactive protein and eosinophils. Many centres monitor **CRP, troponin and creatine kinase weekly for the first four weeks**; a rise prompts an echocardiogram and B-natriuretic peptide to confirm, and confirmed myocarditis means stopping clozapine.

Fever is common and usually benign. Clozapine induces an inflammatory response (raised CRP, interleukin-6 and eosinophils) that produces a benign fever in the first weeks, but a fever always prompts a check for myocarditis, neuroleptic malignant syndrome, pneumonia and neutropenia before it is dismissed.

9.6 The other adverse effects

Constipation can kill. Clozapine causes a gastrointestinal hypomotility whose risk is highest in the first four months and which persists; severe cases progress to ileus, obstruction and death. It is prevented and treated actively with stimulant laxatives (senna or bisacodyl) first-line and osmotics, while bulk-forming laxatives and systemic anticholinergics are avoided because they worsen it.

The rest of the burden. Hypersalivation (troublesome at night), sedation and postural hypotension early in treatment; dose-related seizures, more likely above **600 mg/day**, where prophylactic valproate is added; and substantial weight gain and metabolic disturbance, so metabolic monitoring runs alongside the blood count.

INDIA

Clozapine is available in India as Sizopin and Lozapin. Registration with a clozapine monitoring service and the same absolute-neutrophil-count discipline apply; point-of-care neutrophil testing is increasingly used to make weekly monitoring feasible.

9.7 Rechallenge after a blood dyscrasia

After agranulocytosis, generally do not rechallenge. A clozapine-induced agranulocytosis is a strong contraindication to rechallenge: on re-exposure the dyscrasia tends to recur sooner and

more severely. Relisting a patient for a clozapine rechallenge after agranulocytosis is done only exceptionally, under specialist haematology supervision, when no alternative exists and the benefit is judged to outweigh a potentially fatal recurrence.

After a lesser or non-clozapine neutropenia, rechallenge may be possible. Where the neutropenia was benign, due to benign ethnic neutropenia, or clearly caused by another drug or an infection rather than by clozapine, a specialist-supervised rechallenge with close monitoring can be considered, because the clozapine-induced blood picture was never established.

HOLD THIS

Clozapine is the only evidence-based drug for true resistance; its price is mandatory neutrophil monitoring (green at 2.0 and above, amber 1.5 to 2.0, red below 1.5, agranulocytosis below 0.5) and vigilance for myocarditis in the first month and for a constipation that can be fatal.

GOOD TO REMEMBER

- **Clozapine:** a dibenzodiazepine, the only agent proven superior in treatment-resistant schizophrenia (Kane 1988); start 12.5 mg, target 300 to 450 mg/day (up to 900); the one parameter is the absolute neutrophil count.
- **Neutrophil monitoring:** weekly for 18 weeks, then fortnightly to a year, then 4-weekly; continue at 2.0 or above, recheck at 1.5 to 2.0, stop below 1.5, agranulocytosis below 0.5 ($x10^9$/L).
- **Agranulocytosis:** about 0.8 percent, highest in the first 18 weeks; the reason for the monitoring; do not rechallenge after it.
- **Myocarditis:** first month; persistent tachycardia, chest pain, fever; monitor CRP, troponin and creatine kinase weekly for four weeks; confirmed myocarditis means stopping.
- **Constipation (gastrointestinal hypomotility):** can be fatal; prevent and treat with stimulant laxatives, never bulk-forming or anticholinergic agents.

10 · Clozapine augmentation and rational polypharmacy

Some patients remain symptomatic even on an adequate trial of clozapine, and this **ultra-resistant** group forces the two hardest management decisions in schizophrenia pharmacology: what, if anything, to add on top of clozapine, and when a second antipsychotic is ever defensible outside that setting. Both questions are examined heavily because both are dominated by a weak evidence base and a strong temptation to reach for more drugs. The examiner wants two disciplines from you: optimise the clozapine trial before you augment it, and never let a second antipsychotic become a permanent fixture without a defined target and a plan to stop.

How to use this page. Learn **clozapine augmentation** as the strategy for the patient who has not fully responded to a genuinely optimised clozapine trial, then learn **antipsychotic polypharmacy** as the broader, less defensible practice of combining two antipsychotics outside clozapine augmentation, and hold the single principle that reconciles them: **rational polypharmacy**, meaning a defined target, a defined trial, and a plan to stop if there is no benefit. The illness itself, its phenomenology, aetiology, criteria and course, is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes. Receptor pharmacology, dopamine pathways and CYP metabolism belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; here the

pharmacology is applied, not derived. Clozapine's own dosing, titration and adverse-effect monitoring are developed in the clozapine topic and only referenced here. Electroconvulsive therapy for clozapine augmentation is owned by the ECT and neurostimulation notes and cross-referenced, not taught.

10.1 Optimise the clozapine trial before you augment

Augmentation is the last resort, not the reflex. Inadequate response to clozapine monotherapy is a frequent clinical event, and augmenting is common practice, but the first move in the partial responder is not to add a drug: it is to prove the clozapine trial was truly optimised. That means confirming the **dose**, the **duration**, and the **plasma level** were all adequate before accepting non-response (Maudsley 2021). Response to clozapine is usually seen across a wide dose range and the average maintenance dose is around **450 mg/day**, but dose alone is a poor guide; the more reliable target is a trough clozapine plasma concentration, with most studies placing the threshold for response in the range **350 to 420 mcg/L** (Maudsley 2021). A patient labelled a clozapine non-responder at a plasma level below that threshold has not failed clozapine at all, and augmenting them is treating the wrong problem. The full plasma-level and dose-optimisation logic belongs to the clozapine topic; here it is the mandatory precondition for the word *augmentation*.

RULE **Optimise the clozapine trial (dose, duration, plasma level) before you augment.** A subtherapeutic plasma level is under-treatment, not treatment resistance; fix the trial before adding a second drug.

HOLD THIS

Before augmenting clozapine, confirm the trial was optimised on all three of dose, duration and plasma level (threshold for response about 350 to 420 mcg/L); the evidence for every augmentation strategy is modest at best, so give an adequate trial and stop what does not clearly work.

10.2 The ultra-resistant patient: what clozapine augmentation is

Defining the group. A minority of patients are **ultra-resistant**, meaning they remain significantly symptomatic despite an adequate, optimised trial of clozapine, the single most effective agent in treatment-resistant illness. Clozapine augmentation is the addition of a second agent to clozapine in this group to try to capture the residual symptoms that clozapine alone has not touched. It has become common practice precisely because inadequate response to clozapine on its own is frequent (Maudsley 2021). The critical framing for the exam is that clozapine augmentation is a distinct, partially defensible exception to the general rule against combining antipsychotics, and it is the one polypharmacy scenario that guidelines explicitly permit (Maudsley 2021).

TRAP **Augmenting a clozapine "non-responder" who was never optimised.** Check the plasma level first; a level below about 350 mcg/L means the clozapine trial itself was inadequate, not that the patient needs a second drug.

10.3 The augmentation strategies and how strong the evidence is

The menu, and the honest verdict on it. The augmentation strategies fall into four groups: a second antipsychotic (clozapine plus amisulpride or clozapine plus aripiprazole being the most commonly cited), a mood stabiliser (lamotrigine), an antidepressant for residual negative or depressive symptoms, and electroconvulsive therapy. Despite more than fifty reviews and meta-analyses, the evidence remains insufficient to support any single algorithm, the result of augmentation is often disappointing, and the effect size is small at best (Maudsley 2021). Meta-analyses restricted to large, high-quality studies mostly report no benefit from pharmacological augmentation of clozapine (Maudsley 2021). The practical rule that follows is to pick one strategy, give it an adequate trial, and abandon it after **3 to 6 months** if there is no clear benefit (Maudsley 2021).

AUGMENTATION STRATEGY	TYPICAL ADD-ON DOSE	EVIDENCE AND THE POINT TO HOLD
Clozapine plus amisulpride (second antipsychotic)	**400 to 800 mg/day**	**Some RCT and clinical support; may allow clozapine dose reduction, but watch additive cardiac adverse effects (Maudsley 2021)**
Clozapine plus aripiprazole (second antipsychotic)	**15 to 30 mg/day**	**Very limited efficacy evidence; its real value is reducing weight and LDL cholesterol on clozapine (Maudsley 2021)**
Clozapine plus lamotrigine (mood stabiliser)	**25 to 300 mg/day**	**May help partial or non-responders; several equivocal reports, meta-analytic signal driven by outlying studies (Maudsley 2021)**
Clozapine plus an antidepressant	Agent-specific	**For residual negative or depressive symptoms; weak signal, mirtazapine has the largest (still weak) effect (Maudsley 2021)**
Clozapine plus electroconvulsive therapy	Course-based	**An option in clozapine-resistant illness; technique and evidence owned by the ECT and neurostimulation notes**

Suggested options for augmenting clozapine after 3 to 6 months of optimised clozapine alone has given unsatisfactory benefit; the overall evidence base is modest and no algorithm is established (Maudsley 2021).

GOOD TO REMEMBER

- **Amisulpride:** a benzamide second-generation antipsychotic, predominantly D2/D3 antagonist. Add-on dose **400 to 800 mg/day** in clozapine augmentation (Maudsley 2021). Hold: watch additive cardiac and QTc effects, and it may permit a clozapine dose reduction. Lead Indian brand where a trade name is needed: Amazeo.
- **Aripiprazole:** a dopamine D2 partial agonist. Add-on dose **15 to 30 mg/day** (Maudsley 2021). Hold: efficacy signal is very limited, but it reliably reduces clozapine-associated weight and LDL cholesterol, which is its main rationale. Lead Indian brand: Arip.
- **Lamotrigine:** an anticonvulsant mood stabiliser (sodium-channel blocker). Add-on dose **25 to 300 mg/day** (Maudsley 2021). Hold: titrate slowly and hold the risk of serious rash (Stevens-Johnson syndrome); evidence in clozapine augmentation is equivocal.
- **Electroconvulsive therapy:** a neurostimulation treatment, an augmentation option in clozapine-resistant illness. Discriminator: it is added to, not a substitute for, an optimised clozapine trial. First step and technique: owned by the ECT and neurostimulation notes.

10.4 Rational antipsychotic polypharmacy outside clozapine augmentation

The general rule against combining antipsychotics. Apart from exceptional circumstances such as clozapine augmentation, antipsychotic polypharmacy should generally be avoided because of the increased adverse-effect burden and the risks of QT prolongation and sudden cardiac death (Maudsley 2021). The efficacy evidence for combining two antipsychotics outside clozapine augmentation is weak: a meta-analysis of RCTs comparing augmentation with a second antipsychotic against continued monotherapy found the combination lacked high-quality evidence for overall efficacy (Maudsley 2021). The general consensus across guidelines is that combined antipsychotics for refractory illness should be considered only after evidence-based options such as clozapine have been exhausted (Maudsley 2021).

Why the harm evidence is more convincing than the benefit. The case against antipsychotic polypharmacy is not just absent benefit, it is present harm. Combined antipsychotic regimens carry additive adverse effects, are commonly a high-dose prescription, and are associated with increased extrapyramidal symptoms, metabolic effects and diabetes, sexual dysfunction, hip fracture, paralytic ileus, seizures, prolonged QTc and arrhythmias (Maudsley 2021). They also worsen adherence, because a more complex regimen is harder to take, and they make it difficult to attribute any response to a single drug, which muddies every subsequent decision (Maudsley 2021). Some strategies buy tolerability rather than efficacy: adding aripiprazole to reduce weight on clozapine, or to normalise prolactin on haloperidol or risperidone, has a valid rationale, but in many such cases using aripiprazole alone would be the more logical choice (Maudsley 2021).

3 to 6	350 to 420	450
MONTHS, THEN ABANDON AUGMENTATION IF NO BENEFIT	CLOZAPINE PLASMA THRESHOLD FOR RESPONSE (MCG/L)	AVERAGE CLOZAPINE DOSE (MG/DAY)

10.5 The principle of rational polypharmacy

Three conditions make polypharmacy rational. If a second antipsychotic is ever used, it must be used rationally, and rational polypharmacy has three defining conditions. First, a defined target: a specific symptom or symptom cluster the combination is meant to address, not a vague sense that the patient is unwell. Second, a defined trial: an adequate dose for an adequate period

against that target, so the question can actually be answered. Third, a plan to stop: an explicit commitment to withdraw the second antipsychotic if the target does not improve, rather than letting the combination drift into a permanent, undocumented regimen. Because combined antipsychotics carry a greater adverse-effect burden, the rationale, benefits and adverse effects of the trial should be documented in the records (Maudsley 2021). Where polypharmacy continues, the minimum requirement is systematic monitoring for adverse effects, including an ECG, with any benefit carefully recorded (Maudsley 2021).

TRAP **Long-term two-antipsychotic polypharmacy without a defined target or a stop plan.** A combination started for a crisis or a cross-taper that is never reviewed becomes a permanent high-dose regimen delivering additive harm and no measurable benefit.

COMMON TRAP

Confusing rational clozapine augmentation with routine antipsychotic polypharmacy. Clozapine augmentation is a defined exception in an ultra-resistant patient after clozapine has been optimised; combining two non-clozapine antipsychotics as a first response to poor monotherapy response is the practice guidelines warn against, because the harm evidence is more convincing than any efficacy signal (Maudsley 2021).

INDIA

Where a second antipsychotic or a long-acting injectable is added rationally in Indian practice, lead with the Indian trade name where one is needed: olanzapine long-acting injectable is marketed as Tolaz, and it carries a recognised post-injection delirium/sedation syndrome that mandates a supervised post-dose observation period. Aripiprazole (Arip) and amisulpride (Amazeo) are the augmentation agents most often reached for. The IPS schizophrenia guideline and the community-based DMHP model both frame clozapine, when used, as monotherapy to be optimised first, consistent with the rule above.

MNEMONIC

TARGET, TRIAL, STOP

The three conditions for rational polypharmacy: a defined TARGET (which symptom), a defined TRIAL (adequate dose and duration to answer the question), and a STOP plan (withdraw if the target does not improve). If any one is missing, the combination is not rational.

WORKED EXAMPLE

A man on clozapine 450 mg/day for eight months has persistent delusions; his trough clozapine level is 220 mcg/L. The correct next step is not augmentation but optimisation: his level is below the 350 to 420 mcg/L response threshold, so his clozapine trial was never adequate. You raise the dose (or add a CYP inhibitor with caution) to reach a therapeutic plasma level and reassess. Only if he remains symptomatic on an optimised, plasma-level-confirmed clozapine trial does clozapine augmentation, for example clozapine plus amisulpride 400 to 800 mg/day with a 3 to 6 month trial and a stop plan, become the rational next move (Maudsley 2021).

11 · Management of the negative symptoms

The **negative symptoms** are the diminution or absence of normal function, the expressive deficits (blunted affect, alogia, poor eye contact, decreased spontaneous movement) and the avolition or amotivation cluster (reduced interests, desires, goals and self-initiated activity). They are the domain that responds least to D2 blockade, they carry much of the long-term morbidity and poor functional outcome, and they are the reason a patient whose voices have stopped may still not work, socialise or self-care (Maudsley 2021, Kaplan & Sadock 2024). For the exam this is a high-yield topic precisely because the correct first move is not a drug at all: it is to decide whether the negative symptoms are *secondary* and reversible or *primary* and enduring, because the two demand opposite actions.

How to use this page. Learn the primary-versus-secondary split first, because it drives everything downstream. Then hold the short list of pharmacological options for the primary deficit (modest at best, no drug reliably treats it) and the non-pharmacological mainstay (cognitive remediation and psychosocial rehabilitation) for the functional deficit. The illness itself, its phenomenology, aetiology, criteria and course, is not re-taught here; it belongs to the Schizophrenia: aetiology, phenomenology, classification and course notes. The receptor pharmacology and dopamine pathways behind these agents belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. The rehabilitation interventions named here are developed as clinical programmes in the rehabilitation and psychosocial topics; here they are applied to the negative-symptom problem.

11.1 First separate secondary from primary negative symptoms

The clinical distinction that drives management. Before any treatment is chosen, the negative symptoms must be triaged into two categories, because the treatable causes differ. **Primary negative** symptoms comprise an enduring deficit state, are stable over time and predict a poor prognosis. **Secondary negative** symptoms are consequent upon another, potentially reversible, cause: active positive symptoms, depression or demoralisation, medication side effects such as bradykinesia as part of drug-induced parkinsonism, or understimulation, social deprivation and hospitalisation, and chronic substance or alcohol use (Maudsley 2021, Barnes 1995). "It is important to determine the most likely cause in any individual case before embarking on a treatment regimen" (Maudsley 2021). The whole management strategy pivots on this: a secondary cause is treated at its source, and only what remains after every reversible driver is removed is called primary.

Why it matters for numbers. Negative symptoms are seen to a varying degree in up to three-quarters of people with established schizophrenia, but only around **20%** have persistent primary negative symptoms (Maudsley 2021). In other words most negative symptoms you meet have a reversible component to hunt for first.

RULE **Always look for and treat a secondary cause before calling negative symptoms primary.** Reduce the high-EPS antipsychotic, treat the depression, add stimulation, address the substance use, then reassess what is left.

11.2 The reversible causes of secondary negative symptoms

What to exclude, and the action each demands. The value of the secondary category is that each cause has a specific and often reversible treatment. This is the checklist a viva expects you to run before you accept a deficit as primary.

SECONDARY CAUSE	HOW IT MASQUERADES AS NEGATIVE SYMPTOMS	THE TREATING ACTION
Drug-induced parkinsonism	Bradykinesia, masked facies and reduced movement overlap phenomenologically with expressive deficits	**Reduce dose or switch off a high-EPS antipsychotic; add an anticholinergic if needed**
Depression or demoralisation	Anergia, anhedonia and withdrawal mimic avolition and blunted affect	**Detect and treat the depressive episode; add an antidepressant**
Active positive symptoms	Withdrawal driven by paranoia or preoccupation with hallucinations	**Optimise antipsychotic control of the positive symptoms first**
Understimulation and institutionalisation	Apathy and inactivity from an impoverished, low-demand environment	**Increase stimulation and structured activity; psychosocial rehabilitation**
Chronic substance or alcohol use	Amotivation and social withdrawal sustained by ongoing use	**Address the substance use as a treatment target in its own right**

The reversible drivers of secondary negative symptoms and the specific action each demands: treat the secondary cause first (Maudsley 2021, Barnes 1995).

TRAP **Mislabelling drug-induced parkinsonism or a depressive episode as primary negative symptoms.** Bradykinesia and anergia are treatable secondary causes; do not write "primary deficit" until you have reduced the EPS burden and treated the depression.

11.3 The first move for secondary negative symptoms: treat the cause

The management principle. For secondary negative symptoms the treatment is the treatment of the underlying cause, not a new agent aimed at the negative symptoms themselves. Where drug-induced parkinsonism is the driver, the correct move is to *reduce* the offending high-EPS antipsychotic or switch to a lower-EPS agent, because there is some evidence that reducing antipsychotic dose from very high to high levels improves cognition and negative symptoms (Maudsley 2021). Where a depressive component contributes, treat the depression. Where the environment is impoverished, add stimulation and structured psychosocial input. Antipsychotic medication does improve negative symptoms, but this benefit "seems to be limited to secondary negative symptoms in acute psychotic episodes" (Maudsley 2021): it works on the reversible fraction, not the enduring deficit.

WORKED EXAMPLE

A man on high-dose haloperidol is flat, slow and barely speaks, and the team is discussing "burnt-out" primary negative symptoms. Before accepting that label: he has cogwheel rigidity and a masked face, so the flatness is at least partly neuroleptic-induced. The correct first step is to reduce the haloperidol or switch to a lower-EPS antipsychotic and reassess, not to add a second drug for the negative symptoms. Reducing a high antipsychotic dose can itself improve negative symptoms and cognition (Maudsley 2021).

11.4 Pharmacological options for primary negative symptoms

The honest state of the evidence. The pharmacological management of negative symptoms that are genuinely primary and persistent is nearly bare. The literature is mostly sub-analyses of acute efficacy studies rather than trials recruiting persistent negative symptoms, and "there is no robust evidence for an effective treatment for persistent primary negative symptoms" (Maudsley 2021). There is no consistent evidence for the superiority of second-generation over first-generation agents as a class, and a meta-analysis of second-generation agents found a statistically significant but sub-clinical reduction that did not reach a threshold for minimally detectable clinical improvement (Maudsley 2021, Fusar-Poli 2015). Two management moves nonetheless have some signal and are examinable: switch to an agent with a better negative-symptom signal, or add an antidepressant where a depressive component contributes.

Switch to an agent with a better negative-symptom signal. Certain treatment strategies show more robust superiority for negative symptoms, notably amisulpride and cariprazine, with olanzapine and quetiapine possibly better than risperidone and aripiprazole augmentation possibly effective (Maudsley 2021, Krause 2018). The single strongest piece of evidence is the head-to-head cariprazine-versus-risperidone trial in patients with predominant negative symptoms, which favoured cariprazine (Nemeth 2017). Amisulpride is the classic exam answer here, and the dosing is a discriminator: efficacy for negative symptoms is achieved at *low* doses, while positive symptoms need higher doses (Stahl 2021, Danion 1999). The newer muscarinic agonist agents and the dopamine partial agonists are the emerging additions to this list, but the effect sizes remain modest.

Add an antidepressant where a depressive component contributes. A Cochrane review concluded antidepressant augmentation might reduce affective flattening, alogia and avolition, though randomised evidence is inconsistent and modest, and one meta-analysis found benefit only with augmentation of first-generation agents (Maudsley 2021). The pragmatic reading is that an antidepressant trial is reasonable where a depressive component is plausible, choosing an agent that will not compound side effects, but not as a reliable treatment for the pure deficit.

50 to 300 mg/day	**1.5 to 6 mg/day**	**~20%**
AMISULPRIDE, NEGATIVE SYMPTOMS ONLY	CARIPRAZINE, SCHIZOPHRENIA	HAVE PERSISTENT PRIMARY NEGATIVE SYMPTOMS

RULE **No drug reliably treats primary negative symptoms.** The best you can offer is a switch to a better-signal agent (amisulpride, cariprazine) or an antidepressant where depression contributes, and the evidence for both is modest.

GOOD TO REMEMBER

- **Amisulpride (substituted benzamide, second-generation antipsychotic; preferential blockade of presynaptic D2/D3 at low dose, postsynaptic at high dose):** the classic negative-symptom agent. Dose: schizophrenia **400 to 800 mg/day**, but negative symptoms only **50 to 300 mg/day** (Stahl 2021). One caveat to hold: dose-dependent QTc prolongation and renal accumulation (it is largely renally cleared), so use with caution and check the QTc. Indian brand: Amazeo (also Soltus).
- **Cariprazine (dopamine D3-preferring D2/D3 partial agonist, second-generation antipsychotic):** the strongest randomised negative-symptom signal, favoured over risperidone in predominant negative symptoms (Nemeth 2017). Dose: schizophrenia **1.5 to 6 mg/day** once daily (Stahl 2021). One caveat: its very long half-life means effects and side effects (akathisia, EPS) accumulate slowly, so titrate patiently.
- **Antidepressant augmentation (added to an antipsychotic):** may reduce affective flattening, alogia and avolition, but evidence is inconsistent and modest (Maudsley 2021). One caveat: reserve it for where a depressive component genuinely contributes, and choose an agent that will not compound the antipsychotic's side effects through pharmacokinetic or pharmacodynamic interaction.

11.5 Non-pharmacological approaches: the mainstay for functional deficit

Why these carry the load. Because no drug reliably treats the primary deficit, the mainstay of managing the functional impact of negative symptoms is non-pharmacological: **cognitive remediation**, social-skills training and broader psychosocial rehabilitation. Cognitive remediation is systematic training to enhance attention, memory, executive function and social cognition, and it improves cognition, symptoms and function in schizophrenia, at least in the short term (APA 2020). Its benefits on real-world functioning are most robust when it is delivered as a component of, or adjunct to, wider psychiatric rehabilitation rather than as a stand-alone exercise (APA 2020). Social-skills training and psychosocial rehabilitation, including supported employment, target the disability that avolition and social withdrawal produce, and are developed as programmes in the rehabilitation topics.

COMMON TRAP

Escalating pharmacology, adding drug after drug, in a patient whose problem is enduring primary negative symptoms. Once secondary causes are excluded, the evidence base points toward psychosocial rehabilitation and cognitive remediation for the functional deficit, not a fourth medication. Chasing a pharmacological cure for the pure deficit wastes time and adds side effects.

11.6 The Indian context

INDIA

The Indian Psychiatric Society schizophrenia guideline places psychosocial rehabilitation, family intervention and community-based care at the centre of managing the chronic disability of which negative symptoms are the core, in line with the District Mental Health Programme (DMHP) community model of care delivery. Amisulpride is widely available and inexpensive in India (marketed as Amazeo, among others), which makes the low-dose negative-symptom strategy practical here. Where the treatment plan reduces a high-EPS agent, the olanzapine long-acting injectable is available in India as Tolaz, but note its post-injection syndrome risk requires the mandated post-dose observation period; it is a delivery choice for adherence, not a treatment for the negative symptoms themselves. Verify the exact IPS recommendations and any local availability against the current guideline before quoting them.

MNEMONIC

SECONDARY: Symptoms (positive), EPS/parkinsonism, Cheerless (depression), Off stimulation, Narcotics/substances, Deprivation/institution, Ask before you call it primaRY

Before labelling negative symptoms primary, sweep the reversible causes: active positive *Symptoms*, drug-induced *EPS*/parkinsonism, a *Cheerless* depressive episode, being *Off* stimulation, *Narcotics* or other substance use, and environmental *Deprivation*. Only what survives that sweep is the enduring primary deficit.

PEARL

Clozapine ranks best for negative symptoms in network meta-analysis, but a real confound is its very low liability for parkinsonism: some of its apparent negative-symptom advantage is simply the absence of the bradykinesia that mimics expressive deficits with other agents (Maudsley 2021). The lesson generalises: much of what looks like a drug treating negative symptoms is a drug not causing secondary ones.

HOLD THIS

Separate secondary negative symptoms (from positive symptoms, depression, drug-induced parkinsonism, understimulation or substance use, all reversible) from primary negative symptoms (the enduring deficit), and treat the secondary cause first; for the primary deficit no drug reliably works, so offer a better-signal agent (amisulpride 50 to 300 mg/day, cariprazine 1.5 to 6 mg/day) or an antidepressant where depression contributes, and make cognitive remediation and psychosocial rehabilitation the mainstay.

Psychosocial rehabilitation and psychological treatment

12 · Psychosocial rehabilitation: principles and components

Why this matters. Medication controls the positive symptoms of schizophrenia, but it does not by itself return a patient to work, relationships and an independent life. That return, function and **recovery**, is delivered by **psychosocial rehabilitation**, and this is the single conceptual point the examiner tests: rehabilitation is not an optional extra bolted on once the psychosis settles, it is a core, planned part of treatment from the outset. Antipsychotics and rehabilitation address different targets, symptoms versus disability, and neither substitutes for the other (Kaplan & Sadock 2024). A management answer that stops at the drug has answered half the question.

The illness itself, its phenomenology, aetiology, diagnostic criteria and course, is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes and is not re-taught here; what this topic teaches is the framework and the **components of rehabilitation**. Modern practice frames rehabilitation inside the **recovery model**, which reorients the goal from symptom-elimination alone to a life of hope, agency and meaning beyond the illness (Anthony 1993, Tasman 2015). We take the principle first, then the components, then the assessment and delivery.

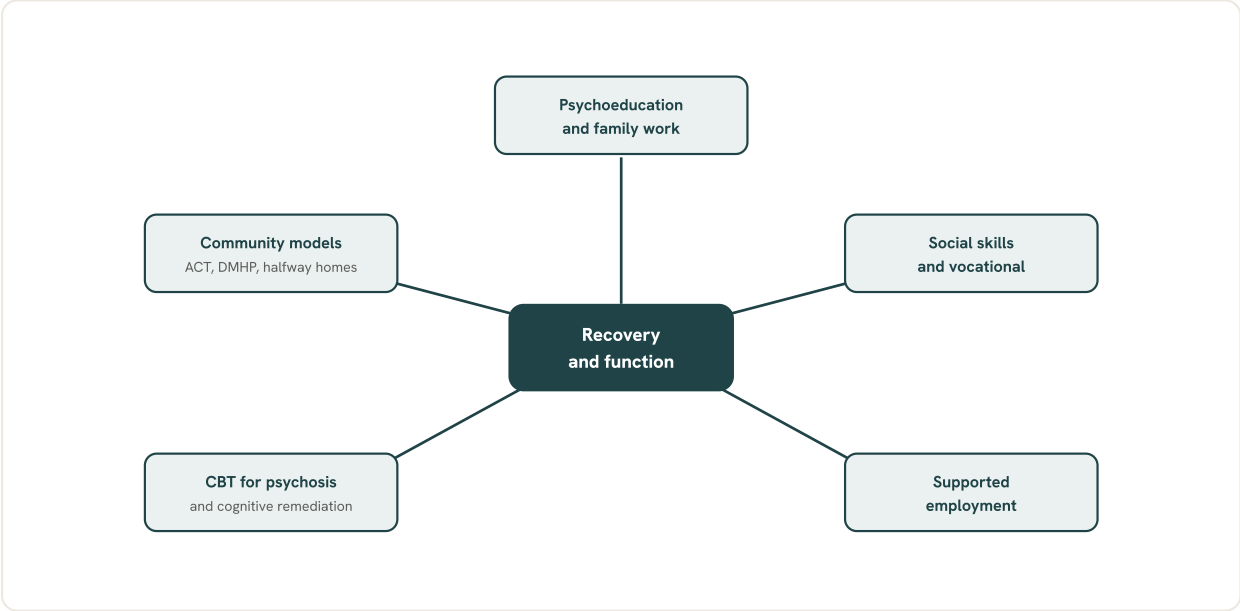

Fig 9.6 The components of psychosocial rehabilitation. Medication controls symptoms, but function and recovery come from the psychosocial half: psychoeducation and family work in high-expressed-emotion households, social skills training and supported employment, the psychological therapies, and the community and Indian service models. These are core to the plan, not an afterthought.

12.1 The core principle: medication controls symptoms, rehabilitation delivers function

The governing principle is a division of labour. Antipsychotic treatment reduces hallucinations, delusions and disorganisation and prevents relapse, the maintenance argument developed in the maintenance topic, but it leaves largely untouched the **disability** that drives long-term outcome: the negative symptoms, cognitive deficits, and lost social and occupational skills that keep a

person out of work and isolated even when frankly psychotic symptoms have gone (Kaplan & Sadock 2024). Function and recovery come from **rehabilitation**, not from medication alone. Because of this, guidelines treat psychosocial interventions as a required component of the plan for essentially every patient, offered alongside pharmacotherapy rather than after it (APA 2020). The practical corollary is that rehabilitation planning begins early, in parallel with drug treatment, not once symptoms have settled.

RULE **Rehabilitation is where function and recovery come from; medication alone does not deliver them.** Drugs treat symptoms, rehabilitation treats disability, and both belong in the plan from the start.

TRAP **Treating rehabilitation as an afterthought once symptoms settle.** Deferring psychosocial work until the psychosis is gone wastes the window in which function can be rebuilt and leaves recovery half-done.

12.2 The recovery model: hope, agency and a life beyond the illness

The **recovery model** is the frame within which rehabilitation is now delivered. Its foundational definition, from Anthony, describes recovery as "a deeply personal, unique process of changing one's attitudes, values, feelings, goals, skills and roles ... a way of living a satisfying, hopeful and contributing life even with limitations caused by the illness" (Anthony 1993, in Tasman 2015). The key move is the separation of **personal recovery** (a subjective, self-defined process of rebuilding a meaningful life) from clinical recovery (symptom remission): a person can be in recovery while symptoms persist, and symptom-free while not yet recovered. Anthony's own gloss captures the division of responsibility precisely: "recovery is what people with disabilities do; treatment, case-management and rehabilitation are what helpers do to facilitate recovery" (Anthony 1993).

The most widely used articulation of what personal recovery contains is the CHIME framework: Connectedness, Hope and optimism, Identity, Meaning, and Empowerment (agency) (Leamy et al. 2011). Hope is treated as vital, encompassing the patient's own outlook and that of the staff around them; empowerment is the restoration of agency and control over one's own care and life (Tasman 2015). For the examiner, the recovery model contributes three testable ideas: **hope** as a therapeutic stance, **agency** and self-determination as goals in their own right, and **a life beyond the illness**, chosen roles and relationships, as the true end-point of rehabilitation rather than mere symptom control.

MNEMONIC

CHIME

The five processes of personal recovery: **C**onnectedness, **H**ope (and optimism), **I**dentity, **M**eaning, **E**mpowerment (agency). Rehabilitation succeeds when it moves these, not only the symptom scores.

12.3 Psychoeducation and family work

Psychoeducation gives the patient and family a working understanding of the illness, its treatment and the early signs of relapse, converting them from passive recipients into active partners in care. Delivered to families, structured family intervention (family psychoeducation) is one of the best-evidenced psychosocial treatments in schizophrenia: it reduces expressed emotion in the home and, most importantly, lowers the relapse rate, and it is a recommended component across guidelines (APA 2020, RANZCP and PORT in Tasman 2015). The core ingredients are illness education, communication and problem-solving skills for the family, and crisis planning, typically over an extended period rather than a single session. Family work is therefore not merely supportive, it is an active relapse-prevention intervention, which is why it earns a guideline recommendation on the same footing as drug treatment.

GOOD TO REMEMBER

- **Psychoeducation:** structured teaching of the patient and family about the illness, treatment and relapse signs; the feature is shared understanding and partnership in care; the first step is to include the family early, not just the patient.
- **Family intervention (family psychoeducation):** extended family programme with illness education plus communication and problem-solving training; the discriminator is that it lowers expressed emotion and reduces relapse; the first step is to offer it to families of patients living with or in close contact with relatives (APA 2020).

12.4 Social-skills training and vocational training

Social skills training uses instruction, modelling, role-play and structured practice with feedback to rebuild the interpersonal behaviours, conversation, assertiveness, self-care, that schizophrenia erodes; the deficits it targets are persistent and largely independent of positive symptoms (Mueser et al. 1991, in Tasman 2015), which is precisely why a drug does not fix them. On the occupational side, **vocational training** aims at competitive employment, and the pivotal shift here is from the old "train-then-place" sheltered-workshop model to the "place-then-train" model of supported employment, best exemplified by Individual Placement and Support (IPS). IPS places the patient in a real, competitive, paid job rapidly according to their own preference and then provides on-the-job coaching, and it consistently outperforms traditional prevocational training on employment outcomes (APA 2020). Both social skills training and supported employment are guideline-recommended components (APA 2020, Statements 18 and 23).

GOOD TO REMEMBER

- **Social skills training:** behavioural teaching of interpersonal and self-care skills via modelling, role-play and feedback; the feature is targeting persistent, symptom-independent social deficits; the first step is structured practice, not advice alone.
- **Supported employment (Individual Placement and Support, IPS):** rapid placement into competitive paid work by patient preference, then on-the-job support; the discriminator is "place-then-train" beating "train-then-place"; the first step is a real job matched to preference, with coaching that follows (APA 2020).

12.5 Cognitive interventions

Cognition, attention, working memory, processing speed and executive function, is impaired in most patients and is a stronger predictor of real-world functioning than positive symptoms, yet responds poorly to antipsychotics (Kaplan & Sadock 2024). Cognitive remediation targets these deficits directly through repeated, structured drill and strategy training, usually computer-assisted, and improves cognitive performance with functional gains that are larger when it is paired with other rehabilitation rather than delivered alone (APA 2020, Statement 22). It is distinct from cognitive behavioural therapy for psychosis (CBTp), which targets the distress and appraisal of residual delusions and hallucinations rather than neurocognition; CBTp is a recommended psychological intervention in its own right (APA 2020, Statement 16). Keeping the two apart, remediation for cognition, CBTp for symptom-related distress, is a common exam discriminator.

GOOD TO REMEMBER

- **Cognitive remediation:** structured drill and strategy training for neurocognitive deficits; the discriminator is that it targets attention, memory and executive function, not delusions; the first step is to pair it with broader rehabilitation for functional benefit (APA 2020).
- **Cognitive behavioural therapy for psychosis (CBTp):** psychological therapy for the distress and appraisal of residual psychotic symptoms; the discriminator is symptom-related distress rather than cognition; the first step is to offer it as an adjunct to medication, not a replacement (APA 2020).

12.6 Supported housing and community support

Stable housing and assertive community follow-up are the structural components that hold the rest together. Supported housing provides secure accommodation with graded support, allowing patients to live in the community rather than in institutions, and is regarded as a core rehabilitation service though the formal evidence base is thinner than for the interventions above (Tasman 2015). Assertive community treatment (ACT) delivers care through a multidisciplinary team with a low caseload that takes services to the patient in their own setting rather than waiting for attendance; the original model recommended each team include a vocational rehabilitation expert and, ideally, peer support workers who are themselves patients in recovery (Killaspy & Rosen 2011, in Tasman 2015). ACT is targeted at the patients who use services most heavily and are hardest to engage, and it reduces hospitalisation and improves engagement (APA 2020, Statement 19). These community components cross-reference the practical management of the acute and first episode, developed in the first-episode management topic.

GOOD TO REMEMBER

- **Supported housing:** secure community accommodation with graded support; the feature is community living over institutional care; the first step is to match the level of support to the patient's assessed need.
- **Assertive community treatment (ACT):** multidisciplinary team, low caseload, care delivered in the patient's own setting; the discriminator is for the heaviest-service-using, hardest-to-engage patients; the first step is proactive outreach rather than clinic-based waiting (APA 2020).

12.7 Assessment of disability and needs

Rehabilitation is driven by a formal **assessment of disability and needs**, not by a generic package. The clinician profiles the patient's strengths and deficits across domains, self-care, social, occupational, cognitive, and their environmental supports and barriers, then works with the patient to set the goals that matter to them. A structured needs assessment such as the Camberwell Assessment of Need (CAN) is commonly used to map met and unmet needs across housing, occupation, social relationships and health so that resources are directed where the gap actually is (Tasman 2015). This assessment step is what makes rehabilitation individualised: the same diagnosis in two patients produces two different plans because their disabilities, environments and personal goals differ.

WORKED EXAMPLE

Two patients have identical residual schizophrenia. One lives with a supportive family and wants to return to a clerical job; his plan foregrounds supported employment (IPS) and cognitive remediation. The other is unemployed, socially isolated and disengaged from services; her plan foregrounds assertive community treatment, supported housing and social skills training. The needs assessment, not the diagnosis, generated two different rehabilitation plans (Tasman 2015).

12.8 Delivery: multidisciplinary, staged and individualised

Rehabilitation is delivered by a **multidisciplinary team**, psychiatrist, clinical psychologist, psychiatric social worker, occupational therapist, nurse and increasingly peer support workers, because no single discipline covers the range of components (Tasman 2015). It is **staged**: goals are matched to the phase of illness, with stabilisation and engagement first, then skills-building, then community integration and role resumption, so that a patient is not pushed into competitive employment before basic engagement is secure. And it is **individualised**: the plan is built around the specific goals and needs identified in assessment and revised as the patient progresses, which is exactly the recovery-model insistence that each person's recovery is a unique process (Anthony 1993, Tasman 2015). The examiner rewards the phrase "multidisciplinary, staged and individualised" as the delivery principle.

RULE **Deliver rehabilitation multidisciplinary, staged and individualised.** Assess needs first, match the component to the illness phase and the patient's own goals, and revise as they progress.

INDIA

Community rehabilitation in India runs largely through the District Mental Health Programme (DMHP), the service-delivery arm of the National Mental Health Programme, which integrates basic mental health care, including follow-up and community support, into the general health system at district level. The Indian Psychiatric Society (IPS) schizophrenia guideline endorses psychoeducation, family intervention and psychosocial rehabilitation as core components alongside pharmacotherapy, consistent with the international position, while recognising that formal supported-employment and assertive-community-treatment services are less widely available and that the family remains the principal locus of long-term community support in Indian practice.

GOOD TO REMEMBER

- **The principle:** medication treats symptoms, psychosocial rehabilitation treats disability and delivers function and recovery; both are core to the plan, offered from the start (Kaplan & Sadock 2024, APA 2020).
- **Recovery model:** personal recovery = hope, agency and a meaningful life beyond the illness (CHIME: Connectedness, Hope, Identity, Meaning, Empowerment); distinct from clinical remission (Anthony 1993).
- **Components of rehabilitation:** psychoeducation and family work; social-skills and vocational training (supported employment / IPS); cognitive interventions (remediation, CBTp); supported housing and community support (ACT).
- **Assessment and delivery:** formal assessment of disability and needs (for example CAN) drives an individualised plan delivered by a multidisciplinary team, staged to the phase of illness.

HOLD THIS

Medication controls symptoms but psychosocial rehabilitation delivers function and recovery, so it is a core not optional part of every plan: framed by the recovery model (hope, agency, a life beyond the illness), built from psychoeducation and family work, social-skills and vocational training, cognitive interventions, and supported housing and community support, driven by an assessment of disability and needs, and delivered multidisciplinary, staged and individualised.

13 · Psychoeducation and family interventions

Antipsychotic medication holds relapse at bay only while it is taken and only for the person prescribed it; the **psychoeducation** and **family intervention** topic is where the examiner tests whether you understand the *other half* of relapse prevention, the psychosocial half that acts on adherence and on the emotional climate the patient recovers into. Two ideas carry the page. The first is that giving the patient and the family an accurate model of the illness, its treatment and its early warning signs improves adherence and reduces relapse. The second is the **expressed emotion** story: families high in criticism, hostility or emotional over-involvement (a high-ee household) predict relapse, and a structured family intervention that educates, teaches communication and problem-solving and lowers that emotional temperature is one of the single best-evidenced psychosocial treatments in the whole of psychiatry (Companion 2010, APA 2020).

How to use this page. Fix the two levers separately: psychoeducation (an information and skills intervention for patient and family) and the expressed-emotion evidence base (why the family climate matters and how a structured family intervention modifies it). The illness itself, its phenomenology, aetiology, criteria and course, is not re-taught here; it belongs to the Schizophrenia: aetiology, phenomenology, classification and course notes, and this page assumes it. The trap the examiner is watching for is the reflex to *blame* the family: high expressed emotion is a target for support, not a fault, and the whole intervention is framed as helping relatives cope, never as accusing them of causing the relapse.

13.1 Psychoeducation: what it is and why it works

An information-and-skills intervention, not a leaflet. Psychoeducation is the systematic, planned delivery of information about the illness and its treatment to the patient and, where they

are involved, the family, combined with training in the skills to act on that information (APA 2020). The content that a good programme conveys is standardised: the diagnosis and symptoms, the rationale for medication and its adverse effects, stress and coping, the crisis plan, and above all the *early warning signs* of relapse and what to do when they appear (APA 2020, Bauml 2006). It is not a one-off handover of a pamphlet; it is delivered over multiple structured sessions, individually or in groups, often alongside family members, in a manner that aims to build hope, reassurance and a sense of mastery rather than simply reciting a prognosis.

Why it changes outcome. Psychoeducation reduces relapse and readmission principally by improving *adherence*, the single most common reversible cause of relapse, and by equipping patient and family to recognise an incipient relapse early enough to act (Xia 2011, APA 2020). Even relatively brief programmes, of ten sessions or fewer, reduce relapse rates over the following 9 to 18 months, an effect comparable to that of much lengthier treatment (Companion 2010, Pekkala 2002). In clinical trials a **12-session** programme is the usual format, with briefer courses of ten sessions or fewer also studied (APA 2020).

RULE **Teach the early warning signs.** The highest-yield content of any psychoeducation programme is the patient's and family's own relapse signature and the agreed action, because catching a relapse early is what converts information into prevented admission.

13.2 The early-warning-signs and adherence mechanism

Adherence is the proximal target. The reason psychoeducation earns its place in every guideline is mechanistic: relapse in schizophrenia is most often driven by stopping medication, and an accurate shared model of *why* the drug is needed (including that it is prophylactic, not merely symptomatic) is the most modifiable lever on adherence. The maintenance and adherence principles behind this sit in the maintenance topic; here the point is that psychoeducation is the intervention that operationalises them for the patient and the household. Behavioural techniques (cueing, packaging, reminders) improve adherence further and are complementary rather than alternative (Companion 2010).

TRAP **Do not front-load the worst prognosis onto a newly diagnosed patient.** Education can harm, particularly in the newly diagnosed hearing about poor outcomes, and family interventions can even raise expressed emotion in already low-expressed-emotion families; pitch the information to build coping, not despair (Companion 2010).

13.3 Expressed emotion: the construct and how it is measured

The emotional climate of the household, operationalised. Expressed emotion is a measured attribute of a key relative's attitude towards the patient, comprising three components: *critical comments*, *hostility* and *emotional over-involvement* (Companion 2010, Tasman 2015). A household is rated **high ee** if the relative exceeds threshold on criticism or shows hostility or marked emotional over-involvement; the shorthand that a family shows high criticism, hostility or emotional over-involvement is exactly the definition of a high-ee household. The reference instrument is the Camberwell Family Interview (Vaughn & Leff 1976), a semi-structured interview of the relative from which critical comments are counted and hostility and over-

involvement rated; the briefer Five Minute Speech Sample (Magana 1986) is the practical field alternative.

It predicts relapse across disorders, not only schizophrenia. High expressed emotion is a robust, replicated predictor of relapse in schizophrenia and, with an even larger effect, in mood and eating disorders (Butzlaff & Hooley 1998). Note the direction-of-causation caveat the examiner may probe: expressed emotion is partly a *response* of relatives to the difficulty of living with a severe illness, and high expressed emotion is less evident in relatives of first-episode than of multiply-relapsing patients, so it is best read as a modifiable relational risk marker rather than a simple external cause (Companion 2010).

Critical comments

Statements of dislike or disapproval of the patient's behaviour, counted over the interview; the commonest high-expressed-emotion component.

Hostility

Generalised rejection or criticism of the patient as a person rather than of a specific behaviour.

Emotional over-involvement

Over-protective, self-sacrificing or intrusively over-concerned attitudes, including excessive distress and over-identification with the patient.

13.4 The expressed-emotion evidence: Brown and the contact threshold

The founding observation. The classic prospective study is Brown et al (1972): patients recovering from an episode of schizophrenia who returned to live with a relative prone to make critical comments relapsed far more often over the following 12 months than those living with a more tolerant, accepting relative, **58% versus 16%** (Companion 2010). Two moderators emerged and are examinable. First, antipsychotic medication *buffered* the effect, so pharmacotherapy and family climate act on relapse together, not in competition. Second, the ill effect of high expressed emotion was mitigated when the patient was in face-to-face contact with the high-expressed-emotion relative for less than **35 hours** a week, so reduced contact, in effect a degree of social distance, was protective (Companion 2010). A later systematic review of 27 studies confirmed the effect as robust, strongest in chronic patients (Butzlaff & Hooley 1998).

58% vs 16%	<35 h/wk	27
RELAPSE AT 12 MO, HIGH VS LOW EE (BROWN 1972)	FACE-TO-FACE CONTACT THAT IS PROTECTIVE	STUDIES IN THE EE META-ANALYSIS (BUTZLAFF 1998)

13.5 Family intervention: the Leff trial and what it contains

Modifying the climate changes the relapse rate. If high expressed emotion drives relapse, then an intervention that lowers it should prevent relapse, and the landmark test is Leff et al (1982). Patients living in high-expressed-emotion households, all on depot antipsychotics, were randomised to routine care or to a package of factual education for the relatives, a relatives' group to share experience, and family sessions in the home aimed at reducing expressed emotion and face-to-face contact. At 9 months the relapse rate was **50% in controls versus 9%** in the treated group, and the only two treated patients who relapsed were those in whom neither expressed

emotion nor contact had actually fallen (Companion 2010). This both proved that a structured family intervention prevents relapse and reinforced that reduced expressed emotion and contact are the operative levers.

The three ingredients of a family intervention. A family intervention is systematic, extends well beyond simply conveying information, and is future- rather than past-focused (APA 2020). Every effective programme combines three elements: *education* about the illness and its treatment; *communication training* and structured *problem-solving* skills for the household; and explicit work to *lower expressed emotion* and stress and to strengthen support (APA 2020, Companion 2010). Across at least 25 trials these reliably reduce relapse; no single therapeutic model is clearly superior, which has led to the view that education may be the common active ingredient (Companion 2010, Pitschel-Walz 2001).

RULE **Offer family intervention wherever the patient is in ongoing contact with relatives.** A structured family intervention in a high-expressed-emotion household is one of the strongest relapse-prevention tools available and is guideline-recommended for any patient in regular family contact (APA 2020).

TRAP **Do not blame the family.** High expressed emotion is a target for support, not a fault; it is largely a coping response to a hard illness, and the intervention is framed as helping relatives cope, never as accusing them of causing the relapse.

13.6 Practical delivery: format, dose and duration

Single-family or multi-family, over months. Family interventions are delivered either as *single-family* work (one household, often including the patient, sometimes led by a member of the care team so a liaison develops between team, patient and relatives) or as *multi-family groups* that bring several families together and add mutual support and shared learning (APA 2020, McFarlane 2016). They are not brief: the benefit is greatest when more than **10** sessions are delivered over a period of at least **7 months** (APA 2020, McDonagh 2017). This "months, not weeks" dosing is a common examinable discriminator, distinguishing a genuine family intervention from a single family meeting.

FEATURE	PSYCHOEDUCATION	FAMILY INTERVENTION
Core aim	Accurate illness model, adherence, early warning signs	**Lower expressed emotion, add communication and problem-solving skills**
Recipient	Patient, and/or family	**Family (with or without the patient)**
Format	Individual or group; can be brief	**Single-family or multi-family group**
Typical course	About 12 sessions (10 or fewer also effective)	**More than 10 sessions over at least 7 months**
Chief benefit	Reduced relapse via adherence and early detection	**Reduced relapse and readmission; lower carer burden**

Psychoeducation and family intervention overlap in content but differ in target and dose; the family intervention is the longer, skills-based, expressed-emotion-lowering programme (APA 2020, Companion 2010).

The boundary condition. These approaches are by definition of no value to patients who have lost contact with family or do not wish relatives involved; conversely, provided the patient-directed intervention is comprehensive, formal family involvement is not always mandatory (Companion 2010, Pitschel-Walz 2001). Most patients, however, do want family involved (APA 2020).

13.7 The Indian family-centred setting

Family as co-therapist, not visitor. In Indian practice the patient overwhelmingly lives within, and is cared for by, the family, so the family is present, informed and involved as a matter of course rather than by special arrangement; this makes psychoeducation and family intervention the natural, high-value backbone of psychosocial care rather than an add-on. Delivering education to the whole household, using the family to supervise and support adherence, and coaching relatives to lower criticism and over-involvement fit the setting directly and are strongly endorsed by the Indian guideline (IPS 2025).

INDIA

The District Mental Health Programme (DMHP), launched in 1995 under the National Mental Health Programme, is the community delivery vehicle through which psychoeducation and family work reach patients at district level. Practical family-centred care leans on the co-resident family to hold adherence and watch for early warning signs. A widely taught cross-cultural observation is that Indian families of patients with schizophrenia tend to show lower rates of high expressed emotion than Western samples, offered as one contributor to the better course of schizophrenia reported in developing-country cohorts; treat the precise percentages as needing verification and hold the qualitative point.

GOOD TO REMEMBER

- **Psychoeducation:** planned information plus skills for patient and family (diagnosis, medication rationale, coping, and above all early warning signs); reduces relapse mainly by improving adherence; usual format about 12 sessions, briefer courses also effective; caveat, avoid front-loading the worst prognosis onto the newly diagnosed.
- **Expressed emotion (EE):** a rated relative attribute of critical comments, hostility and emotional over-involvement, measured by the Camberwell Family Interview or the Five Minute Speech Sample; high EE predicts relapse; caveat, it is a modifiable relational marker and partly a coping response, not a blame.
- **Family intervention:** a systematic programme of education plus communication and problem-solving skills plus expressed-emotion lowering; among the best-evidenced psychosocial relapse-prevention tools; dose to hold, more than 10 sessions over at least 7 months; single-family or multi-family group; caveat, offer wherever the patient is in ongoing family contact.

HOLD THIS

High expressed emotion (criticism, hostility, emotional over-involvement) predicts relapse; a structured family intervention that educates, teaches communication and problem-solving, and lowers expressed emotion is one of the best-evidenced psychosocial relapse-prevention treatments, dosed over months, not weeks.

14 · Social skills training and vocational rehabilitation

Pharmacotherapy controls positive symptoms but does little for the enduring **social and functional disability** that keeps people with schizophrenia out of relationships and work. The recovery-oriented plan therefore couples the antipsychotic with structured psychosocial rehabilitation, and two of its most exam-favoured components are social skills training and vocational rehabilitation. The illness itself, its negative-symptom and cognitive substrate, is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes; here we take the deficits as given and ask how to remediate them behaviourally.

Why examiners love it. The single highest-yield fact is a paradigm shift: vocational rehabilitation moved from the old prevocational "train then place" ladder to the evidence-based supported employment "place then train" model, of which Individual Placement and Support (IPS) is the exemplar. Knowing which one wins, and why, separates a rehearsed answer from a vague one.

14.1 Social skills training: what it is

Definition. Social skills training is a structured, behavioural teaching method that breaks down conversational, self-care and community-living skills into components and trains them one at a time to counter the social deficits of schizophrenia (Companion to Psychiatric Studies; Kaplan & Sadock 2024). It is didactic and skills-focused, not insight-focused: the therapist teaches a discrete social behaviour the way a coach teaches a motor skill.

Targets. Typical goals are everyday behaviours a resident can name in a viva: making eye contact, smiling at appropriate times, actively listening, sustaining a conversation, assertiveness, and appropriate verbal and nonverbal communication, extending to self-care and independent community living (APA 2021).

14.2 The four learning steps: model, rehearse, feedback, reinforce

Mechanism. Social skills training is delivered through a repeating behavioural loop: **instruction and modelling** (the skill is demonstrated), **role-play and rehearsal** (the patient practises it), **corrective feedback and positive reinforcement** (performance is shaped), then **homework** to transfer the skill to real settings (APA 2021; Companion to Psychiatric Studies). It is usually run in a group format so members can practise on each other and receive social reinforcement.

MNEMONIC

M-R-F-G

Model the skill, **R**ehearse it in role-play, give **F**eedback and reinforcement, set **G**eneralisation homework. The four moving parts of every social skills training session.

14.3 Evidence and the honest limits of social skills training

What it does. Social skills training improves social function and can improve negative symptoms and core illness symptoms more than usual care, with reduced relapse and rehospitalisation in some studies (McDonagh et al. 2017, in APA 2021). **The limit.** The strength of evidence is modest, which is why the APA grades it a *suggestion*, not a strong recommendation (APA 2021), and skill gains generalise to daily life only if homework and in-vivo practice are built in. Frame it as a useful adjunct for the patient whose stated goal is better social functioning, not a stand-alone cure.

RULE **Skills are taught, not talked about.** Social skills training works through modelling, rehearsal, feedback and homework; a discussion group without behavioural rehearsal is not social skills training.

14.4 Vocational rehabilitation: the scale of the problem

Why it matters. Impaired work role is one of the most disabling features of schizophrenia, feeding poverty and loss of self-efficacy. In the United States fewer than **15%** of patients are employed, yet **50 to 75%** state that competitive employment is a primary goal (Kaplan & Sadock 2024). Vocational rehabilitation, the systematic effort to help the patient obtain and keep paid work, has always been a centrepiece of psychiatric rehabilitation, but the historically dominant approach was the wrong one.

<15%	50 to 75%	~40	2 to 3x
OF US PATIENTS EMPLOYED	WANT COMPETITIVE WORK	RCTS FAVOUR IPS	EMPLOYMENT RATE VS COMPARISON

The vocational gap and the evidence base for supported employment (Kaplan & Sadock 2024).

14.5 The paradigm shift: train then place versus place then train

The old model. Traditional vocational rehabilitation used **prevocational** "train then place" ladders: extensive pre-employment assessment, counselling, day centres, sheltered workshops and transitional employment intended to build the patient up to a presumed threshold of "work readiness" *before* any real job (Kaplan & Sadock 2024). Evaluations found these stepwise models did not improve competitive-employment rates; most patients became discouraged, disengaged or stalled in the preparatory phase.

The new model. From the late 1980s the field shifted to "place then train", termed supported employment: the patient is helped into a real competitive job first, with training and support delivered *on the job*. Anyone who wants to work is helped, without screening for readiness, and support continues once employed (Kaplan & Sadock 2024).

FEATURE	PREVOCATIONAL "TRAIN THEN PLACE"	SUPPORTED EMPLOYMENT "PLACE THEN TRAIN"
Sequence	Prepare, then place	**Place first, train on the job**
Readiness screen	Extensive pre-employment assessment	**Zero exclusion, no readiness screen**
Intermediate steps	Sheltered workshops, transitional work	None; direct to competitive job
Job type	Sheltered or preparatory	**Competitive, at or above minimum wage**
Support	Ends before real job	Ongoing follow-along, time-unlimited
Competitive-employment outcome	Not improved over usual care	**2 to 3 times higher**

The train-then-place to place-then-train shift; the evidence favours the right-hand column (Kaplan & Sadock 2024).

RULE **Place then train beats train then place.** Supported employment (IPS) achieves better competitive-employment outcomes than prevocational preparation for open-market work.

TRAP **Waiting for "work readiness".** Assuming a patient must be symptom-free before any vocational step contradicts the evidence; IPS uses zero exclusion and starts the job search regardless of residual symptoms.

14.6 Individual Placement and Support: the eight principles

What IPS is. IPS, also called evidence-based supported employment, is the manualised model of supported employment developed in the 1990s for severe mental illness (Kaplan & Sadock 2024). It emphasises the patient's own preferences, a rapid job search without lengthy pre-employment training, and individualised on-the-job support. Its eight fidelity principles are the examinable core.

Zero exclusion

Anyone who wants to work is helped, regardless of symptoms, cognition, work history or substance use.

Competitive employment

The goal is a real job in the open labour market, at or above minimum wage, not a sheltered post.

Rapid job search

Direct job seeking rather than lengthy assessment; a job is applied for within about 30 days, first job typically found within 4 months.

Job development

The employment specialist builds employer relationships to match jobs to the client's skills and preferences.

Integration with treatment

The employment specialist sits inside the clinical or ACT team, not in a separate agency.

Client preferences

Placements follow the patient's stated interests; preference-matched jobs last longer.

Ongoing support

Follow-along support is time-unlimited and continues after the patient is employed.

Benefits counselling

Individualised advice on how work affects welfare or disability benefits, to correct fears of losing them.

14.7 The evidence base for supported employment

Strength. Nearly **40** randomised controlled trials show IPS produces higher employment rates, greater earnings, more hours worked and longer job tenure; competitive-employment rates are **2 to 3 times** those of comparison vocational programmes (Kaplan & Sadock 2024). The European EQOLISE trial replicated the finding outside the United States, with over **50%** of patients working at some point during follow-up (Burns et al. 2007). **Safety.** High work expectations do *not* destabilise patients or raise relapse; employed patients report better self-esteem and quality of life (Kaplan & Sadock 2024). Interventions that do not target placement directly, including counselling and medication alone, have little effect on employment.

> **HOLD THIS**
> Supported employment, place then train (IPS), beats prevocational train-then-place for competitive work; its founding principle is zero exclusion, so you never wait for a patient to become symptom-free before starting the job search.

14.8 Place in the recovery-oriented plan

Integration, not sequence. Neither skills nor work is a graduation prize awarded after symptom control; both run alongside the antipsychotic as part of a recovery-oriented plan aimed at function and personal goals, not just symptom scores. Social skills training and vocational rehabilitation sit beside family psychoeducation, cognitive remediation and assertive community treatment; the employment specialist is embedded in the clinical team (Shorter Oxford Textbook of Psychiatry; Kaplan & Sadock 2024). Cognitive remediation and family intervention are covered in their own management topics; here the point is that vocational and social rehabilitation are woven into the same team, not bolted on afterwards.

14.9 The Indian context

Where the evidence meets Indian practice. Formal IPS supported-employment services are still scarce in India, and much community-based vocational rehabilitation runs through sheltered workshops, occupational-therapy units and, above all, family-supported work within the household or family business. The District Mental Health Programme under the National Mental Health Programme carries community rehabilitation intent, but competitive supported employment is far from routine. The examinable Indian answer holds two things at once: sheltered and family-supported work remain the realistic default here, while the guideline-level evidence still favours supported employment on the place-then-train model wherever it can be offered.

INDIA

Vocational rehabilitation in India leans on sheltered workshops and family-supported work embedded in the joint-family and small-business economy, with the District Mental Health Programme providing the community scaffold. State the local reality, then name supported employment (IPS) as the evidence-based direction of travel.

COMMON TRAP

Do not describe social skills training as a talking or support group. It is a behavioural teaching method: without modelling, role-play rehearsal, feedback and homework it is not social skills training, and the marks are in naming those components.

GOOD TO REMEMBER

- **Social skills training:** structured behavioural teaching of social, self-care and community-living skills; delivered by modelling, role-play rehearsal, feedback and homework, usually in a group; APA graded it a suggestion (2C) for the patient whose goal is better social functioning.
- **Vocational rehabilitation:** the systematic effort to help the patient obtain and keep paid work; the old prevocational "train then place" ladder (sheltered workshops, transitional employment) did not improve competitive-employment rates.
- **Supported employment:** the "place then train" model; help anyone who wants to work into a real competitive job first, with on-the-job support; the discriminator is zero exclusion and no readiness screen.
- **Individual Placement and Support (IPS):** the evidence-based manualised form of supported employment; eight principles (zero exclusion, competitive employment, rapid job search, job development, treatment integration, client preferences, ongoing support, benefits counselling); nearly 40 RCTs, 2 to 3 times higher employment than comparison; the caveat is that it needs the employment specialist embedded in the clinical team to work.

15 · CBT for psychosis and cognitive remediation

Why this matters. Two psychological therapies sit inside the schizophrenia treatment plan alongside the drug, and the examiner tests them precisely because a candidate who answers "management" with medication alone has answered half the question. **CBT for psychosis** works on the residual positive symptoms the antipsychotic leaves behind, the distress and conviction of persistent delusions and voices, while **cognitive remediation** works on the neurocognitive deficits, attention, memory and executive function, that no antipsychotic corrects. Both are guideline-endorsed adjuncts, both have modest and debated effect sizes, and the single commonest error is to confuse the two: CBTp is for symptom-related distress, remediation is for cognition.

The disorder itself, its phenomenology, aetiology, criteria and course, is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes and is not re-taught here; the cognitive domain of the illness and the framing of cognition as a treatment target are developed there. What this topic teaches is the two therapies: what each is, what it targets, the size and the controversy of its evidence, and where each sits in the guidelines. We take **cognitive**

behaviour therapy for psychosis first, then cognitive remediation, then the discriminator that keeps them apart.

15.1 CBT for psychosis: what it is and what it targets

Cognitive behaviour therapy for psychosis (CBTp) is a structured, collaborative psychological therapy adapted from standard CBT for use with people who have psychotic symptoms. Its three signature moves are: it **normalises** psychotic experiences by placing them within a range of ordinary experience, for example hearing a loved one's voice in grief, so the experience is less alien and less frightening; it helps the patient **test the evidence** for delusional beliefs, guiding them to generate their own healthier and more realistic alternative explanations rather than the clinician arguing the delusion down; and it works to **reduce the distress and the impact** of persistent positive symptoms and to improve functioning, using behavioural self-monitoring, coping strategies and graded task assignment (APA 2020, Kingdon & Turkington 2019). The therapeutic stance is deliberately non-judgemental and non-confrontational: the target is not the belief's truth-value in the abstract but the patient's distress, appraisal and conviction, so cbtp is offered as an adjunct to medication for persistent distressing symptoms, never as a replacement for it (APA 2020).

RULE **CBTp is an evidence-based adjunct for persistent distressing symptoms, not a replacement for medication.** It runs alongside the antipsychotic, working on distress, appraisal and conviction, never instead of the drug.

15.2 The evidence base and the guideline position

CBTp is a recommended psychological intervention across guidelines. The APA gives it a strong recommendation, "APA recommends that patients with schizophrenia be treated with cognitive-behavioral therapy for psychosis", rated 1B (APA 2020, Statement 16), and NICE recommends offering CBTp to everyone with schizophrenia, with a suggested minimum of **16 sessions** (NICE 2014, in APA 2020). The pivotal meta-analysis behind the symptom claim is Jauhar and colleagues' review of **34 randomised controlled trials**, which found CBTp more effective than usual care on overall symptoms measured on the PANSS and BPRS, with a standardised mean difference of **-0.33** (95% CI -0.47 to -0.19) (Jauhar et al. 2014, in APA 2020). CBTp also improves global, social and occupational functioning in the short term, up to about **6 months**, but these functional gains are generally not maintained beyond that once the course ends (McDonagh et al. 2017, in APA 2020). CBTp can be delivered individually or in groups, in any setting and any phase, though some initial symptom reduction usually helps the patient engage.

15.3 The modest effect size and the debate over it

The effect size is real but modest, and it is genuinely contested, which the examiner rewards a candidate for knowing. Two points anchor the controversy. First, the magnitude: an SMD of about -0.33 for overall symptoms is a small effect, and the APA itself rates the strength of evidence only as moderate for the outcomes that show a benefit and low or insufficient for the rest, with essentially no meaningful effect on negative symptoms (APA 2020). Second, the sensitivity to blinding: the symptom effect is smaller, though it remains statistically significant,

when the analysis is restricted to trials with blinded outcome assessment (95% CI -0.27 to -0.03), and at least one meta-analysis raised the possibility of publication bias (Jauhar et al. 2014, in APA 2020). The honest summary for a viva is that CBTp produces a small, blinding-sensitive improvement in positive symptoms and short-term function, that it is safe with minimal harms, and that it therefore earns its place as an adjunct even though its effect is modest and disputed rather than large and settled.

-0.33	34	16
CBTP OVERALL-SYMPTOM SMD (JAUHAR 2014)	RCTS IN THE CBTP META-ANALYSIS	MIN SESSIONS SUGGESTED (NICE)

The high-yield numbers for CBTp: a small, blinding-sensitive symptom effect, from a large but heterogeneous evidence base, delivered over a defined minimum course.

GOOD TO REMEMBER

- **CBT for psychosis (CBTp, cognitive behaviour therapy for psychosis):** what it is, a structured collaborative therapy that normalises psychotic experiences, tests the evidence for delusional beliefs and reduces the distress and impact of persistent positive symptoms; the discriminator, it targets symptom-related distress and conviction, not neurocognition; the first step, offer it as an adjunct to medication for persistent distressing symptoms, never as a replacement (APA 2020, Statement 16, recommends 1B).

15.4 Cognitive remediation: what it is and what it targets

Cognitive remediation (also called cognitive remediation therapy, CRT) is a behavioural, training-based intervention that targets the neurocognitive deficits of schizophrenia directly: attention, memory, executive function, and increasingly social cognition and metacognition, with the goal of durable and generalisable improvement (Wykes & Spaulding 2011, in Tasman 2015). The analogy Tasman uses is physiotherapy after a broken leg: the skill lost to the illness is regained through structured exercise. It is delivered individually or in groups, increasingly computer-assisted, and comes in two methodological flavours: **drill and practice**, which teaches a skill through repetition alone, and **drill and practice plus strategy**, which adds explicit learning of strategies to bypass a specific cognitive limitation (Tasman 2015). It is distinct from cognitive compensation or adaptation, which does not try to repair the deficit but supplies external aids such as calendars, alarms and checklists, the "glasses for vision" approach. This cross-references the cognitive domain and the framing of cognition as a core treatment target developed in the Schizophrenia: aetiology, phenomenology, classification and course notes.

15.5 Cognitive remediation: effect on cognition and transfer to function

The evidence is best summarised as a small-to-moderate effect on cognition that transfers to real-world function best when the training is paired with broader rehabilitation. The landmark meta-analysis is McGurk and colleagues', **26 randomised controlled trials** in **1,151 patients**, which concluded that cognitive remediation produces moderate improvements in neurocognitive performance and, critically, that functional outcomes improve when the remediation is combined with psychiatric rehabilitation (McGurk et al. 2007, in Kaplan & Sadock 2024). The APA echoes this: cognitive remediation gives moderate improvement in specific aspects of cognition and small positive effects on social, occupational and global function, with the psychosocial benefit

"particularly robust when cognitive remediation is used as a component of or adjunct to other forms of psychiatric rehabilitation rather than being delivered as a stand-alone intervention" (APA 2020, Statement 22). The caution is real: some gains reflect practice on the trained tasks and may not generalise, so drill without transfer is a known failure mode. This is exactly why the guideline pairs it with rehabilitation and why the APA rates it a suggestion, 2C, rather than a strong recommendation (APA 2020).

TRAP **Expecting cognitive remediation to transfer to function without pairing it with rehabilitation.** Drill alone can improve the trained task and still leave real-world function untouched; the functional gain comes when remediation is embedded in rehabilitation.

26	1,151	2C
RCTS IN THE REMEDIATION META-ANALYSIS	PATIENTS POOLED (MCGURK 2007)	APA STRENGTH FOR REMEDIATION (SUGGESTS)

Cognitive remediation: a moderate cognitive effect from a sizeable evidence base, carried to a weaker guideline recommendation because functional transfer depends on pairing with rehabilitation.

GOOD TO REMEMBER

- **Cognitive remediation (cognitive remediation therapy, CRT):** what it is, drill-and-strategy training of the neurocognitive deficits (attention, memory, executive function); the discriminator, it targets cognition, not the distress of delusions or voices, with a small-to-moderate effect on cognition; the first step, pair it with psychiatric rehabilitation so the cognitive gain transfers to function rather than staying on the trained task (Wykes et al. 2011, APA 2020, Statement 22, suggests 2C).

15.6 Keeping the two apart: the exam discriminator

The single most examined point is the clean separation of the two therapies by their target. CBTp targets the **distress, appraisal and conviction** of persistent positive symptoms, the residual delusions and hallucinations; cognitive remediation targets **neurocognition**, the attention, memory and executive-function deficits that predict functional outcome and respond poorly to drugs. They are not interchangeable and they are not competitors: a single patient with distressing residual voices and marked cognitive impairment can appropriately receive both, each aimed at a different problem. A useful contrast table anchors the discriminator for recall.

FEATURE	CBT FOR PSYCHOSIS (CBTP)	COGNITIVE REMEDIATION (CRT)
Primary target	**Distress and appraisal of persistent positive symptoms**	**Neurocognitive deficits: attention, memory, executive function**
Core method	Normalise, test the evidence for beliefs, reduce distress and impact	Drill and practice, or drill plus strategy training
Effect size	Small, blinding-sensitive (SMD about -0.33 on symptoms)	Small-to-moderate on cognition; functional transfer needs rehab
APA guideline strength	**Recommends (1B)**	**Suggests (2C)**
Key caveat	Modest and debated; not a replacement for medication	Gains may not generalise unless paired with rehabilitation

The clean split the examiner tests: CBTp for symptom-related distress, remediation for cognition; both adjuncts to medication, neither a substitute.

15.7 Placement in the plan and delivery

Both therapies are adjuncts layered onto the pharmacological plan, not alternatives to it. CBTp can be started in any phase and any setting, but usually needs some initial symptom reduction for the patient to engage, and requires a therapist with proper CBTp training and supervision; the commonest real-world barrier is simply availability of trained staff (APA 2020). Cognitive remediation is best placed inside a broader rehabilitation package rather than run alone, for the transfer reason above, and its main barrier is again programme availability, which online and computer-assisted delivery is beginning to address (APA 2020). Both fold into the psychosocial rehabilitation plan whose principles and other components, family work, supported employment, assertive community treatment, are developed in the psychosocial rehabilitation topic. Where medication resistance is the driver, the review of psychosocial treatments, including whether CBTp has been offered, is an explicit step in the treatment-resistant pathway (APA 2020).

INDIA

The Indian Psychiatric Society schizophrenia guideline endorses structured psychosocial interventions, psychoeducation, family intervention and rehabilitation, as core components of care alongside pharmacotherapy, consistent with the international position. In Indian practice, formal CBTp and structured cognitive-remediation programmes are far less widely available than antipsychotic treatment and family-based support, so the realistic plan for most settings foregrounds medication, psychoeducation and family work, with CBTp and remediation offered where a trained therapist and a rehabilitation programme actually exist rather than assumed to be universally accessible.

PEARL

The tidiest way to hold the pair: **CBTp changes how the patient relates to the symptom; remediation changes the machinery underneath.** One works on the distress and conviction of a delusion or voice, the other exercises attention, memory and executive function. Neither replaces the antipsychotic, and remediation only reaches function when it rides on rehabilitation.

HOLD THIS

CBT for psychosis is an evidence-based adjunct that normalises psychotic experiences, tests the evidence for delusions and reduces the distress of persistent positive symptoms, with a small blinding-sensitive effect (recommended, APA 1B); cognitive remediation drills attention, memory and executive function with a small-to-moderate cognitive effect that transfers to function only when paired with rehabilitation (suggested, APA 2C); both are adjuncts to medication, never replacements, and the discriminator is target, distress for CBTp, cognition for remediation.

16 · Community models and the Indian services

Why this matters. Once the acute episode is treated and the patient is discharged, the question the examiner asks is not "which drug" but "who delivers care, where, and to whom". **Community psychiatry** is the answer: a shift of the locus of care from the mental hospital to the patient's own setting, and the models that operationalise it. The two testable ideas are a Western service model, **assertive community treatment** and the case-management family that sits around it, and the Indian service architecture built on the National Mental Health Programme and its **district mental health** arm. A management answer that names the drug but cannot name the service that keeps a disengaged patient in treatment has answered only half the question.

This topic teaches the service scaffolding, not the illness. The phenomenology, aetiology, criteria and course of schizophrenia are owned by the Schizophrenia: aetiology, phenomenology, classification and course notes and are not re-taught here; the individual rehabilitation components (supported employment, social skills training, cognitive remediation) sit in the psychosocial rehabilitation topic. What this topic adds is the *delivery vehicle*: how care is organised as a team, a caseload and a district-level programme. We take assertive community treatment first, then case management, then the Indian models, then telepsychiatry and the non-governmental sector.

16.1 Assertive community treatment: the team that goes to the patient

Assertive community treatment (ACT) is a community-care model in which a **multidisciplinary team** delivers treatment, rehabilitation and support directly in the patient's own environment rather than waiting for the patient to attend a clinic (Kaplan & Sadock 2024). Its defining features are a **low, shared caseload**, **assertive outreach**, services provided directly by the team rather than brokered out, time-unlimited care and around-the-clock coverage. The caseload per worker is **about ten to fifteen**, in deliberate contrast to standard case management, and the caseloads are shared across the whole team rather than held by one clinician, so care continues when any one worker is away (Tasman 2015). K&S describe ACT as a program with mobile mental-health teams providing an array of treatment, rehabilitation and housing services available 24 hours a day, whose goal is to keep the person with serious mental illness out of hospital and functioning in the community (Kaplan & Sadock 2024).

The target is not everyone. ACT is reserved for the **most disabled, hardest-to-engage and most frequently-admitted** patients, the "revolving-door" group, for whom ordinary clinic-based follow-up repeatedly fails. In this group ACT reliably **reduces admissions and improves**

engagement and adherence, and it improves housing stability, employment, quality of life and satisfaction; where its outcomes have been compared head-to-head with intensive case management the clinical differences are small, so the benefit is largely about engagement and reduced hospital use rather than symptom change (Tasman 2015). The APA guideline recommends ACT specifically for patients with a history of poor engagement leading to frequent relapse or homelessness (APA 2020, Statement 19).

RULE **Assertive community treatment targets the high-need, frequently-admitted patient, not everyone.** Low shared caseload plus assertive outreach is a scarce, intensive resource aimed at the disengaged revolving-door group; it reduces admissions and improves engagement.

TRAP **Transplanting a Western caseload model without adapting it to the Indian family-and-district reality.** A 24/7 team-based, low-caseload service is resource-heavy; in India the family is the de-facto case manager and the district is the unit of delivery, so the model must be adapted, not copied.

16.2 Case management and its models: broker versus clinical/intensive

Case management is the broader family of models for coordinating care across services for a person with serious mental illness; ACT is best understood as its most intensive, team-delivered form. The models differ mainly in who does the work and how large the caseload is.

MODEL	HOW CARE IS DELIVERED	CASELOAD / TARGET
Broker case management	Case manager **arranges and links** the patient to services (assesses, refers, coordinates) but does not deliver clinical care directly; the thinnest model	Large caseload; the classic "broker" who brokers services out
Clinical case management	Case manager also **provides direct clinical care** (therapy, monitoring, medication support) as well as coordinating services	Moderate caseload; care not brokered out
Intensive case management (ICM) / intensive clinical case management (ICCM)	Clinical case management at **low caseload**; the case manager does *not* share the caseload (the point that separates it from ACT)	Caseload low, similar to ACT
Standard case management (SCM)	Conventional coordinated follow-up	Caseload **30 to 35 patients** per worker
Assertive community treatment (ACT)	Multidisciplinary team, direct care, assertive outreach, 24/7, **shared** caseload	Caseload **about ten to fifteen**; heaviest-service-using group

The case-management spectrum: from the broker who only links, through clinical and intensive models, to team-based ACT. The two exam discriminators are caseload size (ACT about ten to fifteen versus standard 30 to 35) and whether the caseload is shared (ACT) or held individually (ICCM).

The single line to hold: **ACT differs from intensive clinical case management chiefly in that ACT shares the caseload across a team while ICCM does not**, and both differ from standard case management by a much lower caseload (Tasman 2015). The broker model, which only

assesses and refers without delivering care, is the weakest and is largely superseded by clinical and assertive models.

16.3 The Indian frame: the National Mental Health Programme and community psychiatry

The Indian service architecture is not built on ACT teams but on a public-health, decentralised model. The National Mental Health Programme (NMHP) was launched in **1982** with three objectives: to ensure availability and accessibility of minimum mental-health care for all, to encourage application of mental-health knowledge in general health care and social development, and to promote community participation in mental-health service development. Its governing idea is **integration of basic mental-health care into general (primary) health care** delivered by trained non-specialist personnel, because specialist psychiatrists are far too few to reach the population directly. This is **community psychiatry** in the Indian public-health sense: not a mobile specialist team, but mental-health care pushed down the existing primary-care system.

INDIA

The District Mental Health Programme (DMHP), use "district mental health", was launched in **1995** as the delivery component of the NMHP, decentralising care to the **district** as the operational unit. Its prototype was the **Bellary model** in Karnataka (started 1985, catering to a population of about 1.5 million), which demonstrated that trained primary-care staff could deliver mental-health care at the district and primary-health-centre level. Successive plans expanded the DMHP across districts. The DMHP, use "dmhp", is the answer the examiner wants to the question "how does India decentralise psychiatric care", and it is the Indian analogue of the community-service question that ACT answers in the West.

16.4 The Indian service settings: day care and the halfway home

Within community psychiatry, Indian rehabilitation spans a graded ladder of settings "in a living, learning or working environment ranging from the inpatient psychiatric unit to day-care hospitals and half-way homes". Two of these settings are named service devices the examiner tests.

Day care centre / day hospital

A non-residential setting the patient attends during the day for supervised treatment, activity and rehabilitation, returning home at night; it delivers structured care and monitoring without the cost and dependency of an inpatient bed, and bridges the gap between the ward and full community living.

Halfway home

A supported, transitional residential facility for the patient who is no longer acutely ill but not yet ready for fully independent living; it provides supervised accommodation and rehabilitation "halfway" between hospital and home, rebuilding self-care, social and occupational skills before discharge to the community.

The phrase to reproduce is that the day care, use "day care", centre and the halfway home, use "halfway home", occupy the middle of the rehabilitation ladder: more support than living at home, less restriction than a hospital ward. In Indian practice, where families are usually

available, these settings are often used to give the family respite and the patient graded exposure to community demands rather than as permanent placements.

16.5 Telepsychiatry and the non-governmental sector in India

Two features are specific to how community care is actually extended in India. **Telepsychiatry**, the delivery of psychiatric assessment and follow-up over a video/telecommunication link, is a strategy to overcome the severe shortage and uneven distribution of psychiatrists across a large, largely rural population: it lets a specialist in a medical college support a distant district or primary-health-centre team, and it is increasingly written into the DMHP and formalised through national telepsychiatry guidance. It extends specialist reach without moving the specialist, which is exactly the constraint the Indian system faces. **Non-governmental-organisation (NGO)-run rehabilitation** supplies much of the day-care, halfway-home, vocational and community-support capacity that the public sector cannot fully staff; voluntary agencies and self-help/family organisations are an explicit part of the NMHP's community-participation objective and, in practice, carry a large share of psychosocial rehabilitation in India. For the examiner, telepsychiatry and NGO-run rehabilitation are the two adaptations that make a Western community model workable in the Indian setting.

> **PEARL**
>
> The Western question "which community team?" and the Indian question "how do we reach the district?" are answered differently: ACT is a low-caseload specialist team that goes to the patient; the DMHP is a decentralised public-health programme that pushes care into primary care, backed by telepsychiatry for specialist reach and NGOs for rehabilitation capacity. Name the right model for the setting the examiner specifies.

16.6 Putting the models together: what to say in a management answer

In a discharge or long-term-management answer, the community-services paragraph should do three things. First, **match intensity to need**: reserve assertive community treatment (and its low, shared caseload) for the frequently-admitted, disengaged patient, and use ordinary or clinical case management for the rest. Second, **name the Indian delivery frame**: the National Mental Health Programme and its District Mental Health Programme decentralising care to the district and primary-health-centre level within community psychiatry, with the day care centre and halfway home as graded transitional settings. Third, **name the two Indian force-multipliers**: telepsychiatry to extend scarce specialist reach and NGO-run rehabilitation to supply community capacity, both leaning on the family as the ever-present real-world case manager. The ECT question for treatment-resistant or catatonic cases belongs to the ECT and neurostimulation notes and is not part of the community-services answer.

GOOD TO REMEMBER

- **Assertive community treatment (ACT):** what it is, a multidisciplinary team delivering care in the patient's own setting with assertive outreach; caseload about ten to fifteen, shared across the team, 24/7; the one thing to hold, it is for the most disabled and frequently-admitted patients and it reduces admissions and improves engagement (not for everyone) (Kaplan & Sadock 2024, Tasman 2015, APA 2020).
- **Case management (broker vs clinical/intensive):** what it is, coordination of care across services; the discriminator, the broker only links and refers, the clinical model also delivers care, and intensive/ACT run at low caseload; the one thing to hold, ACT shares the caseload while intensive clinical case management does not, and standard case management runs at 30 to 35 patients per worker (Tasman 2015).
- **National Mental Health Programme (NMHP):** what it is, India's 1982 programme to integrate mental-health care into general health care; the one thing to hold, its method is decentralisation and community participation, not specialist expansion.
- **District Mental Health Programme (DMHP):** what it is, the 1995 delivery arm of the NMHP decentralising care to the district; the discriminator, prototype was the Bellary model in Karnataka (1985); the one thing to hold, the district and primary-health-centre are the unit of delivery.
- **Day care centre:** what it is, non-residential daytime supervised treatment and rehabilitation with the patient going home at night; the one thing to hold, it bridges ward and community without an inpatient bed.
- **Halfway home:** what it is, supported transitional residential living between hospital and independent home; the one thing to hold, it rebuilds skills before full discharge and gives the family graded handover.
- **Telepsychiatry and NGO-run rehabilitation:** what they are, video-link specialist care and voluntary-sector rehabilitation capacity; the one thing to hold, they are the Indian adaptations that overcome specialist shortage and staffing gaps, working with the family as case manager.

HOLD THIS

Assertive community treatment is a low-caseload (about ten to fifteen, shared) multidisciplinary team with assertive outreach reserved for the most disabled, frequently-admitted patients, reducing admissions and improving engagement; India delivers community psychiatry instead through the National Mental Health Programme (1982) and its District Mental Health Programme (1995, Bellary prototype) decentralising care to the district, including the day care centres, halfway homes, telepsychiatry and NGO-run rehabilitation, and the family as the real case manager.

Antipsychotic adverse effects and emergencies

17 · Extrapyramidal side effects

Why this matters. The extrapyramidal side effects, the eps, are the signature motor toxicity of dopamine D2 blockade in the **nigrostriatal pathway**, and the examiner tests them in one disciplined way: by their onset timeline. The single most reliable way to tell the three acute reactions apart, and to separate them from the delayed one, is when they appear after the drug is started or the dose is raised. Acute dystonia strikes in hours, akathisia in days, drug-induced parkinsonism in weeks, and tardive dyskinesia only after months to years (Maudsley 2021,

Kaplan & Sadock 2024). Get the clock right and the diagnosis, and usually the management, follows.

This topic teaches the three acute-to-subacute reactions with their timing, features and first management step; tardive dyskinesia (months to years) is developed in the next topic. The receptor and pathway mechanics of D2 blockade are not re-derived here (they are owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes); the illness itself is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes. Here we apply the pharmacology at the bedside. The one governing sentence: eps come from too much nigrostriatal D2 blockade, and their timing is diagnostic.

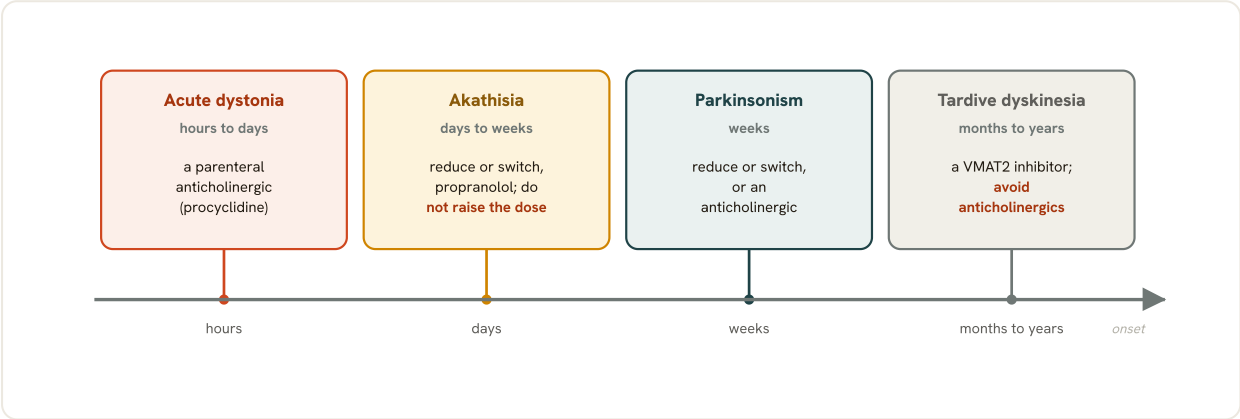

Fig 9.7 The extrapyramidal timeline, ordered by onset. Acute dystonia strikes in hours, akathisia in days, parkinsonism in weeks, and tardive dyskinesia after months to years. The management differs: an anticholinergic helps dystonia and parkinsonism but worsens tardive dyskinesia, akathisia is treated by reducing the dose and never by raising it, and established tardive dyskinesia responds to a VMAT2 inhibitor.

17.1 The unifying mechanism and the onset timeline

All the classical eps arise from blockade of dopamine D2 receptors in the nigrostriatal pathway, which shifts the striatal dopamine-acetylcholine balance toward relative cholinergic excess (Stahl 2021). This is why the acute reactions are commonest with high-potency first-generation agents (haloperidol) at higher D2 occupancy, and why anticholinergic drugs relieve dystonia and parkinsonism. The four disorders are best learned as points on a single clock measured from starting the drug or raising the dose: acute dystonia within hours to a few days, akathisia within days to weeks, drug-induced parkinsonism within weeks, and tardive dyskinesia only after months to years (Maudsley 2021). The timeline is the spine of the whole topic and the fastest route to the answer in a viva.

RULE **Timing dates the reaction.** Acute dystonia is hours, akathisia is days, parkinsonism is weeks, and tardive dyskinesia is months to years; when in doubt, put the reaction on the clock from the last dose change.

17.2 Acute dystonia: sustained spasm within hours

Acute dystonia is a sustained, often painful muscle spasm that appears within hours of starting a high-potency antipsychotic, or within minutes if the drug is given intramuscularly or intravenously (Maudsley 2021). The spasm is of any muscle group but the classic sites are the eyes rolling upward (oculogyric crisis), the head and neck twisted to one side (torticollis), the jaw,

tongue and pharynx (impairing speech and swallowing), and, most dangerously, the larynx (laryngeal dystonia), which can threaten the airway. In extreme cases the back arches (opisthotonos). It is commonest in young men who are antipsychotic-naive and on a high-potency agent (Maudsley 2021, Kaplan & Sadock 2024). It is frightening, and because patients often report it as an allergy, it drives non-adherence unless explained.

Management. The first step is a parenteral anticholinergic, given intramuscularly or intravenously because the patient may be unable to swallow. Benztropine **1 to 2 mg** IM or IV, or an antihistaminic-anticholinergic such as diphenhydramine **50 mg** IM or IV, or promethazine, produces rapid relief; the response to the intravenous route is seen within about 5 minutes and to the intramuscular route within about 20 minutes (Kaplan & Sadock 2024, Maudsley 2021). Laryngeal dystonia is an emergency and is treated at once. After the acute episode, reduce the dose or switch to a lower-potency or second-generation agent, and consider short-term prophylactic anticholinergic cover if a high-potency first-generation drug must continue.

GOOD TO REMEMBER

- **Acute dystonia:** feature, sustained painful spasm (oculogyric crisis, torticollis, jaw, tongue, laryngeal); discriminator, onset within hours to days, young man on a high-potency agent, and the muscle is held in spasm rather than restless or tremulous; first management step, parenteral anticholinergic (benztropine 1 to 2 mg IM/IV, or diphenhydramine 50 mg, or promethazine), treating laryngeal dystonia as an emergency.

17.3 Akathisia: inner restlessness within days to weeks

Akathisia, from the Greek meaning "never to sit down", is a subjective, unpleasant inner restlessness with a compulsion or urge to move, appearing within days to weeks of starting the antipsychotic or increasing the dose (Kaplan & Sadock 2024, Maudsley 2021). The subjective dysphoria is the core; the objective signs are foot-stamping when seated, constantly crossing and uncrossing the legs, rocking from foot to foot when standing, and pacing. It is genuinely distressing and is an established suicide-risk factor, having been linked to suicidal ideation and to aggression (Maudsley 2021). Its great danger is diagnostic: it is readily mistaken for psychotic agitation, and if the antipsychotic is then raised the akathisia worsens.

Management. The principle is the opposite of raising the drug. Reduce the antipsychotic dose, or switch to an agent with a lower liability for akathisia (olanzapine, quetiapine and clozapine carry the lowest risk; haloperidol among the highest); add a beta-blocker, low-dose propranolol **30 to 80 mg/day**, which is the most commonly used adjunct, or a benzodiazepine such as clonazepam or lorazepam (Kaplan & Sadock 2024, Maudsley 2021). Anticholinergics are generally unhelpful for pure akathisia unless it is part of a wider eps spectrum (Maudsley 2021). Critically, do NOT raise the antipsychotic.

TRAP **Treating akathisia as psychotic agitation and raising the antipsychotic.** The extra dose worsens the very restlessness it was meant to calm; when a patient becomes more agitated after a dose increase, think akathisia and go down, not up.

GOOD TO REMEMBER

- **Akathisia:** feature, subjective inner restlessness with an urge to move plus observable pacing, rocking and leg-crossing; discriminator, onset within days to weeks, dysphoric and worse after a dose increase (unlike agitation, which the drug should calm), and a recognised suicide-risk factor; first management step, reduce the dose or switch, add propranolol 30 to 80 mg/day or a benzodiazepine, and never raise the antipsychotic.

17.4 Drug-induced parkinsonism: bradykinesia, rigidity and tremor within weeks

Drug-induced parkinsonism (pseudoparkinsonism) is the antipsychotic-induced triad of bradykinesia, rigidity and tremor, appearing days to weeks after starting the drug or raising the dose (Maudsley 2021). Bradykinesia gives decreased facial expression, a flat monotone voice, slow movement and difficulty initiating movement; there may be bradyphrenia (slowed thinking), a coarse resting tremor and increased salivation. It is more common in the elderly, in women and in those with pre-existing neurological damage (Maudsley 2021). The examiner's favourite point is that its mask-like face, monotone and slowness are readily mistaken for depression or for the negative symptoms of schizophrenia, so it is under-recognised.

Management. Reduce the antipsychotic dose, switch to an agent with a lower propensity for parkinsonism (a second-generation agent such as quetiapine or olanzapine), or add an anticholinergic such as trihexyphenidyl **2 to 10 mg/day** or benztropine (Maudsley 2021, Kaplan & Sadock 2024). Most patients do not need long-term anticholinergics; review the need at least every 3 months, and do not dose them at night, since symptoms are usually absent during sleep (Maudsley 2021).

GOOD TO REMEMBER

- **Drug-induced parkinsonism:** feature, bradykinesia, rigidity and tremor with mask-like face and monotone voice; discriminator, onset within weeks, symmetrical, and easily mistaken for depression or negative symptoms (so it is under-recognised); first management step, reduce the dose or switch to a lower-eps agent, or add an anticholinergic (trihexyphenidyl 2 to 10 mg/day or benztropine), reviewed at least every 3 months.

17.5 Putting the reactions side by side

The table sets the acute-to-subacute eps against the delayed reaction on the four axes an examiner tests: effect, onset, features and management. Read the onset column downward as the clock that dates the diagnosis. Tardive dyskinesia is included only to complete the timeline; its phenomenology and treatment are developed in the next topic.

EFFECT	ONSET	FEATURES	MANAGEMENT
Acute dystonia	**Hours to days (minutes if IM/IV)**	Sustained spasm: oculogyric crisis, torticollis, laryngeal; young men, high-potency agent	Parenteral anticholinergic (benztropine 1 to 2 mg IM/IV, diphenhydramine 50 mg, or promethazine)

EFFECT	ONSET	FEATURES	MANAGEMENT
Akathisia	**Days to weeks**	Subjective inner restlessness, urge to move, pacing; distressing, suicide-risk factor	Reduce dose or switch; propranolol 30 to 80 mg/day or a benzodiazepine; NOT raising the antipsychotic
Drug-induced parkinsonism	**Weeks**	Bradykinesia, rigidity, tremor; mask-like face, monotone; mimics depression/negative symptoms	Reduce dose, switch to lower-eps agent, or anticholinergic (trihexyphenidyl 2 to 10 mg/day, benztropine)
Tardive dyskinesia	**Months to years**	Choreoathetoid orofacial and limb movements; developed in the next topic	Withdraw anticholinergic, reduce or switch (clozapine best supported), VMAT2 inhibitor; see next topic

The eps by onset timeline: hours (dystonia), days (akathisia), weeks (parkinsonism), months to years (tardive dyskinesia), the clock that dates the diagnosis.

17.6 India and practical points

The acute anticholinergics used for dystonia and parkinsonism are cheap and available in Indian practice: trihexyphenidyl (benzhexol) is the everyday oral anticholinergic, and promethazine and diphenhydramine cover the parenteral acute-dystonia need where injectable benztropine is not stocked. High-potency first-generation agents remain in wide use on cost grounds, so acute dystonia in a young man on injectable haloperidol (marketed as Serenace) is a scenario a resident will actually meet. Among the second-generation agents, verified Indian brands include olanzapine as Oleanz and quetiapine as Qutipin, the two lower-akathisia switch options; risperidone (marketed as Sizodon) is intermediate.

INDIA

For acute dystonia where injectable benztropine is unavailable, parenteral promethazine or diphenhydramine is the practical Indian substitute, and oral trihexyphenidyl (benzhexol) is the workhorse for drug-induced parkinsonism. Because high-potency first-generation agents such as haloperidol (Serenace) stay in routine use, keep a parenteral anticholinergic readily to hand when starting them, especially in a young, antipsychotic-naive man.

17.7 The one distinction that decides management

The whole topic reduces to reading the movement and the clock together, because the two errors that hurt patients are opposite in direction. Miss akathisia behind "psychotic agitation" and you raise the drug and make it worse; miss parkinsonism behind "depression or negative symptoms" and you under-treat a reversible motor effect. Both are avoided by asking, first, when did this start relative to the last dose change, and second, is the patient restless-and-driven (akathisia), spasm-held (dystonia) or slow-and-stiff (parkinsonism). That single discrimination, plus the onset clock, is what the examiner is testing.

Hours	Days to weeks	Weeks	30 to 80 mg/day
ACUTE DYSTONIA ONSET	AKATHISIA ONSET	PARKINSONISM ONSET	PROPRANOLOL FOR AKATHISIA

HOLD THIS
Date the reaction by the clock from the last dose change: acute dystonia in hours (parenteral anticholinergic), akathisia in days (reduce or switch, add propranolol, never raise the drug), parkinsonism in weeks (reduce, switch or anticholinergic), tardive dyskinesia in months to years.

18 · Tardive dyskinesia

Why this matters. **Tardive dyskinesia** is the adverse effect that most defines the long-term risk of antipsychotic prescribing, and the examiner returns to it because it inverts the logic that governs the acute movement disorders. Where acute dystonia, parkinsonism and akathisia arrive early and are eased by lowering dopamine blockade or adding an anticholinergic, tardive dyskinesia arrives late, is potentially irreversible, and is made worse, not better, by an anticholinergic. The whole topic hinges on holding that reversal and on knowing the one class of drug, the **vmat2** inhibitor, that is genuinely evidence-based for the established disorder (Kaplan & Sadock 2024, Maudsley 2021).

This is a management topic: the phenomenology and course of schizophrenia itself belong to the Schizophrenia: aetiology, phenomenology, classification and course notes, and the dopamine-pathway and receptor mechanics that explain why chronic D2 blockade produces a hyperkinetic movement disorder belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. Here we recognise it, screen for it, weigh the risk factors, and treat it.

18.1 The features: a late-onset, potentially irreversible movement disorder

Tardive dyskinesia is a late-onset, potentially irreversible choreoathetoid **abnormal involuntary movement** disorder that emerges after months to years of antipsychotic exposure (Kaplan & Sadock 2024). "Tardive" means late: unlike the acute extrapyramidal syndromes that appear within hours to weeks, tardive dyskinesia by convention requires a sustained period of exposure, and it may persist or progress even after the offending drug is withdrawn, which is what makes prevention and early detection so much more important than late rescue. The movements are involuntary, repetitive and purposeless, and the patient is often unaware of them.

RULE **Late, choreoathetoid, and possibly permanent.** Tardive dyskinesia follows months to years of exposure, is a choreoathetoid abnormal involuntary movement, and may be irreversible, so the whole game is prevention and early detection, not late treatment.

18.2 The phenomenology: where the movements are and what they look like

The classic and earliest picture is orofacial-lingual-buccal: lip-smacking, puckering and pursing, chewing and lateral jaw movements, tongue protrusion and writhing ("fly-catcher" tongue), and grimacing. Beyond the face the disorder extends to chorea of the limbs and trunk, with piano-playing finger movements, choreoathetoid writhing of the hands and feet, and truncal rocking or

pelvic thrusting; respiratory dyskinesia and irregular breathing can also occur. The movements typically worsen with emotional arousal, lessen with voluntary action over the affected part, and disappear in sleep. Recognising the orofacial-lingual-buccal pattern is the single most exam-relevant discriminator, because it is the presentation the AIMS was built to capture.

Orofacial-lingual-buccal movements
Lip-smacking and puckering, chewing, tongue protrusion and writhing, grimacing; the earliest and most characteristic pattern.

Chorea of the limbs and trunk
Piano-playing finger and toe movements, choreoathetoid writhing of hands and feet, truncal rocking and pelvic thrusting.

Choreoathetoid
A blend of chorea (rapid, irregular, flowing) and athetosis (slow, sinuous, writhing); the defining quality of the tardive movements.

18.3 Screening and quantification: the AIMS

Tardive dyskinesia is screened for and quantified with the Abnormal Involuntary Movement Scale (AIMS), the standard structured examination that rates involuntary movements across facial, oral, extremity and trunk regions on a graded scale together with global severity and the patient's awareness and distress (Stahl 2021). Guidance is to examine patients periodically for the development of abnormal movements using a neurological examination and the AIMS, so that emerging tardive dyskinesia is caught while it is mild and potentially reversible rather than after it has become established. The scale is a monitoring instrument, not a diagnostic test on its own: the diagnosis is clinical, made in a patient with the requisite exposure once other causes of dyskinesia are excluded.

WORKED EXAMPLE

A woman in her sixties on long-term haloperidol is noticed at follow-up to have subtle lip-smacking and tongue movements she has not remarked on. Rather than "just her dentures", the correct step is a structured AIMS examination, review of the antipsychotic (dose reduction or switch where the illness allows), and, because the movements are established, consideration of a vmat2 inhibitor. Reaching for an anticholinergic here would be the classic error.

18.4 The risk factors

The risk factors cluster into patient factors and drug factors, and the examiner expects both. Patient factors: older age (the strongest and most consistent), female sex, diabetes and an affective (mood) illness, and early or prominent extrapyramidal symptoms after starting the drug, which flag a susceptible nigrostriatal system. Drug factors: longer duration of exposure and higher cumulative dose, and the use of first-generation (typical) agents, which carry a substantially higher tardive dyskinesia risk than second-generation agents (Kaplan & Sadock 2024). The composite high-risk patient the textbooks describe is an older woman with a mood disorder on a first-generation antipsychotic who developed extrapyramidal symptoms early.

DOMAIN	RISK FACTOR
Patient	**Older age (strongest)**
	Female sex
	Diabetes
	Affective (mood) illness
	Early extrapyramidal symptoms after starting the drug
Drug	Longer duration of exposure
	Higher cumulative dose
	First-generation (typical) agents

Tardive dyskinesia risk factors: older age and first-generation agents are the two most consistently emphasised, one patient and one drug factor.

18.5 Management overview: prevention first, then reduce or switch, then treat

Management runs in three tiers and the order is deliberate. First, prevention: use the lowest effective dose, prefer second-generation agents over first-generation ones where clinically appropriate, and detect early through periodic AIMS screening, because an established disorder may not reverse. Second, once tardive dyskinesia is present, reduce or switch the antipsychotic where the illness allows: a switch to clozapine or quetiapine is the classic manoeuvre, since these lowest-D2-affinity agents are least likely to drive the movements and clozapine in particular may improve tardive symptoms (Maudsley 2021, Kaplan & Sadock 2024). Third, add an evidence-based drug treatment: a vmat2 inhibitor. Throughout, one thing is never done, which is to add an anticholinergic, because anticholinergics worsen tardive dyskinesia.

MNEMONIC

PREVENT, SWITCH, VMAT2 (never anticholinergic)

PREVENT with the lowest effective dose, second-generation agents and early AIMS detection; SWITCH or reduce the antipsychotic, classically to clozapine or quetiapine; treat the established disorder with a VMAT2 inhibitor; and never reach for an anticholinergic, which worsens it.

18.6 The VMAT2 inhibitors: valbenazine and deutetrabenazine

The evidence-based drug treatment for established tardive dyskinesia is a vmat2 inhibitor. VMAT2 (the vesicular monoamine transporter 2) packages dopamine and other monoamines into presynaptic vesicles; inhibiting it depletes the dopamine available for release, dampening the dopaminergic overactivity that drives the movements (Kaplan & Sadock 2024). Two agents are specifically evidence-based and approved for tardive dyskinesia. Valbenazine is a highly selective, once-daily VMAT2 inhibitor that produced significantly greater reductions in AIMS scores than placebo in randomised trials (Hauser 2017, Kaplan & Sadock 2024). Deutetrabenazine is a deuterated form of tetrabenazine given twice daily with food, also with randomised evidence of AIMS improvement. The older agent, tetrabenazine, is the first-generation VMAT2 inhibitor: it

has a short half-life (active metabolites about 2 to 8 hours) requiring multiple daily dosing and carries more depression and parkinsonism, so where available the newer agents are generally preferred (Maudsley 2021, Kaplan & Sadock 2024). All three can prolong the QT interval and carry warnings around depression and suicidality; VMAT2 inhibitor doses are lowered in hepatic impairment.

40 to 80	12 to 48	2 to 10 h
VALBENAZINE MG ONCE DAILY (TD)	DEUTETRABENAZINE MG/DAY, 2 DIVIDED (TD)	TETRABENAZINE HALF-LIFE

RULE **The VMAT2 inhibitors, valbenazine and deutetrabenazine, are the evidence-based treatment for established tardive dyskinesia.** They are the drugs approved and trial-supported specifically for tardive dyskinesia; tetrabenazine is the older, less-preferred option.

TRAP **Do not give an anticholinergic for tardive dyskinesia; it worsens it.** Anticholinergics help acute dystonia and drug-induced parkinsonism, but in tardive dyskinesia they aggravate the movements, so they are exactly the wrong reflex here.

18.7 Why the anticholinergic reflex fails here

The trap is worth its own paragraph because it is the commonest single error and the cleanest discriminator between the tardive and the acute syndromes. Acute dystonia and drug-induced parkinsonism arise from a relative dopaminergic deficit against unopposed cholinergic tone in the striatum, so an anticholinergic (benztropine, trihexyphenidyl) restores the balance and relieves them. Tardive dyskinesia is the opposite state, a hyperkinetic disorder linked to dopaminergic supersensitivity, so blocking cholinergic tone tips the balance further towards the dyskinesia and makes it worse. This is why the correct pharmacological lever is a VMAT2 inhibitor, which reduces dopamine availability, and why any prescribed anticholinergic should if anything be withdrawn when tardive dyskinesia appears.

COMMON TRAP

Reflexively prescribing benztropine or trihexyphenidyl for any antipsychotic-associated movement. For acute dystonia and parkinsonism that is right; for tardive dyskinesia it worsens the movements. The tardive patient needs antipsychotic review plus a VMAT2 inhibitor, not an anticholinergic.

INDIA

In Indian practice the affordable and available levers dominate: prevention through the lowest effective dose and preferential second-generation prescribing, periodic clinical and AIMS screening, and antipsychotic reduction or a switch (classically to clozapine, marketed as Sizopin, or to quetiapine, marketed as Qutipin) where the illness allows. The VMAT2 inhibitors valbenazine and deutetrabenazine are not routinely available or affordable in most Indian settings at the time of writing, which makes prevention and early detection, not late rescue, the practical backbone of care.

GOOD TO REMEMBER

- **Tardive dyskinesia:** FEATURE, a late-onset, potentially irreversible choreoathetoid abnormal involuntary movement (orofacial-lingual-buccal movements, chorea of the limbs and trunk) after months to years of antipsychotic exposure. DISCRIMINATOR, it is worsened by an anticholinergic (unlike acute dystonia and parkinsonism, which improve). FIRST MANAGEMENT STEP, screen and quantify with the AIMS, then review the antipsychotic (lowest effective dose, reduce or switch where possible).
- **Valbenazine:** WHAT, a selective VMAT2 inhibitor, evidence-based for established tardive dyskinesia. DOSE, **40 to 80 mg once daily** (Stahl). CAVEAT, QT prolongation and a warning for depression/suicidality; lower the dose in hepatic impairment.
- **Deutetrabenazine:** WHAT, a deuterated VMAT2 inhibitor, evidence-based for tardive dyskinesia. DOSE, **12 to 48 mg/day** in two divided doses, taken with food (Stahl). CAVEAT, QT prolongation and depression/suicidality warning; lower the dose in hepatic impairment.
- **Tetrabenazine:** WHAT, the older first-generation VMAT2 inhibitor, the less-preferred option. DOSE/CAVEAT, short half-life (**2 to 10 hours**) needing multiple daily dosing (Kaplan & Sadock); more depression and parkinsonism than the newer agents.

HOLD THIS

Established tardive dyskinesia is treated with a VMAT2 inhibitor (valbenazine or deutetrabenazine) after reducing or switching the antipsychotic; an anticholinergic worsens it, which is the reverse of acute dystonia and parkinsonism.

19 · Neuroleptic malignant syndrome

Why this matters. Neuroleptic malignant syndrome is the antipsychotic emergency the examiner will not forgive you for missing. It is rare, with an estimated incidence of the order of **0.02 to 0.16 per cent** of antipsychotic-treated patients, but it kills, with a reported mortality of about **5.6 per cent** overall and up to **20 per cent** in advanced cases (Maudsley 2021, Kaplan & Sadock 2024). The whole of its management turns on one reflex: recognise it early and stop the drug. This topic teaches the features, the investigations and the management; it deliberately does not re-teach the illness itself, which is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes.

Neuroleptic malignant syndrome, the nms, is an idiosyncratic reaction to dopamine D2 blockade, best understood as an acute disorder of thermoregulation and neuromotor control produced by an abrupt hypodopaminergic state in the **striatum and hypothalamus** (Kaplan & Sadock 2024). The receptor and pathway mechanics of D2 antagonism are not re-derived here (they are owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes); here we apply that pharmacology at the bedside. The one governing sentence: any antipsychotic-treated patient with fever and rigidity is nms until proven otherwise, and the first move is to stop the drug.

19.1 The clinical tetrad and its timing

The classic presentation is a tetrad, worth memorising as a block. First, lead-pipe rigidity: a generalised, uniform (not cogwheel) increase in tone that is the motor signature of the syndrome and the source of the heat and the muscle breakdown. Second, hyperthermia: a true pyrexia,

often marked, driven by muscular heat generation and impaired hypothalamic heat loss. Third, autonomic instability: labile or high blood pressure, tachycardia and profuse diaphoresis. Fourth, an altered mental state, ranging from confusion and fluctuating consciousness to stupor and coma (Maudsley 2021, Kaplan & Sadock 2024). The syndrome typically evolves over **1 to 3 days** (roughly 24 to 72 hours), and characteristically appears early in treatment, after a recent dose increase, or with a high-potency agent (Maudsley 2021). Presentation is heterogeneous, and atypical cases lacking hyperthermia or rigidity are described, particularly with second-generation agents, so a high index of suspicion is the safeguard.

RULE **Fever and rigidity on an antipsychotic is nms until proven otherwise.** Stop the drug first and investigate second; do not wait for the creatine kinase before acting.

19.2 Risk factors: who and when

The risk is concentrated at predictable points. Drug factors dominate: high-potency first-generation agents (haloperidol above all), parenteral administration, a recent or rapid dose increase, high doses, antipsychotic polypharmacy, and intermittent non-adherence with re-exposure (Maudsley 2021, Kaplan & Sadock 2024). Patient factors add to it: dehydration, exhaustion, psychomotor agitation, pre-existing catatonia, an organic brain disorder, adjunctive lithium, a low serum iron, and a past history of nms. Demographically, young adult males are over-represented, while the outcome is more often lethal in older patients (Maudsley 2021). The practical lesson is that nms clusters around the agitated, dehydrated young man just started on, or recently escalated on, injectable high-potency haloperidol, which is exactly the patient a resident manages on an acute ward.

19.3 Investigations: the creatine kinase and its company

The signature laboratory finding is a markedly raised creatine kinase, often above **1000 units/L** and sometimes into the tens of thousands, released from the rigid, breaking-down muscle (Maudsley 2021, Kaplan & Sadock 2024). It is accompanied by a leukocytosis and frequently by deranged liver function tests. One caveat the examiner likes: asymptomatic creatine kinase rises are common with antipsychotics and with any agitation or intramuscular injection, so a raised creatine kinase supports but does not by itself diagnose nms, and it is the clinical picture that decides (Maudsley 2021). The dangerous downstream sequelae are what make the bloods urgent: the muscle breakdown causes rhabdomyolysis, which with the myoglobinuria and dehydration produces acute kidney injury, and in severe cases disseminated intravascular coagulation supervenes. Monitor renal function, electrolytes, coagulation and creatine kinase serially.

19.4 The differential: what else is rigid and febrile

The exam value of nms is in telling it apart from its mimics. Serotonin syndrome shares hyperthermia, autonomic instability and altered mental state, but is distinguished by neuromuscular hyperactivity of a different quality, clonus and hyperreflexia rather than lead-pipe rigidity, and by a serotonergic drug and a faster onset (over hours). Malignant hyperthermia is an anaesthetic reaction to volatile agents and depolarising muscle relaxants; there are no direct data linking it to nms, but antipsychotics are used cautiously in patients with a malignant

hyperthermia history (Kaplan & Sadock 2024). Malignant catatonia can be clinically indistinguishable from nms and shares its rigidity, hyperthermia and autonomic storm; as an entity it is owned by the Other psychotic disorders, delusional syndromes and catatonia notes, and it appears here only to be named in the nms differential. Also exclude a central nervous system infection (meningitis, encephalitis) and, in a febrile patient, a straightforward chest or other infection, which is precisely the trap below.

TRAP **Calling it "just EPS" or "just a chest infection" and continuing the antipsychotic.** Rigidity plus fever plus a raised creatine kinase is not ordinary parkinsonism and not a simple pneumonia; missing nms behind either label and leaving the drug running is the classic fatal error.

19.5 Management: stop the drug, support aggressively

The first and non-negotiable step is to **stop the antipsychotic immediately**, and stop any other contributing dopamine antagonist (Maudsley 2021, Kaplan & Sadock 2024). Everything else is built on that. The second pillar is aggressive supportive care in a high-dependency or intensive-care setting: active cooling, generous intravenous rehydration to protect the kidneys from the rhabdomyolysis, correction of electrolytes, and close monitoring of temperature, pulse and blood pressure, with ventilatory support or dialysis in severe cases (Kaplan & Sadock 2024). Supportive care alone, started early, is often enough in mild cases. Reduce environmental and pharmacological aggravants, treating dehydration and stopping adjunctive lithium.

19.6 Pharmacological options: dantrolene, bromocriptine and benzodiazepines

Where the picture is more severe, specific agents are added, on limited evidence and with guideline recommendations that vary widely (Maudsley 2021). The muscle relaxant dantrolene acts directly on skeletal muscle to reduce the rigidity and heat generation, with benefit sometimes seen within minutes to hours (Kaplan & Sadock 2024). The dopamine agonist bromocriptine counteracts the underlying hypodopaminergic state. Benzodiazepines (for example a lorazepam test dose) are useful, particularly where catatonic features are present, and are a recommended treatment. Dopamine agonists and dantrolene are often combined. For refractory cases, and where malignant catatonia cannot be excluded, electroconvulsive therapy is effective even after pharmacotherapy has failed; the technique itself is not taught here and is owned by the ECT and neurostimulation notes (Maudsley 2021, Kaplan & Sadock 2024).

GOOD TO REMEMBER

- **Dantrolene:** a direct-acting skeletal-muscle relaxant (reduces calcium release from the sarcoplasmic reticulum) for the rigidity and hyperthermia; a regimen is 0.8 to 2.5 mg/kg intravenously every 6 hours, up to a maximum of 10 mg/kg/day, then oral 100 to 200 mg/day once the patient can swallow (Kaplan and Sadock 2024); the caveat to hold is hepatotoxicity, so watch liver function.
- **Bromocriptine:** an oral dopamine agonist that reverses the hypodopaminergic state; start at 2.5 mg two to three times daily and build to the therapeutic 20 to 30 mg/day given in *four* divided doses, ceiling 45 mg/day; the caveat is that it may worsen psychosis and lower blood pressure.
- **Benzodiazepines:** for example lorazepam as a 1 to 2 mg parenteral test dose; useful adjunct, especially with catatonic features; the caveat is respiratory depression and sedation, so monitor consciousness.

19.7 The features and management at a glance

The table pins the tetrad, the key investigations and the management steps in one place, with the discriminator that separates each feature from its benign mimic in the highlighted column. Read the management column top to bottom as the running order: stop the drug, support, then add specific agents.

DOMAIN	FEATURE	DISCRIMINATOR	FIRST MANAGEMENT STEP
Motor	Lead-pipe rigidity	**Uniform (not cogwheel) tone, generalised, not relieved by anticholinergics**	Stop the antipsychotic; dantrolene if severe
Temperature	Hyperthermia	**True pyrexia driven by muscle heat, not a source of infection**	Active cooling; stop the drug
Autonomic	Autonomic instability	**Labile or high BP, tachycardia, diaphoresis**	Supportive monitoring in a high-dependency setting
Mental state	Altered mental state	**Fluctuating consciousness, confusion to stupor/coma**	Supportive care; exclude CNS infection
Laboratory	Raised creatine kinase, leukocytosis	**Creatine kinase often >1000 units/L; supports but does not alone diagnose**	IV fluids, monitor renal function (rhabdomyolysis, AKI, DIC)

The nms tetrad plus the laboratory signature, each with its discriminator and its first management step, the first of which is always to stop the drug.

19.8 Restarting an antipsychotic afterwards

Most patients still need an antipsychotic, and cautious rechallenge carries an acceptable risk (Maudsley 2021). Wait until the features of nms have resolved completely, stopping the drug for at least **5 days** and preferably longer (Maudsley 2021); Kaplan & Sadock advise waiting at least **2 weeks** after symptoms resolve (Kaplan & Sadock 2024). Correct the prior risk factors first, rehydrate and avoid concomitant lithium. Then begin with a very small dose and titrate slowly

with close monitoring of temperature, pulse and blood pressure, choosing an agent structurally unrelated to the culprit and of lower dopamine affinity, that is, a low-potency or second-generation agent such as quetiapine or clozapine. Avoid high-potency first-generation drugs and avoid all depot or long-acting injectable preparations, because the drug cannot be withdrawn quickly if nms recurs (Maudsley 2021).

RULE **Rechallenge low and slow, never by depot.** After full resolution and at least 5 days off, restart a low-potency or second-generation oral agent at a tiny dose with close observation, and never with a long-acting injectable.

INDIA

The scenario a resident actually meets is nms in an agitated, dehydrated young man recently started on injectable high-potency haloperidol (marketed as Serenace), still widely used on cost grounds. For safe rechallenge the lower-potency second-generation switch options are readily available: quetiapine (marketed as Qutipin), olanzapine (marketed as Oleanz), and clozapine (marketed as Sizopin) where a structurally unrelated, low-affinity agent is wanted. Depot and long-acting injectable preparations are avoided after nms because they cannot be withdrawn quickly.

1 to 3 days	>1000 units/L	5 days	~5.6 per cent
TYPICAL EVOLUTION OF NMS	CREATINE KINASE (OFTEN)	MINIMUM OFF-DRUG BEFORE RECHALLENGE	OVERALL MORTALITY

PEARL

Lead-pipe rigidity plus true hyperthermia plus a creatine kinase in the thousands, evolving over a couple of days in someone recently started or escalated on a high-potency antipsychotic, is nms until proven otherwise. The rigidity is uniform and unrelieved by anticholinergics, which is what separates it from ordinary drug-induced parkinsonism.

HOLD THIS

Any antipsychotic-treated patient with fever and rigidity is neuroleptic malignant syndrome until proven otherwise: stop the drug immediately, support aggressively (cooling, fluids, high-dependency monitoring), add dantrolene and bromocriptine (and benzodiazepines, ECT for refractory cases) if severe, and rechallenge later low and slow with a low-potency or second-generation agent, never a depot.

20 · Metabolic syndrome and the monitoring schedule

Why this matters. The antipsychotics that control psychosis also, for many patients, quietly engineer a cardiometabolic catastrophe: **weight gain**, dyslipidaemia, insulin resistance and type 2 diabetes that together constitute the **metabolic syndrome**. This burden is not a footnote to treatment; it is the principal driver of the fifteen-to-twenty-year mortality gap between people with schizophrenia and the general population, most of that excess being cardiovascular (Maudsley 2021, Tasman 2015). The examiner tests one competence above all here: whether you

know the **monitoring schedule** and will actually take a metabolic baseline before you prescribe. This is a schedule-heavy topic, and the intervals are the marks.

The illness itself, its phenomenology, aetiology, criteria and course, is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes and is not re-taught here; the receptor pharmacology behind why H1 and 5HT2C blockade drive appetite, and the CYP metabolism of individual agents, belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes and are applied, not re-derived. What this topic teaches is the metabolic burden, its measurement, its verified monitoring schedule, and its management.

Fig 9.8 The metabolic monitoring schedule. Weight is tracked most closely, at baseline, six and twelve weeks and then at least annually; waist at baseline and annually; and fasting glucose or HbA1c, lipids and blood pressure at baseline, twelve weeks and annually. Olanzapine and clozapine carry the highest metabolic risk, so a baseline before starting is not optional.

20.1 The burden: why the metabolic hit dominates the mortality gap

People with schizophrenia die roughly fifteen to twenty years earlier than the general population, and the largest single contributor is cardiovascular disease, not suicide (Maudsley 2021). Around half of all people with schizophrenia meet criteria for obesity, a relative risk of nearly two against the general population, and while genetic and lifestyle factors contribute, antipsychotic-induced weight gain is in large measure responsible (Tasman 2015). The chain is mechanistic: weight gain and central adiposity drive insulin resistance, which drives dyslipidaemia and ultimately type 2 diabetes, and each step compounds cardiovascular risk. Antipsychotics can also, rarely, precipitate diabetic ketoacidosis or hyperosmolar hyperglycaemic states de novo, sometimes without preceding obesity, which is why glucose is monitored in every patient and not only the visibly overweight (Stahl 2021).

PEARL

The headline the examiner wants is that the mortality gap in schizophrenia is driven mainly by cardiovascular disease, and antipsychotic-induced weight gain and metabolic syndrome are a modifiable slice of it. Monitoring is not box-ticking, it is the intervention that lets you catch and reverse the process before it becomes irreversible cardiac disease.

20.2 The weight-gain league table: olanzapine and clozapine worst, aripiprazole/lurasidone/ziprasidone most weight-neutral

Not all antipsychotics carry equal metabolic risk, and the ranking is examinable. A classic meta-analysis of ten-week weight change at standard doses found mean gains of **4.45 kg** with clozapine, **4.15 kg** with olanzapine, **2.10 kg** with risperidone and **0.04 kg** with ziprasidone (Allison et al. 1999, in Tasman 2015). Over a year the hierarchy holds: aripiprazole and ziprasidone around 1 kg, amisulpride about 1.5 kg, quetiapine and risperidone 2 to 3 kg, and olanzapine more than 6 kg, with clozapine at least as bad as olanzapine (Newcomer & Haupt 2006, in Tasman 2015). Lurasidone, among the newer agents, causes the least weight gain (De Hert et al. 2012). The practical output is that where a patient is metabolically vulnerable you preferentially choose a **weight-neutral agent**: **aripiprazole, lurasidone or ziprasidone** are the most weight-neutral of the commonly used drugs, while **olanzapine and clozapine carry the highest risk** and demand the tightest monitoring.

ANTIPSYCHOTIC	RELATIVE METABOLIC / WEIGHT-GAIN RISK	QUANTIFIED SIGNAL (VERIFIED)
Clozapine	**Highest (worst)**	~4.45 kg at 10 weeks; at least as much long-term as olanzapine
Olanzapine	**Highest (worst)**	~4.15 kg at 10 weeks; >6 kg over 1 year
Quetiapine	Intermediate	~2 to 3 kg over 1 year (like risperidone)
Risperidone / paliperidone	Intermediate	~2.10 kg at 10 weeks; 2 to 3 kg over 1 year
Amisulpride	Lower-intermediate	~1.5 kg over 1 year
Aripiprazole	**Most weight-neutral**	~1 kg over 1 year; largely lipid/glucose neutral
Ziprasidone	**Most weight-neutral**	~0.04 kg at 10 weeks; ~1 kg over 1 year
Lurasidone	**Most weight-neutral**	Least weight gain among newer agents

Weight-gain hierarchy: clozapine and olanzapine are worst; aripiprazole, ziprasidone and lurasidone are the most weight-neutral. Figures from Allison et al. 1999 and Newcomer & Haupt 2006 (in Tasman 2015).

GOOD TO REMEMBER

- **Olanzapine:** second-generation (atypical) antipsychotic, D2/5HT2A antagonist with high H1 affinity; oral 5 to 20 mg/day (verify per patient); the one caveat to hold is that it is among the worst two agents for weight gain and metabolic syndrome, so it mandates the tightest metabolic monitoring. Indian brand: Oleanz.
- **Clozapine:** the only agent licensed for treatment-resistant schizophrenia (owned by the treatment-resistance topic); metabolically it is at least as bad as olanzapine for weight gain, dyslipidaemia and diabetes; the caveat is that its haematological monitoring never displaces metabolic monitoring, both run in parallel. Indian brand: Sizopin (or Lozapin).
- **Aripiprazole:** D2 partial agonist, second-generation; oral 10 to 30 mg/day (verify per patient); the point to hold is that it is one of the most weight-neutral agents and a reasonable metabolic-sparing switch target. Indian brand: Arip (or Arip MT).
- **Lurasidone / ziprasidone:** second-generation antipsychotics; both are among the most weight-neutral options; the caveat is that weight-neutrality does not exempt them from monitoring, because obesity prevalence in this population is high regardless of drug.

20.3 Defining the metabolic syndrome: the five components and their thresholds

The **metabolic syndrome** is a cluster diagnosis, not a single number, and you should be able to name its components. It is defined by central obesity plus a combination of the cardiometabolic abnormalities: raised **waist** circumference, raised fasting glucose, raised triglycerides, low HDL cholesterol and raised blood pressure. In the widely quoted NCEP ATP III framing, three or more of five criteria establish the syndrome, and the abdominal-obesity threshold is a **waist** circumference above **102 cm** (40 inches) in men or above **88 cm** (35 inches) in women (Newcomer 2007, in Tasman 2015). The parameters you actually measure to capture it are **waist** circumference, BMI, fasting glucose or **hba1c**, and lipids, with blood pressure completing the set.

Central obesity (waist)

Waist circumference >102 cm (men) or >88 cm (women); measured at the umbilicus (Stahl 2021, Tasman 2015).

BMI

Weight (kg) / height (m) squared; overweight 25 to 29.9, obese 30 or above (verified WHO cut-offs).

Dysglycaemia

Impaired fasting glucose (fasting plasma glucose 100 to 125 mg/dL) or diabetes (fasting plasma glucose 126 mg/dL or above); fasting glucose or hba1c both acceptable measures (Stahl 2021).

Dyslipidaemia

Raised triglycerides and/or low HDL cholesterol on a fasting lipid profile (Maudsley 2021).

Hypertension

Raised blood pressure (thresholds vary by criteria set; NICE and local hypertension guidance apply).

GOOD TO REMEMBER

- **Metabolic syndrome:** feature, a cluster of central obesity, dysglycaemia, dyslipidaemia and raised blood pressure (three or more of five criteria, NCEP ATP III); discriminator from simple weight gain, it is the constellation, not the number, and the waist threshold is >102 cm in men or >88 cm in women; first management step, lifestyle intervention plus consider switching to a weight-neutral agent and treat each risk factor medically.

20.4 The metabolic baseline: what to record before the first dose

Every schedule begins at the same non-negotiable point: a metabolic baseline taken before, or as soon as possible after, the first dose. Before starting an antipsychotic, record weight and BMI, waist circumference, pulse and blood pressure, a fasting blood glucose plus **hba1c**, and a fasting lipid profile, alongside a personal and family history of diabetes, obesity, dyslipidaemia, hypertension and cardiovascular disease (Maudsley 2021, Stahl 2021). Without this baseline you cannot later tell antipsychotic-induced change from pre-existing disease, and you cannot demonstrate that a rise happened on your watch. The baseline is the single most commonly omitted step in real practice and the easiest mark to lose.

TRAP **Starting an antipsychotic without a metabolic baseline.** No baseline means no way to attribute later weight, glucose or lipid change to the drug, and it is the classic omission the examiner is probing; take weight/BMI/waist, fasting glucose/HbA1c, lipids and blood pressure before the first dose.

20.5 The monitoring schedule: baseline, then early (6 and 12 weeks), then annually

The **metabolic monitoring** principle across guidelines is the same shape: **baseline, then early re-checks in the first weeks, then annually** once stable, with more frequent checks for the highest-risk drugs and patients. The verified NICE schedule, reproduced in the Maudsley, measures weight weekly for the first six weeks, then at twelve weeks, one year and annually; waist circumference annually; pulse and blood pressure at twelve weeks, one year and annually; and fasting blood glucose, **hba1c** and blood lipids at twelve weeks, one year and annually (Maudsley 2021). The Maudsley's own summary table places blood lipids and weight at baseline, then at three months, then yearly, and plasma glucose at baseline, at four to six months, then yearly, with clozapine and olanzapine re-checked three-monthly through the first year (Maudsley 2021). The ADA/APA-derived US schedule that Stahl uses is stated cell by cell: BMI monthly for three months then quarterly; blood pressure, fasting plasma glucose and fasting lipids within three months then annually, earlier and more often for those with diabetes or who gain more than five percent of initial weight (Stahl 2021). All three agree on the crunchy summary: baseline, an early check in the first six to twelve weeks, then at least annual review.

Baseline	6 wk	12 wk	Annually
WEIGHT/BMI/WAIST, FASTING GLUCOSE+HBA1C, LIPIDS, BP BEFORE DOSE	EARLY RE-CHECK (WEIGHT WEEKLY TO 6 WK, NICE)	GLUCOSE/HBA1C, LIPIDS, BP, WEIGHT (NICE)	FULL PANEL THEREAFTER ONCE STABLE

PARAMETER	BASELINE	EARLY (FIRST WEEKS)	12 WEEKS	1 YEAR / ANNUALLY
Weight / BMI	**Yes**	Weekly to 6 weeks (NICE); monthly x3 (ADA/APA)	Yes	Yes, then annually
Waist circumference	**Yes**	(with weight where possible)	–	Annually

PARAMETER	BASELINE	EARLY (FIRST WEEKS)	12 WEEKS	1 YEAR / ANNUALLY
Fasting glucose or HbA1c	**Yes**	Maudsley: at 4 to 6 months	Yes (NICE)	Yes, then annually
Fasting lipids	**Yes**	Maudsley: at 3 months	Yes (NICE)	Yes, then annually
Blood pressure	**Yes**	During titration	Yes (NICE)	Yes, then annually
Highest-risk drugs (clozapine, olanzapine)	Yes	More frequent	3-monthly through first year	Then yearly (Maudsley)

Verified monitoring schedule, harmonised from NICE (in Maudsley 2021), the Maudsley summary table, and the ADA/APA schedule in Stahl 2021. The convergent rule is baseline, early re-check at 6 to 12 weeks, then annual; clozapine and olanzapine monitored more frequently.

WORKED EXAMPLE

A 24-year-old man is to start olanzapine for a first episode. Before the first dose you record weight, BMI and waist, pulse and blood pressure, a fasting glucose with HbA1c and a fasting lipid panel, and note his family history of diabetes. Because olanzapine is a high-risk agent you check weight in the early weeks, review the full metabolic panel at twelve weeks, and, given his youth and the drug, keep glucose and lipids under closer-than-annual review through the first year. If he gains more than five percent of his baseline weight, you bring the next check forward rather than waiting for the annual review (Stahl 2021).

20.6 Management: prevent, intervene on lifestyle, add metformin, treat the risk factors

Management runs on four tiers, and the exam wants them in order. First, **prevention**: where the patient is metabolically vulnerable, choose a weight-neutral agent (aripiprazole, lurasidone or ziprasidone) rather than olanzapine or clozapine at the outset (Maudsley 2021). Second, **lifestyle intervention**: structured diet and exercise advice, plus counselling on smoking and alcohol, offered from the start and not only once weight has risen (Maudsley 2021, BAP/Cooper et al. 2016 in Shorter Oxford 2018). Third, **pharmacological**: adjunctive metformin is the best-evidenced drug intervention for antipsychotic-induced weight gain, with monitoring of renal function and B12 (Maudsley 2021); switching to a less obesogenic antipsychotic is the other lever, weighed against relapse risk. Fourth, **treat the established cardiometabolic risk factors**: manage diabetes, dyslipidaemia (statin where indicated) and hypertension according to standard medical guidelines, because reducing weight alone does not undo an established cardiovascular risk (Maudsley 2021). Where the patient is already on the worst-offending drug and cannot switch, all four tiers run together.

RULE **Metabolic monitoring is baseline, early (6 and 12 weeks), then annual, and olanzapine and clozapine carry the highest risk.** Prevent with a weight-neutral agent where you can, intervene on lifestyle from the start, add metformin for antipsychotic weight gain, and treat each cardiometabolic risk factor medically.

GOOD TO REMEMBER

- **Metformin (for antipsychotic weight gain):** what it is, a biguanide used off-label as the best-evidenced adjunct for antipsychotic-induced weight gain; the caveat to hold is that it requires monitoring of renal function and B12 (Maudsley 2021).
- **Antipsychotic-induced weight gain:** feature, progressive weight gain, often early and appetite-driven (H1/5HT2C mechanism); discriminator, dose- and drug-dependent, worst with clozapine and olanzapine; first management step, lifestyle intervention plus consider switching to a weight-neutral agent, and add metformin if weight gain persists.

INDIA

The Indian IPS schizophrenia guideline endorses routine baseline and follow-up metabolic monitoring, and in the Indian setting real-world monitoring rates are low (Poojari et al. 2020, cited in Maudsley 2021), so the baseline is the practical failure point to guard. The olanzapine long-acting injectable is marketed in India as Tolaz LA (Torrent), and carries the same metabolic monitoring obligation as oral olanzapine plus its own three-hour post-injection observation for post-injection delirium/sedation syndrome. Verify current thresholds against IPS and NICE at the point of care.

HOLD THIS

Take a metabolic baseline before the first dose, then re-check weight/glucose/lipids/BP early (by 6 to 12 weeks) and at least annually, monitor olanzapine and clozapine most closely, and manage with prevention, lifestyle, metformin and treatment of each risk factor.

21 · Hyperprolactinaemia, QTc prolongation and the cardiac effects

Why this matters. Two of the antipsychotic harms an examiner will always test are silent until they are looked for: the endocrine harm of raised prolactin and the cardiac harm of a lengthened QT interval. Both flow directly from the same D2 blockade that treats the psychosis, both are agent-specific so the answer is largely a matter of knowing which drug does what, and both are managed by the same governing move, switch to a safer agent or add a sparing one. Hyperprolactinaemia (hyperprolactinemia) is common, under-reported and does long-term damage to bone; QTc (qtc) prolongation is rarer but lethal, because it is the road to torsades de pointes and sudden death (Maudsley 2021, Kaplan & Sadock 2024).

This topic teaches the endocrine and cardiac adverse effects only. The receptor pharmacology and the tuberoinfundibular dopamine pathway are not re-derived here (they are owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes); the illness itself is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes. Here we apply the pharmacology at the bedside: recognise the effect, name the offending agent, and act.

21.1 Hyperprolactinaemia: the mechanism

Dopamine tonically inhibits prolactin (prolactin) release from the anterior pituitary lactotrophs, acting through D2 receptors in the tuberoinfundibular pathway. An antipsychotic that blocks those D2 receptors removes the brake, and prolactin rises (Maudsley 2021, Stahl 2021). The

elevation is roughly dose-related, and for most agents the D2 occupancy that raises prolactin sits very close to the occupancy needed for antipsychotic efficacy, which is why hyperprolactinaemia is so common. A drug that spares prolactin does so either because it is a partial agonist at D2 (aripiprazole, which behaves as a dopamine agonist at the pituitary and can actually lower prolactin) or because it occupies pituitary D2 receptors only loosely and transiently (quetiapine, clozapine). The pituitary sits outside the blood-brain barrier, so drugs that are actively pumped out of the brain but not the pituitary (amisulpride, and to a large degree paliperidone and risperidone) raise prolactin disproportionately (Maudsley 2021).

RULE **A raised prolactin is a tuberoinfundibular D2 effect.** Confirm it is drug-related, then switch to a prolactin-sparing agent or add aripiprazole; treat the symptoms and the long-term bone risk, not the number alone.

21.2 Which agents raise prolactin, and which spare it

The single highest-yield fact is the agent grouping. The worst offenders are risperidone and its active metabolite paliperidone, amisulpride, sulpiride, and the high-potency first-generation antipsychotics (haloperidol, the phenothiazines); risperidone and amisulpride can raise prolactin more than the typicals do (Maudsley 2021, Leucht 2013). The prolactin-sparing agents are aripiprazole (and the other partial agonists brexpiprazole, cariprazine), quetiapine and clozapine, which raise prolactin only rarely; olanzapine and ziprasidone are intermediate, giving a modest dose-related rise. This ordering is worth memorising verbatim because it drives every switch decision.

PROLACTIN EFFECT	AGENTS	NOTE
Marked rise (worst)	Risperidone, paliperidone, amisulpride, sulpiride; high-potency typicals (haloperidol, phenothiazines)	Risperidone and amisulpride can exceed the typicals
Modest, dose-related rise	Olanzapine, ziprasidone	Intermediate liability
Sparing (little or no rise)	Aripiprazole, brexpiprazole, cariprazine, quetiapine, clozapine	Aripiprazole can lower prolactin (partial D2 agonist)

Antipsychotic effect on prolactin: the switch target is always a drug from the sparing row (Maudsley 2021).

GOOD TO REMEMBER

- **Risperidone / paliperidone:** second-generation D2/5HT2A antagonists (risperidone as Sizodon; paliperidone as Paliris); the leading cause of antipsychotic hyperprolactinaemia among the atypicals, so ask about galactorrhoea and menstrual change at every review.
- **Amisulpride:** substituted benzamide, selective D2/D3 antagonist (marketed as Amazeo), oral dose about **400 to 800 mg/day** for positive symptoms; a potent prolactin-raiser because it acts preferentially on pituitary D2 outside the blood-brain barrier, and adjunctive aripiprazole may not fully normalise amisulpride-induced hyperprolactinaemia.
- **Aripiprazole:** D2 partial agonist (marketed as Arip / Arip MT); prolactin-sparing and the first-choice add-on to correct raised prolactin, adjunct dose **5 mg/day**; the one caveat is akathisia.
- **Quetiapine:** loosely-binding D2/5HT2A antagonist (marketed as Qutipin); prolactin-sparing, a sound switch target when raised prolactin is the problem; hold the caveat of sedation and postural drop rather than prolactin.

21.3 The clinical consequences of raised prolactin

Hyperprolactinaemia is often superficially asymptomatic, the patient does not spontaneously complain, which is exactly why it is missed (Maudsley 2021). When symptomatic, persistent elevation suppresses the hypothalamic-pituitary-gonadal axis and produces galactorrhoea, menstrual disturbance and amenorrhoea in women, sexual dysfunction (loss of libido, arousal and orgasmic difficulty) in both sexes, breast growth and, occasionally, gynaecomastia in men. The consequence that matters most in the long term is a fall in bone mineral density from chronic hypogonadism, which raises fracture risk, and there is a debated small increase in breast-cancer risk (Maudsley 2021, De Hert 2016). Because prolactin also rises with stress, pregnancy, lactation, seizures, renal impairment and, importantly, a prolactinoma, the sample should be taken early in the morning with venepuncture stress minimised, and a very high level must be worked up rather than assumed drug-related.

Galactorrhoea

Inappropriate milk secretion from HPG-axis suppression; volunteered rarely, so ask.

Amenorrhoea / oligomenorrhoea

Menstrual disturbance from hypogonadism; a red flag for symptomatic hyperprolactinaemia.

Sexual dysfunction

Reduced libido, arousal and orgasm; multifactorial but prolactin is one driver.

Bone-density loss

The key long-term harm; chronic hypogonadism lowers bone mineral density and raises fracture risk.

21.4 Interpreting the prolactin level and managing it

Measure plasma prolactin at baseline in all patients, and again if hyperprolactinaemia is suspected or a prolactin-elevating agent is being used. On the Maudsley interpretation, a normal prolactin is about **0 to 25 ng/ml** in women and **0 to 20 ng/ml** in men; a level of **25 to 118 ng/ml** is elevated; and a highly elevated level of **over 118 ng/ml** (over 2500 mIU/L) should prompt referral to rule out a prolactinoma (Maudsley 2021). Treatment is driven by symptoms and long-term risk, not by the number in isolation. If treatment is needed, the first choice is to switch to an agent with a lower prolactin liability, accepting that any switch risks destabilising the

illness; where a switch is inappropriate or fails, add adjunctive aripiprazole **5 mg/day**, which lowers prolactin dose-dependently. Where aripiprazole cannot be used, verified second-line options are vitamin B6 (pyridoxine) **600 mg/day** and, less preferably, a dopamine agonist such as cabergoline or bromocriptine (each carrying a theoretical risk of worsening psychosis). Address the bone risk directly: weight-bearing exercise, smoking cessation, and adequate calcium and vitamin D (Maudsley 2021).

0 to 25 ng/ml	25 to 118 ng/ml	>118 ng/ml	5 mg/day
NORMAL PROLACTIN, WOMEN	ELEVATED	HIGHLY ELEVATED: RULE OUT PROLACTINOMA	ADJUNCTIVE ARIPIPRAZOLE

GOOD TO REMEMBER

- **Hyperprolactinaemia:** feature, galactorrhoea, amenorrhoea, sexual dysfunction and long-term bone-density loss, often asymptomatic; discriminator, on a marked prolactin-raiser (risperidone, paliperidone, amisulpride, high-potency typical) with a raised morning level, once stress, pregnancy and a prolactinoma (level over 118 ng/ml) are excluded; first management step, switch to a prolactin-sparing agent, or add aripiprazole 5 to 10 mg/day, and manage the bone risk.

21.5 QTc prolongation: the mechanism and the agents

Many antipsychotics block the cardiac potassium channel IKr (the hERG channel), which slows ventricular repolarisation and produces QT prolongation on the ECG (Maudsley 2021, Kaplan & Sadock 2024). Because the raw QT shortens as heart rate rises, it is corrected for rate and reported as the QTc. The danger of a long QTc is torsades de pointes (torsades), a polymorphic ventricular tachycardia that can degenerate into ventricular fibrillation and sudden cardiac death. The risk is agent-specific. The highest-effect antipsychotics are pimozide and sertindole; thioridazine is the classic and most notorious offender, withdrawn from routine use precisely because it caused substantial QTc prolongation, torsades and sudden death (Kaplan & Sadock 2024). Also carrying meaningful, moderate effect are ziprasidone, high-dose haloperidol (especially given intravenously), chlorpromazine, amisulpride and quetiapine. The low-effect or no-effect agents include aripiprazole, brexpiprazole, cariprazine, lurasidone and olanzapine (Maudsley 2021).

QT EFFECT	ANTIPSYCHOTICS	EXAM HANDLE
High effect	Pimozide, sertindole; thioridazine (classic offender, restricted)	ECG mandatory; thioridazine and pimozide are the named "avoid / monitor" drugs
Moderate effect	Ziprasidone, haloperidol (worst high-dose and IV), chlorpromazine, amisulpride, quetiapine	Haloperidol IV or high-dose carries an explicit sudden-death warning
Low / no effect	Aripiprazole (~8 ms), brexpiprazole, cariprazine, lurasidone, olanzapine	The switch targets when QTc is the problem

Antipsychotic effect on QTc: pimozide and sertindole highest, thioridazine the classic offender; move toward the low/no-effect row (Maudsley 2021).

GOOD TO REMEMBER

- **Thioridazine:** low-potency phenothiazine; the classic high-QTc offender associated with substantial QTc prolongation, torsades and sudden death, now reserved for refractory cases with an ECG before and during treatment.
- **Pimozide:** high-potency diphenylbutylpiperidine; high QTc effect (and seizures) at higher doses, so an ECG is mandatory and dose is kept low.
- **Ziprasidone:** second-generation D2/5HT2A antagonist; a moderate, dose-related QTc effect, so it is avoided in cardiac risk and co-prescription with other QT-prolonging drugs.
- **Haloperidol:** high-potency butyrophenone (marketed as Serenace); QTc, torsades and sudden-death risk is greatest with intravenous use and at doses higher than recommended, so keep IV use monitored and dose modest.

21.6 The QTc thresholds and monitoring with an ECG

Learn the numbers exactly. The upper limit of normal QTc is **440 ms** in men and **470 ms** in women; a QTc **over 500 ms** is clearly associated with an increased risk of arrhythmia and is the threshold that mandates action; a QTc **over 650 ms** may be more likely than not to induce torsades (Maudsley 2021). The management ladder follows those bands. Below 440 ms (men) or 470 ms (women), no action is needed unless the T-wave morphology is abnormal. Between the normal limit and 500 ms, consider reducing the dose or switching to a lower-effect agent and repeat the ECG. Above 500 ms, repeat the ECG, stop the suspected causative drug, switch to a lower-effect agent, and refer to a cardiologist immediately; abnormal T-wave morphology at any QTc also prompts urgent review. Measure the QTc with an ECG in all patients on admission (before or at the start of treatment), and at the annual physical health check if there is a previous abnormality or a known additional risk factor (Maudsley 2021, APA 2021).

440 ms	470 ms	>500 ms	>650 ms
UPPER NORMAL QTC, MEN	UPPER NORMAL QTC, WOMEN	ACT: STOP / SWITCH, REFER	MAY INDUCE TORSADES

21.7 Additive risk: other QT drugs and electrolytes

QTc risk is additive, and this is where residents come unstuck. Stacking a QT-prolonging antipsychotic on top of another QT-prolonging drug multiplies the danger: the common culprits are macrolide and quinolone antibiotics (erythromycin, clarithromycin), antimalarials (chloroquine, quinine), class Ia and III antiarrhythmics (quinidine, sotalol, amiodarone), methadone, and other psychotropics (Maudsley 2021). Electrolyte disturbance is the other multiplier: hypokalaemia, hypomagnesaemia and hypocalcaemia all prolong QTc, and hypokalaemia is especially common in acute psychotic admissions (poor intake, vomiting, refeeding). Bradycardia, congenital long-QT syndrome, ischaemic heart disease, myocardial infarction, female sex and extremes of age add further risk. The practical rule before adding any drug to an antipsychotic is to ask whether it prolongs QT and to check potassium and magnesium first.

TRAP **Stacking two QT-prolonging drugs without checking the QTc and electrolytes.** Adding a macrolide, an antiarrhythmic or a second QT-prolonging antipsychotic to an existing one, in a patient who may be hypokalaemic, is how a preventable torsades happens; check the ECG and potassium/magnesium first.

21.8 The other cardiac effect concerns

Beyond the QT interval, two further cardiac effect concerns are examined. The first is clozapine-associated myocarditis (and cardiomyopathy), an inflammatory injury of the heart muscle that typically presents in the first weeks of clozapine treatment with tachycardia, fever, chest pain, dyspnoea, a rising troponin and CRP, and ECG or echocardiographic change; it is a reason to stop clozapine and is developed in full in the clozapine topic, so it is cross-referenced here rather than re-taught. The second is postural (orthostatic) hypotension from alpha-1 adrenergic blockade, prominent with low-potency phenothiazines (chlorpromazine), clozapine and quetiapine, and worst on initiation and dose titration; it causes dizziness and falls, particularly in the elderly, and is managed by slow titration, splitting or lowering the dose, and advising the patient to stand up slowly (Maudsley 2021, Kaplan & Sadock 2024).

GOOD TO REMEMBER

- **QTc prolongation / torsades:** feature, a lengthened QTc on the ECG risking torsades de pointes and sudden death; discriminator, worst with pimozide, sertindole, thioridazine, ziprasidone and high-dose or IV haloperidol, and amplified by other QT drugs and by low potassium or magnesium; first management step, if QTc over 500 ms stop the causative drug, switch to a lower-effect agent, correct electrolytes and refer to cardiology.
- **Clozapine myocarditis:** feature, early inflammatory cardiac injury (tachycardia, fever, chest pain, dyspnoea, raised troponin/CRP); discriminator, onset in the first weeks of clozapine; first management step, stop clozapine and refer, see the clozapine topic.
- **Postural hypotension:** feature, a drop in standing blood pressure with dizziness and fall risk from alpha-1 blockade; discriminator, worst on initiation and titration with chlorpromazine, clozapine and quetiapine; first management step, titrate slowly, lower or split the dose, advise standing up slowly.

INDIA

Verified Indian brands keep the endocrine-and-cardiac decisions concrete at the bedside: risperidone (Sizodon) and paliperidone (Paliris) are the common prolactin-raisers to switch away from, aripiprazole (Arip) and quetiapine (Qutipin) the sparing targets, and haloperidol (Serenace) the high-potency typical whose intravenous and high-dose QTc risk applies in the emergency room. Baseline ECG before starting a moderate or high QT-effect agent, and a serum potassium and magnesium before adding any second QT-prolonging drug, are low-cost, high-value habits in Indian practice.

PEARL

Both harms in this topic are "silent-until-sought and agent-specific". The endocrine harm is found by asking about galactorrhoea, periods and libido and checking a morning prolactin; the cardiac harm is found by an ECG and a potassium. In both, the fix is the same shape: switch to a safer agent, or in the case of prolactin, add aripiprazole.

HOLD THIS

Raised prolactin means a tuberoinfundibular D2 effect (worst with risperidone, paliperidone, amisulpride), so switch to a sparing agent or add aripiprazole 5 to 10 mg/day; a QTc over 500 ms (normal 440 ms men, 470 ms women) means stop the drug, correct potassium and magnesium, and refer, and never stack two QT-prolonging drugs without checking the ECG and electrolytes first.

22 · Discriminate: the adverse-effect and emergency differential

Why this matters. A hyperthermic, rigid or agitated patient on psychotropics is a differential, not a diagnosis, and the examiner rewards the trainee who separates the look-alikes on the correct single discriminator rather than reaching for a reflex label. The raw entity of neuroleptic malignant syndrome is developed alongside; here the payoff is the interleaved **differential** that tells it apart from the three syndromes it is most often confused with, each of which is fatal if managed as the wrong one (Kaplan & Sadock 2024). Kaplan & Sadock name the exact company nms keeps: "conditions with clinical similarity to NMS include serotonin syndrome, malignant hyperthermia, drug toxicity, heat stroke, and malignant catatonia" (Kaplan & Sadock 2024).

The discipline is to run one axis at a time across all four entities: the **trigger drug**, the quality of the motor sign, the reflexes, the pupils, the bowel sounds, and the tempo. Read that way, four syndromes that share fever and altered mental state pull cleanly apart. The receptor and pathway mechanics of dopamine blockade and serotonergic and muscarinic excess are not re-derived here (they are owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes); this topic applies them at the bedside as discriminators. The disorder that the patient carries underneath, its phenomenology and course, belongs to the Schizophrenia: aetiology, phenomenology, classification and course notes.

	NMS	Serotonin syndrome	Malignant catatonia	Anticholinergic toxicity
Trigger	antipsychotic	serotonergic drug	psychiatric illness	anticholinergic load
Onset	1 to 3 days	hours	days	hours
Muscle tone	lead-pipe rigidity	rigidity, tremor	waxy or rigid	normal
Reflexes	hyporeflexia	clonus, hyperreflexia	variable	normal
Pupils, skin	normal, sweating	dilated, sweating	sweating	dilated, dry, flushed
The one discriminator	rigidity, very high CK	clonus, hyperreflexia	catatonic signs first	dry skin, no bowel sounds

Malignant catatonia as an entity is developed in the Other psychotic disorders, delusional syndromes and catatonia notes.

Fig 9.9 The hyperthermic-rigid emergency differential. Rigidity with hyporeflexia and a very high creatine kinase is neuroleptic malignant syndrome; clonus and hyperreflexia after a serotonergic drug is serotonin syndrome; catatonic signs that precede the picture point to malignant catatonia; and hot, dry, flushed skin with absent bowel sounds is anticholinergic toxicity. The discriminator, not the fever they share, makes the diagnosis.

22.1 Neuroleptic malignant syndrome: rigidity with hyporeflexia, over days

Trigger and signature. Neuroleptic malignant syndrome follows antipsychotic exposure (dopamine D2 blockade, or abrupt withdrawal of a dopamine agonist), and its motor signature is lead-pipe rigidity: a uniform, generalised increase in tone with hyporeflexia or normal reflexes, never the brisk hyperreflexia of serotonergic excess (Kaplan & Sadock 2024). The tempo is slow: it evolves over **1 to 3 days** (about 24 to 72 hours), and the muscle breakdown drives a very high creatine kinase, often above **1000 units/L** and sometimes into the tens of thousands. The single discriminator to hold is rigidity with hyporeflexia and a days-long onset in an antipsychotic-treated patient with a very high creatine kinase. Pupils are typically normal and bowel sounds are unremarkable. The raw entity, its investigations and its full management are developed alongside.

22.2 Serotonin syndrome: clonus with hyperreflexia, over hours

Trigger and signature. Serotonin syndrome follows a serotonergic drug, usually the initiation or dose increase of a serotonergic agent, or the combination of two (an SSRI with an MAOI, tramadol, linezolid, or a triptan); the raw entity is developed in the mood-disorders pharmacology notes, and here it is the key nms mimic. Its motor signature is neuromuscular **hyperactivity** of a wholly different quality: clonus (spontaneous, inducible, or ocular), hyperreflexia, myoclonus and tremor, greater in the lower limbs (Kaplan & Sadock 2024). It adds dilated pupils (mydriasis), hyperactive bowel sounds with diarrhoea, and a rapid onset, over **hours** rather than days. The single discriminator is clonus with hyperreflexia coming on within hours of a serotonergic drug. Diagnosis rests on the Hunter Serotonin Toxicity Criteria (clonus being the pivotal sign) or the older Sternbach criteria, and the specific antidote is the serotonin antagonist cyproheptadine (Kaplan & Sadock 2024).

RULE **Rigidity with hyporeflexia is neuroleptic malignant syndrome; clonus with hyperreflexia is serotonin syndrome.** The reflexes and the quality of the motor sign, read together with the tempo (days versus hours), separate the two before any blood result returns.

22.3 Malignant catatonia: the mimic that can be indistinguishable

Trigger and signature. Malignant catatonia is the most treacherous look-alike, because it can be clinically indistinguishable from neuroleptic malignant syndrome and can precede it; indeed nms is regarded by some as a drug-induced form of malignant catatonia (Kaplan & Sadock 2024). It carries the same hyperthermia, rigidity and autonomic storm, but is distinguished by antecedent and accompanying **catatonic signs**, that is, a preceding phase of excitement, stupor, mutism, negativism, posturing or waxy flexibility, often before any antipsychotic was given. As an entity it is owned by the Other psychotic disorders, delusional syndromes and catatonia notes; it appears here only as the mimic to name in the differential. The practical consequence is decisive: a benzodiazepine (lorazepam) challenge and electroconvulsive therapy treat malignant catatonia, whereas a dopamine antagonist can worsen it, which is why the catatonic history must be sought before an antipsychotic is given to a rigid, febrile patient. The technique of electroconvulsive therapy is not taught here and is owned by the ECT and neurostimulation notes.

22.4 Anticholinergic toxicity: hot and DRY, "mad as a hatter"

Trigger and signature. Anticholinergic toxicity follows an anticholinergic load, from antimuscarinic antiparkinsonian agents (trihexyphenidyl, benztropine), low-potency antipsychotics, tricyclics, antihistamines and their combinations, and it is the great pretender because it also produces hyperthermia and delirium (APA 2021, Kaplan & Sadock 2024). The discriminator is the skin and the secretions: the patient is **hot but DRY**, with flushing, dilated pupils, urinary retention, **absent bowel sounds** and a florid delirium with visual hallucinations, and the creatine kinase is normal to only mildly raised, because there is no lead-pipe rigidity to break the muscle down. The classic teaching phrase is "hot, dry, red, mad" (hot as a hare, dry as a bone, red as a beet, mad as a hatter, blind as a bat). Muscle tone is not rigid, which alone separates it from neuroleptic malignant syndrome; the dry skin separates it from the drenching diaphoresis of both nms and serotonin syndrome. Kaplan & Sadock warn that "in some cases, anticholinergic toxicity may be mistaken for an exacerbation of psychosis, and the antipsychotic dose may be increased inappropriately" (Kaplan & Sadock 2024).

MNEMONIC

HOT, DRY, RED, MAD

The anticholinergic toxidrome: hot (hyperthermia), dry (dry skin and mucosae, the pivotal discriminator against the sweaty nms and serotonin syndrome), red (flushing), and mad (delirium), rounded out by dilated pupils, urinary retention and absent bowel sounds. If the febrile patient is sweating, it is not anticholinergic toxicity.

22.5 The one discriminator per entity

Stripping each syndrome to its single most decisive sign is what makes the differential usable under pressure. For each, one axis carries the diagnosis: the reflexes for the two neuromuscular emergencies, the catatonic history for the third, and the dry skin for the fourth. Everything else is corroboration.

PEARL

Bowel sounds triage the febrile, altered patient faster than any blood test: hyperactive points to serotonin syndrome, absent points to anticholinergic toxicity, and unremarkable with lead-pipe rigidity points to neuroleptic malignant syndrome. Pair that with the reflexes (brisk with clonus versus depressed) and the tempo (hours versus days) and the four-way differential resolves at the bedside.

22.6 The emergency differential grid

The table runs the six axes across all four entities, with the single discriminator for each highlighted in the final column. Read it column by column when a hyperthermic, rigid or agitated patient arrives: the trigger drug narrows the field, the motor sign and the reflexes separate nms from serotonin syndrome, the catatonic history flags malignant catatonia, and the dry skin with absent bowel sounds flags anticholinergic toxicity.

ENTITY	TRIGGER	RIGIDITY VS CLONUS	REFLEXES	PUPILS	BOWEL SOUNDS	THE ONE DISCRIMINATOR
Neuroleptic malignant syndrome	Antipsychotic (D2 block) or dopamine-agonist withdrawal	Lead-pipe rigidity	Hyporeflexia / normal	Normal	Normal	**Rigidity with hyporeflexia, days-long onset, very high creatine kinase (>1000 units/L)**
Serotonin syndrome	Serotonergic drug (start, increase, or combination)	Clonus, myoclonus (no lead-pipe rigidity)	Hyperreflexia	Dilated	Hyperactive (diarrhoea)	**Clonus with hyperreflexia, rapid (hours) onset**
Malignant catatonia	Often none (may precede any antipsychotic)	Rigidity, can be indistinguishable from nms	Variable	Variable	Variable	**Antecedent catatonic signs (stupor, mutism, posturing, negativism); responds to lorazepam / ECT**

ENTITY	TRIGGER	RIGIDITY VS CLONUS	REFLEXES	PUPILS	BOWEL SOUNDS	THE ONE DISCRIMINATOR
Anticholinergic toxicity	Anticholinergic load (antimuscarinics, TCAs, antihistamines)	Not rigid	Normal	Dilated	Absent	**Hyperthermia with DRY skin, flushing, urinary retention, delirium; creatine kinase normal to mild**

The four hyperthermic or rigid or agitated look-alikes across six axes, each keyed on its single discriminator; skin (dry versus sweaty), reflexes and bowel sounds carry the most diagnostic weight (Kaplan & Sadock 2024, APA 2021).

TRAP **Giving an anticholinergic to a hyperthermic, rigid patient before separating nms from anticholinergic toxicity.** Reaching for benztropine or promethazine "for the rigidity" in a patient who is actually in anticholinergic delirium pours petrol on the fire, and a warm sweaty nms patient does not benefit from an antimuscarinic either; separate the two on the dry-skin discriminator first.

Hours
SEROTONIN SYNDROME ONSET

1 to 3 days
NEUROLEPTIC MALIGNANT SYNDROME ONSET

>1000 units/L
CREATINE KINASE IN NMS (OFTEN); NORMAL-TO-MILD IN ANTICHOLINERGIC

INDIA

The everyday Indian anticholinergic load is trihexyphenidyl (benzhexol), routinely co-prescribed with high-potency first-generation agents such as haloperidol (marketed as Serenace), plus parenteral promethazine used for acute dystonia; stacking these on a low-potency antipsychotic is how a resident meets anticholinergic delirium on the ward. The reflex to add "one more anticholinergic for the stiffness" is exactly the trap, so the dry-skin discriminator must be checked before any antimuscarinic is given to a hot, rigid patient.

GOOD TO REMEMBER

- **Neuroleptic malignant syndrome:** feature, lead-pipe rigidity with hyperthermia and autonomic instability over 1 to 3 days; discriminator, rigidity with hyporeflexia and a very high creatine kinase; first step, stop the antipsychotic and support (cooling, IV fluids, high-dependency monitoring).
- **Serotonin syndrome:** feature, neuromuscular hyperactivity with hyperthermia over hours; discriminator, clonus with hyperreflexia, dilated pupils and hyperactive bowel sounds after a serotonergic drug; first step, stop the serotonergic agent, support, and give cyproheptadine.
- **Malignant catatonia:** feature, hyperthermia and rigidity that can be indistinguishable from nms; discriminator, antecedent catatonic signs (stupor, mutism, posturing); first step, a lorazepam challenge and consideration of ECT, and avoid a dopamine antagonist.
- **Anticholinergic toxicity:** feature, hyperthermia with delirium; discriminator, DRY skin, flushing, dilated pupils, urinary retention, absent bowel sounds ("hot, dry, red, mad") with a normal-to-mild creatine kinase; first step, stop the anticholinergic agents and give supportive care (physostigmine only in specialist hands).

HOLD THIS

Four hyperthermic look-alikes, four discriminators: rigidity with hyporeflexia over days is neuroleptic malignant syndrome, clonus with hyperreflexia over hours is serotonin syndrome, antecedent catatonic signs is malignant catatonia, and hot-but-DRY with absent bowel sounds and delirium is anticholinergic toxicity; never give an anticholinergic to a rigid febrile patient until you have separated nms from anticholinergic toxicity on the dry-skin sign.

Apply and consolidate

23 · Apply: four worked management vignettes

Everything in the preceding topics converges here into four short clinical decisions, each a **vignette** written as scenario, then reasoning, then plan. This is the format the examiner actually rewards: not a recital of doses but a defended choice, where the drug or the emergency step falls out of a weighing of efficacy against harm and a named discriminator. Nothing new is taught; the four moves are the four commonest management questions in the paper, worked to their answer.

How to use this page. Each of the four sub-topics is one worked example: a **first-episode** drug choice, a **treatment-resistant** case moving to clozapine, an acute **rigidity-and-fever** differential, and a maintenance **monitoring** case. The illness itself, its criteria and course, is not re-taught: it is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes. The receptor pharmacology, dopamine pathways and CYP metabolism behind the drugs belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; here the pharmacology is applied, not derived. Every dose, range and threshold below is verified against the cited source; anything not confirmable is flagged, not guessed.

23.1 Vignette 1: first-episode drug choice, weighing the adverse-effect profile

The decision. The first prescribing decision in a drug-naive young patient is not "which drug is strongest" but "which adverse-effect profile can this particular person live with", because among

the non-clozapine antipsychotics there is no clear efficacy winner, only minor individual advantages, so the choice is driven almost entirely by tolerability and by the **metabolic** versus extrapyramidal versus hyperprolactinaemia trade-off (Maudsley 2021, Leucht 2013). The reasoning below is the worked example the examiner wants.

WORKED EXAMPLE

Case: a 21-year-old man, antipsychotic-naive, first episode of a schizophrenia-spectrum psychosis, physically well, normal weight, keen to return to college, no cardiac history. **Reasoning.** He is drug-naive and therefore dose-sensitive, so whatever is chosen starts low and titrates slowly against response and tolerability. Efficacy will not separate the reasonable options, so the choice turns on the harm he can least afford. A young man who wants to study and stay engaged will be lost by heavy sedation and by weight gain, so a markedly metabolic agent (olanzapine) is a poor first choice despite good efficacy; a strongly prolactin-raising or EPS-prone agent risks sexual dysfunction and motor side effects that also drive covert non-adherence. **Plan.** Take a full baseline first (weight, height and BMI, fasting glucose and lipids, blood pressure, ECG where indicated), then start a single antipsychotic at the lowest effective dose: a reasonable, defensible first choice is aripiprazole, weight-neutral and prolactin-sparing, at **10 mg/day** (a valid first-episode starting dose), or risperidone **2 mg/day** if a more sedating, more familiar agent is wanted, accepting its dose-related prolactin rise. Titrate slowly, run an adequate trial before judging response, and decide the drug with the patient. This is shared decision-making, not a default.

RULE **First episode: choose on adverse effects, start low.** Efficacy does not separate the non-clozapine agents, so pick the one whose harm profile the patient can live with, take the baseline, then start at the lowest effective dose in a dose-sensitive drug-naive brain.

TRAP **Reaching for the strongest drug or the loading dose.** Starting a metabolically heavy agent, or front-loading a high dose in a drug-naive patient, buys adverse effects and non-adherence for no efficacy gain; "lowest effective" is not homeopathic, but the first episode is where over-dosing loses the alliance.

23.2 Vignette 2: treatment resistance, confirming it and moving to clozapine

The decision. The move to clozapine is earned, not assumed: it is triggered the moment true **treatment resistance** is confirmed, and the classic error is a third same-class switch instead. The definition is failure of two adequate antipsychotic trials, each at an adequate dose (about 600 mg chlorpromazine-equivalent) for an adequate duration (at least 6 weeks), with adherence confirmed and misdiagnosis and pseudo-resistance excluded (Maudsley 2021, APA 2020, Kane 1988). This worked example walks the confirmation, then sets up the monitoring.

WORKED EXAMPLE

Case: a 29-year-old woman with persistent positive symptoms of at least moderate severity despite two antipsychotics. **Reasoning: confirm resistance first.** Were both trials genuinely adequate: an adequate dose (about **600 mg/day** chlorpromazine-equivalent) for an adequate duration (at least **6 weeks** at optimum dose, which is the TRRIP resistance minimum, not the looser 4-to-6-week general switching rule)? Was adherence real (target 80% or more, checked, not assumed, since covert non-adherence is the commonest fake resistance)? Is the diagnosis right, and are substance use, an untreated depression and inadequate psychosocial support excluded? Only when all of that is cleared is this true resistance, not pseudo-resistance. **Plan.** Move to clozapine, not a third me-too antipsychotic. Response is usually seen across **150 to 900 mg/day** (UK average around 450 mg/day; maximum 900 mg/day), titrated slowly against tolerability and plasma level (Maudsley 2021). Set up the mandatory haematological monitoring before the first dose: baseline full blood count, then FBC **weekly for 18 weeks**, then two-weekly to one year, then monthly. Hold the two neutrophil cut-offs as the safety spine: stop clozapine if the neutrophil count falls below **1.5 x10^9/L**, and refer to specialist medical care if it falls below **0.5 x10^9/L** (Maudsley 2021). Baseline an ECG (myocarditis and QT risk), give a gastrointestinal history for the hypomotility risk, and warn of the transient benign fever of early titration.

RULE **Two adequate failed trials means clozapine.** Confirm adequacy of dose, duration and adherence and exclude pseudo-resistance, then move to clozapine, never to a third antipsychotic of the same broad class.

TRAP **Stopping clozapine for a benign transient neutropenia.** The action threshold is a neutrophil count below 1.5 x10^9/L; a mild dip that stays above it, or benign ethnic neutropenia, is not an automatic stop, and pulling the one drug that works on a misread count harms the patient.

23.3 Vignette 3: acute rigidity and fever, the NMS differential

The decision. A patient on an antipsychotic who becomes rigid and febrile is neuroleptic malignant syndrome until proven otherwise, and the whole of management is: recognise it, stop the drug, support the patient. The reasoning is a three-way differential against serotonin syndrome and malignant catatonia, each separated by a named discriminator (Maudsley 2021, Kaplan & Sadock 2024). Malignant catatonia as an entity is owned by the Other psychotic disorders, delusional syndromes and catatonia notes; it appears here only inside this differential.

ENTITY	KEY FEATURE	DISCRIMINATOR	FIRST STEP
NMS	Lead-pipe rigidity, hyperthermia, autonomic instability, altered consciousness; CK often >1000 units/L	**Uniform lead-pipe rigidity + a dopamine-blocker trigger, evolving over 1 to 3 days**	Stop the antipsychotic, supportive care
Serotonin syndrome	Hyperthermia, autonomic instability, altered mental state, neuromuscular hyperactivity	**Clonus and hyperreflexia (not lead-pipe rigidity) + a serotonergic drug, faster onset (hours)**	Stop the serotonergic agent, supportive care
Malignant catatonia	Rigidity, hyperthermia, autonomic storm, may be clinically indistinguishable from NMS	**Often a preceding psychiatric excitement/catatonic phase; may occur without a dopamine-blocker trigger; responds to ECT**	Supportive care; benzodiazepines/ECT (owned by the ECT notes)

The rigidity-and-fever differential: the discriminator column carries the exam answer, and the first step for NMS is always to stop the drug and support (Maudsley 2021, Kaplan & Sadock 2024).

WORKED EXAMPLE

Case: a 34-year-old man, five days into an escalated dose of a high-potency antipsychotic, brought in confused, with a temperature of 39.5 degrees, generalised stiffness and labile blood pressure. **Reasoning.** The rigidity is uniform and lead-pipe, not the clonus-and-hyperreflexia of serotonin syndrome, and there is a clear dopamine-blocker trigger with the characteristic 1-to-3-day evolution, so this is NMS, not serotonin syndrome; there is no preceding catatonic excitement and no serotonergic drug. A creatine kinase, which is often above **1000 units/L** in NMS, supports the picture but does not by itself make the diagnosis (asymptomatic rises are common). **Plan.** The first step is not a drug: **stop the antipsychotic immediately** and start supportive care (cooling, fluids and rehydration, correction of electrolytes, and monitoring for renal failure from rhabdomyolysis). Only then consider specific pharmacology (dantrolene, bromocriptine, benzodiazepines) for severe or refractory cases. When restarting later, wait a minimum of **5 days** off the drug and preferably longer, then rechallenge with a lower-potency or second-generation agent (Maudsley 2021).

TRAP **Missing NMS behind "just rigid from the antipsychotic".** Fever plus a raised creatine kinase plus autonomic instability is not ordinary parkinsonism; a stiff, febrile patient on a dopamine blocker is NMS until proven otherwise, and the cost of the miss is death.

23.4 Vignette 4: adverse-effect monitoring on maintenance, and what to change

The decision. A stable patient on a maintenance antipsychotic is not "done": the silent harms (metabolic, prolactin, cardiac) are what shorten this population's life, so the maintenance job is to run the **monitoring schedule**, read it, and change the drug when a threshold is crossed (Maudsley 2021, APA 2020). This worked example runs the three tracks and lands the switch decision.

1.5 to 0.5	3 mo then yearly	440 / 470 ms	>500 ms
CLOZAPINE NEUTROPHIL CUT-OFFS (X10^9/L): STOP, THEN REFER	GLUCOSE AND LIPIDS AFTER BASELINE (MAUDSLEY)	UPPER-NORMAL QTC, MEN / WOMEN	QTC THAT MANDATES ACTION

WORKED EXAMPLE

Case: a 42-year-old man, well for two years on maintenance olanzapine, comes for review having gained weight, and separately a woman on risperidone reports galactorrhoea and amenorrhoea. **Reasoning: run three tracks.** *Metabolic*: weight, waist and BMI are recorded frequently for the first three months then at least yearly, and fasting glucose (or HbA1c) and a fasting lipid panel are taken at baseline, at 3 months, then yearly (more often, 3-monthly in the first year, for olanzapine and clozapine) (Maudsley 2021). His weight gain on a high-metabolic-risk agent is a signal to act. *Prolactin*: the woman's galactorrhoea and amenorrhoea point to hyperprolactinaemia; treatment is driven by the symptoms and the long-term bone risk, not by the number in isolation, and a level over **2500 mIU/L** prompts referral to exclude a prolactinoma. *Cardiac*: check the QTc against the upper-normal bands, **440 ms** in men and **470 ms** in women, with a QTc **over 500 ms** mandating action. **Plan: what to change.** For the metabolic case, offer lifestyle advice and switch toward a weight-neutral agent (aripiprazole) or add a metabolic-sparing adjunct; for the prolactin case, once a prolactinoma is excluded, switch to a prolactin-sparing agent (aripiprazole) or add adjunctive aripiprazole; for a QTc over 500 ms, stop or switch the offending QT-prolonging agent (haloperidol at high dose or IV is the worst offender) and correct electrolytes.

RULE **Maintenance is monitoring plus a switch.** Run the metabolic, prolactin and cardiac tracks on schedule; when weight climbs, prolactin is symptomatic, or the QTc crosses its band, the action is to switch to a sparing agent, not to keep watching.

HOLD THIS

Four moves, four discriminators: first episode, choose on the adverse-effect profile and start low; treatment resistance, confirm two adequate failed trials then move to clozapine with its neutrophil monitoring; acute rigidity and fever, call it NMS until proven otherwise, stop the drug and support; maintenance, run the metabolic, prolactin and cardiac monitoring and switch to a sparing agent when a threshold is crossed.

GOOD TO REMEMBER

- **Aripiprazole (first-episode and switch target):** a dopamine D2 partial agonist (mechanism owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes); a valid first-episode starting dose is 10 mg/day; the one thing to hold is that it is weight-neutral and prolactin-sparing, which is exactly why it is the first-choice switch or add-on for antipsychotic-induced metabolic burden or hyperprolactinaemia.
- **Risperidone (a reasonable first-episode alternative):** a second-generation D2/5-HT2A antagonist; a valid first-episode starting dose is 2 mg/day; the one caveat is its dose-related rise in prolactin, so ask about galactorrhoea, menstrual change and sexual dysfunction at review.
- **Clozapine (the treatment-resistance answer):** the only agent with proven superiority in true resistance; response usually across 150 to 900 mg/day (UK average around 450 mg/day, maximum 900 mg/day); the monitoring parameter to hold is the neutrophil count, FBC weekly for 18 weeks then two-weekly to one year then monthly, stop below 1.5 x10^9/L and refer below 0.5 x10^9/L (Maudsley 2021).
- **NMS (the rigidity-and-fever emergency):** feature, lead-pipe rigidity + hyperthermia + autonomic instability + altered consciousness, CK often >1000 units/L; discriminator from serotonin syndrome, uniform rigidity (not clonus/hyperreflexia) with a dopamine-blocker trigger over 1 to 3 days; first step, stop the antipsychotic and give supportive care, wait a minimum of 5 days before a lower-potency rechallenge.
- **Hyperprolactinaemia (the maintenance endocrine harm):** feature, galactorrhoea, amenorrhoea and sexual dysfunction from tuberoinfundibular D2 blockade; discriminator, symptom-driven with a level over 2500 mIU/L prompting a prolactinoma referral; first step, once a prolactinoma is excluded, switch to a prolactin-sparing agent (aripiprazole) or add adjunctive aripiprazole.
- **QTc prolongation (the maintenance cardiac harm):** feature, a lengthened QT interval on the road to torsades de pointes; discriminator, upper-normal 440 ms (men) and 470 ms (women), with over 500 ms the threshold that mandates action; first step, stop or switch the offending agent (haloperidol high-dose or IV is the worst) and correct electrolytes (Maudsley 2021).

INDIA

Clozapine monitoring in the Indian setting follows the same neutrophil logic but is run through the treating psychiatrist and local laboratory rather than a mandatory national registry, so the discipline of the schedule sits with the clinician; benign ethnic neutropenia is a genuine consideration when reading borderline counts. The Indian Psychiatric Society (IPS) schizophrenia guideline endorses the same core pathway: confirm resistance across two adequate trials, then move to clozapine. Where an early long-acting injectable is chosen to secure adherence, olanzapine long-acting injection is marketed in India as Tolaz (Torrent), with its binding constraint the post-injection syndrome that mandates a supervised post-injection observation period after every dose. Verify the local brand and formulation before naming one; generic prescribing dominates and is affordable.

Figure. A four-panel decision map, one panel per vignette (first-episode choice by adverse-effect axis; the confirm-resistance-then-clozapine ladder with neutrophil cut-offs; the NMS-versus-serotonin-versus-catatonia discriminator triangle; the three maintenance monitoring tracks with their switch thresholds), is flagged for a concept figure.

24 · Consolidate: mnemonic, retrieval and synthesis

Everything in this chapter has been laid out in bands: the plan and the algorithm, drug choice and the receptor trade-off, treatment resistance and clozapine, psychosocial rehabilitation, and the adverse effects and emergencies. This closing topic does not add facts; it fuses them. The examinable payoff of the whole note is the ability to unpack one seed cue into the entire management chapter, to recall each band cold under viva pressure, and to redraw the structure of treatment from a blank page. Consolidation is the step that turns a read note into a retrievable one, and on a management question it is where marks are won or lost: the examiner rewards the candidate who can place a patient on the algorithm, defend a drug against its adverse-effect trade-off, recognise resistance and reach clozapine, and spot the emergency, all from one chained cue.

How to use this page. Three tools, in order. First, the master **mnemonic** that chains the whole chapter so a single cue unpacks the note, the payoff of the seed planted in the orientation topic. Second, a set of **answer-free recall prompts**: the single highest-yield revision technique for this material is **active recall**, so test yourself against these before you re-read anything. Third, a **synthesis map** to redraw from memory, the four-branch skeleton on which every drug, adverse effect and emergency hangs. Do not treat this as a summary to skim; treat it as a set of exercises to perform. The illness itself, its phenomenology, aetiology, criteria and course, is not re-taught here; it belongs to the Schizophrenia: aetiology, phenomenology, classification and course notes.

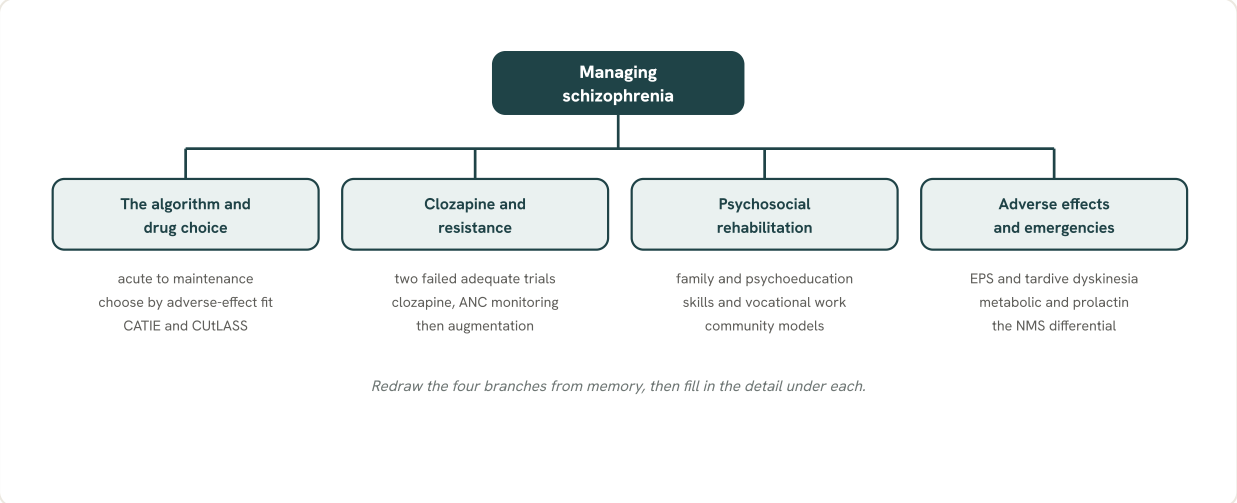

Fig 9.10 The whole-chapter synthesis map. Managing schizophrenia has four branches: the treatment algorithm and drug choice, clozapine and treatment resistance, psychosocial rehabilitation, and the adverse effects and their emergencies. Cover the detail, redraw the four branches from memory, then reconstruct what sits under each.

24.1 The master mnemonic: the whole chapter on one seed

The seed unpacked. The chapter runs as one management sequence, and one master mnemonic chains it so that a single cue delivers the entire note: *choose* the drug, *maintain* it, *resist*ance turns you to clozapine, *rehabilitate* across all phases, then *watch the harms*. This is the payoff of the seed set at orientation: *CHOOSE, MAINTAIN, RESIST, REHABILITATE, WATCH THE HARMS*, in reading order. Fix the five links and every later topic slots onto its band; the harms link is the longest, because the adverse effects and emergencies carry the most marks. The box below

unpacks every letter of the chain, chaining the plan and the algorithm from acute to maintenance, drug choice and the receptor trade-off, treatment resistance and clozapine, psychosocial rehabilitation, and the adverse effects and emergencies.

MNEMONIC

"CHOOSE, MAINTAIN, RESIST, REHABILITATE, WATCH THE HARMS" — the management chain. CHOOSE = the plan (locus, focus, modus), the algorithm (acute, stabilisation, maintenance) and drug choice on the D2-versus-adverse-effect trade-off. MAINTAIN = long-term, lowest effective dose, the LAI for adherence. RESIST = two failed adequate trials, then clozapine, then augmentation. REHABILITATE = family work, CBT for psychosis, skills and vocational rehabilitation. WATCH THE HARMS = EPS and tardive dyskinesia, metabolic, prolactin and QTc, then NMS and clozapine neutropenia.

Unpack it link by link. **CHOOSE** is the plan and the algorithm: set the biopsychosocial plan as *locus* (least-restrictive care), *focus* (the symptoms set by the phase) and *modus* (every mode of treatment), run the algorithm forward through the acute, stabilisation and maintenance phases, and choose a single antipsychotic on the receptor trade-off, more D2 blockade buys antipsychotic effect but also extrapyramidal and prolactin harm, while broader receptor action buys metabolic harm (the receptor and pathway mechanics are owned by the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; here we apply them). An adequate trial is 4 to 6 weeks at optimum dose (Maudsley 2021). **MAINTAIN** is the maintenance phase: continue long-term at the lowest effective dose for relapse prevention, reaching for a long-acting injectable where adherence is the limiting problem. **RESIST** is the treatment-resistance branch: non-response across two adequate antipsychotic trials turns the algorithm to clozapine, the one drug with evidence in refractory illness, and only then to augmentation (developed in the treatment-resistance and clozapine topics; ECT for augmentation, resistance and catatonia belongs to the ECT and neurostimulation notes). **REHABILITATE** is the psychosocial modus that runs across all phases: family intervention and psychoeducation to reduce high expressed emotion, CBT for psychosis, and social-skills and vocational rehabilitation, because the drug alone does not restore function. **WATCH THE HARMS** is the safety spine and the highest-yield band: the movement disorders (acute extrapyramidal side-effects and tardive dyskinesia), the metabolic syndrome, hyperprolactinaemia and QTc prolongation, and the two emergencies, neuroleptic malignant syndrome and clozapine-related neutropenia. One seed, the whole chapter.

RULE **One cue, five links.** If you can say "CHOOSE, MAINTAIN, RESIST, REHABILITATE, WATCH THE HARMS" and unpack each link into its topic, you can rebuild the entire management chapter without notes; that is the whole point of the seed.

TRAP **Memorising the acronym without the unpacking.** A mnemonic you cannot expand is a dead cue; drill the expansion (plan and algorithm, LAI, two failed trials to clozapine, the psychosocial limbs, and each named harm) until every link opens its own paragraph, or the chain buys you nothing in the viva.

24.2 Retrieval practice across the three bands

Why testing beats re-reading. The evidence on studying is unambiguous: **active recall** and spaced **retrieval practice** outperform passive re-reading and highlighting for durable memory. Use the prompts below as your first pass, not your last. **Cover the answers** that live in the topics above, attempt each prompt aloud or on paper from memory, and only then check yourself against the relevant topic. The prompts span the three bands, the algorithm and drug choice, resistance and clozapine, and the adverse effects and emergencies, so that a single sitting exercises the whole chapter. Do not print or peek at the answers first; the learning is in the effort of retrieval.

RETRIEVAL PRACTICE, COVER THE ANSWERS

These are answer-free recall prompts. This is **active recall**: **retrieval practice** works only if you attempt each one from memory before checking, so **cover the answers** in the topics above and write your own before you look.

1. State the three limbs of the biopsychosocial plan (locus, focus, modus) and say what sets the focus.
2. Name the three phases of the treatment algorithm in order and give the single target of each.
3. Define an adequate antipsychotic trial in duration and dose, and say why it matters before relabelling a patient resistant.
4. Give the staged escalation for acute agitation, from the first move to the last resort.
5. State the receptor trade-off that governs drug choice: what more D2 blockade buys you and what it costs you.
6. Contrast a first-generation with a second-generation antipsychotic on the two adverse-effect axes that separate them.
7. Name the single indication for a long-acting injectable in the maintenance phase.
8. Define treatment-resistant schizophrenia: how many adequate trials of how many drugs must fail.
9. Name the one drug licensed for treatment-resistant schizophrenia and the one blood parameter that must be monitored on it.
10. List the acute extrapyramidal side-effects and give the first management step for akathisia.
11. Distinguish tardive dyskinesia from an acute dystonia on timing and on the effect of the offending drug.
12. Name the components of antipsychotic-induced metabolic syndrome and the parameters recorded at baseline.
13. State the clinical tetrad of neuroleptic malignant syndrome and the single first management step.
14. Distinguish neuroleptic malignant syndrome from serotonin syndrome and from malignant catatonia on the two features that separate them.
15. Name the two antipsychotic emergencies that are true medical emergencies and the immediate action for each.

RULE **Attempt before you check.** The learning is in the effortful retrieval, not in reading the answer; a prompt you look up without trying teaches almost nothing.

24.3 The synthesis map: redraw the chapter from memory

One skeleton, four branches. The final consolidation exercise is to draw the synthesis map of the whole chapter on a blank page: a central node, managing schizophrenia, with four branches, the algorithm and drug choice; clozapine and resistance; psychosocial rehabilitation; and adverse effects and emergencies. Off *the algorithm and drug choice* hang the three phases from acute to maintenance and the receptor-versus-adverse-effect trade-off that picks the molecule; off *clozapine and resistance* hang the two-failed-trials definition, clozapine and its haematological

monitoring, and then augmentation; off *psychosocial rehabilitation* hang family intervention and psychoeducation, CBT for psychosis, and skills and vocational work; off *adverse effects and emergencies* hang the extrapyramidal side-effects and tardive dyskinesia, the metabolic syndrome and prolactin and QTc, and the neuroleptic malignant syndrome and clozapine neutropenia emergencies. Rebuild this map from memory, and redraw from memory each week until the four branches and their twigs come without prompting, and you own the chapter; the mnemonic in 24.1 is the verbal form of this same synthesis map, and each recall prompt in 24.2 tests one twig of it.

HOLD THIS

The whole chapter is one seed, "CHOOSE, MAINTAIN, RESIST, REHABILITATE, WATCH THE HARMS", unpacking into four branches, the algorithm and drug choice, clozapine and resistance, psychosocial rehabilitation, and adverse effects and emergencies; recall it by active retrieval with the answers covered, and redraw the four-branch synthesis map from memory until every twig comes unprompted.

GOOD TO REMEMBER

- **Master mnemonic (CHOOSE, MAINTAIN, RESIST, REHABILITATE, WATCH THE HARMS):** the management chapter chained in reading order; central claim is that one seed cue unpacks the whole note (plan and algorithm, drug choice, resistance to clozapine, psychosocial rehabilitation, adverse effects and emergencies); the discriminator to hold is that the fifth link, the harms, is the longest and highest-yield on a management question.
- **Active recall and retrieval practice:** testing yourself from memory with the answers covered before re-reading; central claim is that effortful retrieval produces more durable memory than passive review; the discriminator is that the benefit depends on attempting each prompt before checking, so answer-free prompts are the correct format and the answers are never printed.
- **Synthesis map (Fig 9.10):** a central managing-schizophrenia node with four branches, the algorithm and drug choice, clozapine and resistance, psychosocial rehabilitation, and adverse effects and emergencies; central claim is that redrawing it from memory proves the structure is held, not just the facts; the discriminator is that it is the visual twin of the master mnemonic and of the recall-prompt set, so all three tools test the same skeleton.

Figure. The whole-chapter synthesis map, a central managing-schizophrenia node with its four branches, the algorithm and drug choice (acute to maintenance, choose by the receptor trade-off), clozapine and resistance (two failed adequate trials, clozapine and monitoring, then augmentation), psychosocial rehabilitation (family and psychoeducation, CBT for psychosis, skills and vocational work), and adverse effects and emergencies (extrapyramidal side-effects and tardive dyskinesia, metabolic and prolactin and QTc, the neuroleptic malignant syndrome differential and clozapine neutropenia), to be redrawn from memory, is drawn as Fig 9.10.

Previously asked

The treatment of schizophrenia is examined as heavily as the illness, and it splits cleanly along the three bands of these notes. The management and the drugs come as long essays with a diagnosis-and-manage stem and as short notes on the individual agents; rehabilitation is a

recurring full essay; and the adverse effects and emergencies are a perennial source of both the 25-mark movement-disorder case and a stream of short notes. The genuine questions below are grouped by the three bands.

HOW THIS TERRITORY IS ACTUALLY TESTED

Q **Antipsychotic pharmacotherapy and management.** The recurring long-essay tail of the schizophrenia papers is the management, and it is also asked directly as "management of treatment-resistant schizophrenia" more than once. The drugs themselves come as short notes, "clozapine", "clozapine, adverse effects and management", and single agents such as "aripiprazole". Build the treatment algorithm and the two-failed-trials definition to answer these. long essay and short note, recurring

Q **Psychosocial rehabilitation and psychological treatment.** "Discuss rehabilitation in schizophrenia" is a repeated full essay, and the components come as their own short notes, "social skills training in schizophrenia", "psychoeducation", "therapeutic community", and "rehabilitation in psychiatry practice". The Indian service frame is asked as "community mental health in the Indian context" and "the national mental health plan and community psychiatry in India". long essay and short note, recurring

Q **Adverse effects and emergencies.** The classic 25-mark case is a patient on an antipsychotic and an antidepressant who develops involuntary movements, to investigate, diagnose, manage and explain the pathophysiology, and "neuroleptic malignant syndrome and its differential diagnosis" is asked as its own essay. The short notes are steady, "tardive dyskinesia", "antipsychotic drug-induced movement disorders", "drug-induced extrapyramidal reactions", "antipsychotic-induced metabolic syndrome", "adverse effects of atypical antipsychotics", "adverse effects of olanzapine", and "management of hyperprolactinaemia in psychiatry". long essay and short note, recurring

Prepare this material to be argued, not just recited: the treatment algorithm, the drug-choice and emergency-differential selectors, and the four worked vignettes in these notes are built to the way the topic is examined. The phenomenology, aetiology, criteria and course of the illness are developed in the Schizophrenia: aetiology, phenomenology, classification and course notes; malignant catatonia and the other psychotic disorders as entities live in the Other psychotic disorders, delusional syndromes and catatonia notes; these notes own the antipsychotics, the psychosocial treatment, and the adverse effects and their emergencies.

Quick review

The whole subject in one table	
THE PLAN AND THE ALGORITHM	A biopsychosocial plan on the LOCUS (where), FOCUS (target by phase) and MODUS (every mode of treatment) spine. Antipsychotics run acute to stabilisation to maintenance; acute agitation is managed by de-escalation first, then rapid tranquillisation and, least-restrictive, restraint. When two adequate trials fail, the illness is treatment-resistant and the next step is clozapine.
MECHANISM AND RECEPTORS	All effective antipsychotics block dopamine D2; the antipsychotic effect maps to about 65 to 80 percent striatal D2 occupancy, above which extrapyramidal risk rises without added benefit. The 5-HT2A to D2 balance defines the atypicals. The receptor profile predicts the harm: D2 for extrapyramidal effects and prolactin, H1 for sedation and weight, M1 anticholinergic, alpha-1 postural hypotension.
TYPICAL ANTIPSYCHOTICS	First-generation agents split by potency: high-potency (haloperidol, marketed as Serenace) with more extrapyramidal effects and prolactin, low-potency (chlorpromazine) with more sedation, anticholinergic and metabolic effects. Effective against positive symptoms, cheap, but a higher extrapyramidal and tardive burden.
ATYPICAL AND NEWER AGENTS	Second-generation agents (risperidone as Sizodon, olanzapine as Oleanz, quetiapine as Qutipin, amisulpride) trade a lower extrapyramidal burden for a metabolic one. Partial agonists (aripiprazole as Arip, cariprazine, brexpiprazole) are metabolically light. Lurasidone is metabolically favourable, taken with food; asenapine is sublingual; zotepine carries seizure risk. Xanomeline-trospium acts by muscarinic M1 and M4 agonism, not D2 blockade.
CHOOSING THE DRUG	Apart from clozapine, CATIE and CUtLASS found no large efficacy gap between the generations, so choice is driven by the adverse-effect fit for the patient (metabolic vs extrapyramidal vs prolactin vs sedation vs cardiac), not by a claimed superiority.
FIRST EPISODE AND MAINTENANCE	Treat the first episode early at the lowest effective dose (these patients are dose-sensitive); a long duration of untreated psychosis worsens outcome, the rationale for early-intervention services. Maintenance at the lowest effective dose is relapse prevention: relapse is far higher off medication, and intermittent or targeted dosing raises relapse and is not recommended.
DEPOT AND LONG-ACTING INJECTABLES	Assured-adherence maintenance that cuts relapse and rehospitalisation by roughly 20 to 30 percent versus the same oral drug; offer early. Risperidone microspheres need about 3 weeks of oral cover; paliperidone palmitate is 1-monthly and 3-monthly; the olanzapine injectable (Tolaz in India) needs a 3-hour post-injection observation for the post-injection syndrome.

The whole subject in one table	
TREATMENT RESISTANCE	Treatment-resistant schizophrenia is a failure of two adequate antipsychotic trials, each of adequate dose and duration with confirmed adherence. Exclude pseudo-resistance (non-adherence, inadequate trial, substance use, wrong diagnosis) first, then move to clozapine, not a third me-too switch.
CLOZAPINE	The only agent proven superior in true resistance (Kane 1988). Start 12.5 mg, build to 300 to 450 mg/day (up to 900). Neutrophils weekly for 18 weeks, then fortnightly to a year, then 4-weekly: continue at an absolute neutrophil count of 2.0 or above, recheck at 1.5 to 2.0, stop below 1.5, agranulocytosis below 0.5. Watch for myocarditis in the first month and a constipation that can be fatal.
AUGMENTATION AND POLYPHARMACY	For the ultra-resistant patient after an optimised clozapine trial: add a second antipsychotic (amisulpride, aripiprazole), lamotrigine, or electroconvulsive therapy (the ECT and neurostimulation notes). Rational polypharmacy needs a defined target, a defined trial and a plan to stop; long-term two-antipsychotic use without benefit is avoided.
NEGATIVE SYMPTOMS	Separate secondary negatives (from positive symptoms, depression, extrapyramidal effects, understimulation, all reversible) from primary; treat the secondary cause first. No drug reliably treats primary negatives; consider an agent with a better negative signal (amisulpride, cariprazine) and the psychosocial and cognitive approaches.
PSYCHOSOCIAL REHABILITATION	Medication controls symptoms but rehabilitation delivers function and recovery, so it is core, not optional. Its components are psychoeducation and family work, social skills and vocational training, the psychological therapies and community support.
FAMILY AND SKILLS INTERVENTIONS	Family intervention in high-expressed-emotion households is one of the best-evidenced relapse-prevention tools. Supported employment (place then train, the Individual Placement and Support model) beats prevocational train-then-place for competitive work.
PSYCHOLOGICAL THERAPIES	CBT for psychosis is an evidence-based adjunct for persistent distressing symptoms; cognitive remediation improves cognition with a small-to-moderate effect that transfers to function best when paired with rehabilitation.
COMMUNITY MODELS	Assertive community treatment and case management target the most disabled, frequently-admitted patients. The Indian models are the District Mental Health Programme, day care and halfway homes, within the National Mental Health Programme.
EXTRAPYRAMIDAL EFFECTS	By onset: acute dystonia in hours (a parenteral anticholinergic), akathisia in days (reduce or switch, propranolol, never raise the dose), parkinsonism in weeks (reduce or switch, or an anticholinergic).

The whole subject in one table	
	Akathisia mistaken for agitation and treated with more antipsychotic is the classic error.
TARDIVE DYSKINESIA	Late choreoathetoid movements after months to years, screened with the AIMS; risk with older age, first-generation agents and longer exposure. Prevent with the lowest effective dose and second-generation agents; treat established disease with a VMAT2 inhibitor (valbenazine, deutetrabenazine); anticholinergics worsen it.
NEUROLEPTIC MALIGNANT SYNDROME	Lead-pipe rigidity, hyperthermia, autonomic instability and altered mental state over one to three days, with a markedly raised creatine kinase. Stop the antipsychotic, give supportive care, and use dantrolene or bromocriptine. Fever with rigidity in a treated patient is NMS until proven otherwise.
METABOLIC AND CARDIAC EFFECTS	Olanzapine and clozapine carry the highest metabolic risk. Monitor weight at baseline, 6 and 12 weeks then annually, and glucose or HbA1c, lipids and blood pressure at baseline, 12 weeks and annually. Hyperprolactinaemia is worst with risperidone, paliperidone and amisulpride; watch QTc (worst with thioridazine, pimozide, high-dose intravenous haloperidol) and do not stack QT-prolonging drugs.
THE EMERGENCY DIFFERENTIAL	Rigidity with hyporeflexia and a very high creatine kinase is NMS; clonus and hyperreflexia after a serotonergic drug is serotonin syndrome; catatonic signs that precede the picture point to malignant catatonia; hot, dry, flushed skin with absent bowel sounds is anticholinergic toxicity. The discriminator, not the shared fever, makes the call.
APPLY AND CONSOLIDATE	Four worked cases: a first-episode drug choice by adverse-effect fit, a treatment-resistant case reasoned to clozapine, an acute rigidity-and-fever case worked as the NMS differential, and an adverse-effect monitoring case. Then the master mnemonic, answer-free retrieval prompts, and the four-branch synthesis map to redraw from memory.

References

The management content is grounded in the standard prescribing and clinical texts (the source hierarchy below), which anchor the settled facts on antipsychotic pharmacology, dosing, adverse effects and their management; the treatment-algorithm and monitoring detail follows the Maudsley Prescribing Guidelines, Stahl and the schizophrenia treatment guidance of NICE, the American Psychiatric Association and the Indian Psychiatric Society. Every landmark trial, dose, therapeutic range and monitoring threshold has been checked against these sources, and every named clinical trial carries a PubMed-verified journal citation. Each PMID here was checked against PubMed this build, matched on title, first author and year; any identifier that did not resolve to the cited paper was dropped rather than guessed. A few citations that support a claim but have no stable PubMed record (society guidelines, the expressed-emotion classics of Brown

and of Butzlaff and Hooley, and the Individual Placement and Support and recovery literature) are cited by author, title and year in the text, and the same claims are also covered by the verified references retained here.

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