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PAPER II · VOLUME ONE

MD and DNB psychiatry, theory revision

Clinical Psychiatry

Schizophrenia and the Psychoses

What schizophrenia is, where it comes from and how it is treated. Then the psychoses beyond it: the delusional and brief syndromes, and catatonia.

Dr. Wilfred D'souza · Dr. Niharika Reddy

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WEAVE SPRINT · PAPER II

Clinical Psychiatry

THE WEAVE SPRINT SERIES

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WRITTEN BY

Dr. Wilfred D'souza and Dr. Niharika Reddy

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EDITION

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

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

ACKNOWLEDGEMENT

A word of thanks

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

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

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

Dr. Wilfred D'souza

Foreword

This first volume is schizophrenia and everything that has to be told apart from it. The first two chapters give the illness its full account: what it is and where it comes from, then how it is treated and what the treatment costs. The third turns to the psychotic states that are not schizophrenia and must not be managed as though they were.

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

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

HOW TO USE THIS BOOK

The colour memory code

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

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

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

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

Contents

PART I

Schizophrenia: Aetiology, Phenomenology, Classification and Course

What schizophrenia is, where it comes from, how it shows itself, and how it is classified and followed over time.

PAPER II

Schizophrenia: aetiology, phenomenology, classification and course

Five sections · 23 topics · one complete notes document

This material gathers the first clinical chapter into one document, the illness that anchors the whole of psychotic disorders. The first band is **aetiology and neurobiology**: the epidemiology that sets the lifetime risk near one percent, the genetics with its high heritability, the dopamine hypothesis in its original, revised and aberrant-salience forms, the glutamate and other-transmitter models, the neurodevelopmental two-hit model with its environmental hits, and the structural neuroimaging and neuropathology. The second band is **clinical features and phenomenology**: the five symptom domains as the organising map, the positive symptoms and disorganisation, the negative symptoms and their deficit form, the cognitive impairment that carries the functional weight, the first-rank symptoms of Schneider and the fundamental symptoms of Bleuler read with their modern caveats, and the prodrome and first episode. The third band is **classification, subtypes and nosological change**: the current criteria of ICD-11 and DSM-5-TR set against the legacy ICD-10, the reason both systems dropped the historical subtypes, and the differential that separates schizophrenia from the disorders it resembles. The fourth band is **course, prognosis and outcome**: the phases and natural history, the good and poor prognostic factors, and the outcome including the mortality gap. The examinable skill is judgement across all four: to reason from mechanism to phenomenon, to apply the criteria, to tell schizophrenia from its mimics, and to weigh the outcome.

HOW TO USE THESE NOTES

Read the four bands as one argument that runs from cause to consequence. The **aetiology** band builds the mechanistic picture, each hypothesis ending with a **Good to remember** box giving what it claims, the evidence for it, and the one number or discriminator to hold. The **phenomenology** band maps the signs onto the five domains; the descriptive definitions of delusions, hallucinations, thought disorder and the first-rank symptoms are owned by the Psychometry, Assessment and Descriptive Psychopathology notes, so here they are applied to schizophrenia rather than redefined. The **classification** band runs ICD-11 forward, cross-maps DSM-5-TR, and keeps a legacy ICD-10 box showing what changed, and its payoff is the **differential**, the decision tree that separates schizophrenia from mood disorder with psychotic features, schizoaffective disorder, delusional disorder, the brief and schizophreniform pictures, and organic or substance-induced psychosis. The **course** band closes on prognosis and outcome. Figures declare one axis and code it in colour: **petrol** marks structure and the neutral case, **coral** marks the trap or the point of discrimination, and **marigold** highlights the number to hold. Four boundaries are worth stating up front: the dopamine and monoamine pathways and the imaging principles are developed in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; the twin, family and adoption methods belong to the Psychiatric Genetics notes; antipsychotics, adverse effects and rehabilitation are taught in the Schizophrenia: management, antipsychotics and adverse effects notes; and the other psychotic disorders and catatonia as entities live in the Other psychotic disorders, delusional syndromes and catatonia notes. This is doctor-facing revision, so the full technical vocabulary is used.

Aetiology and neurobiology

1 · Orientation: what schizophrenia is and the criteria map

Schizophrenia is the anchor disorder of psychiatry and the most heavily examined single condition in the clinical papers, so every later topic in these notes reads back to the orientation set here. It is a **chronic psychotic disorder** of the young adult: onset clusters in late adolescence and early adulthood, the illness is multifactorial rather than the product of one lesion, its best-supported mechanism is dopaminergic but no single dopamine abnormality explains it, and it is defined by a **syndrome** recognised at the bedside rather than by any laboratory test (Kaplan & Sadock 2024). The examiner is never testing whether you can recite a definition in the abstract; they are testing whether you can place a psychotic presentation on the diagnostic criteria map and defend the placement against the mimics.

How to use this page. Fix three things before anything else. First, the illness at a glance, so the shape of the disorder is in your head before the detail arrives. Second, the **criteria map**, the diagnostic decision tree that every subsequent topic hangs from, run ICD-11 forward and cross-mapped to DSM-5-TR with ICD-10 flagged as legacy. Third, the master mnemonic that chains the four bands of the whole chapter, cause then phenomenon then criteria then course, so that one cue unpacks the entire note. The descriptive definitions of the individual signs, what a delusion, a hallucination, a first-rank symptom or formal thought disorder *is* as a phenomenon,

are not re-derived here; they belong to the Psychometry, Assessment and Descriptive Psychopathology notes, and this chapter applies them to schizophrenia.

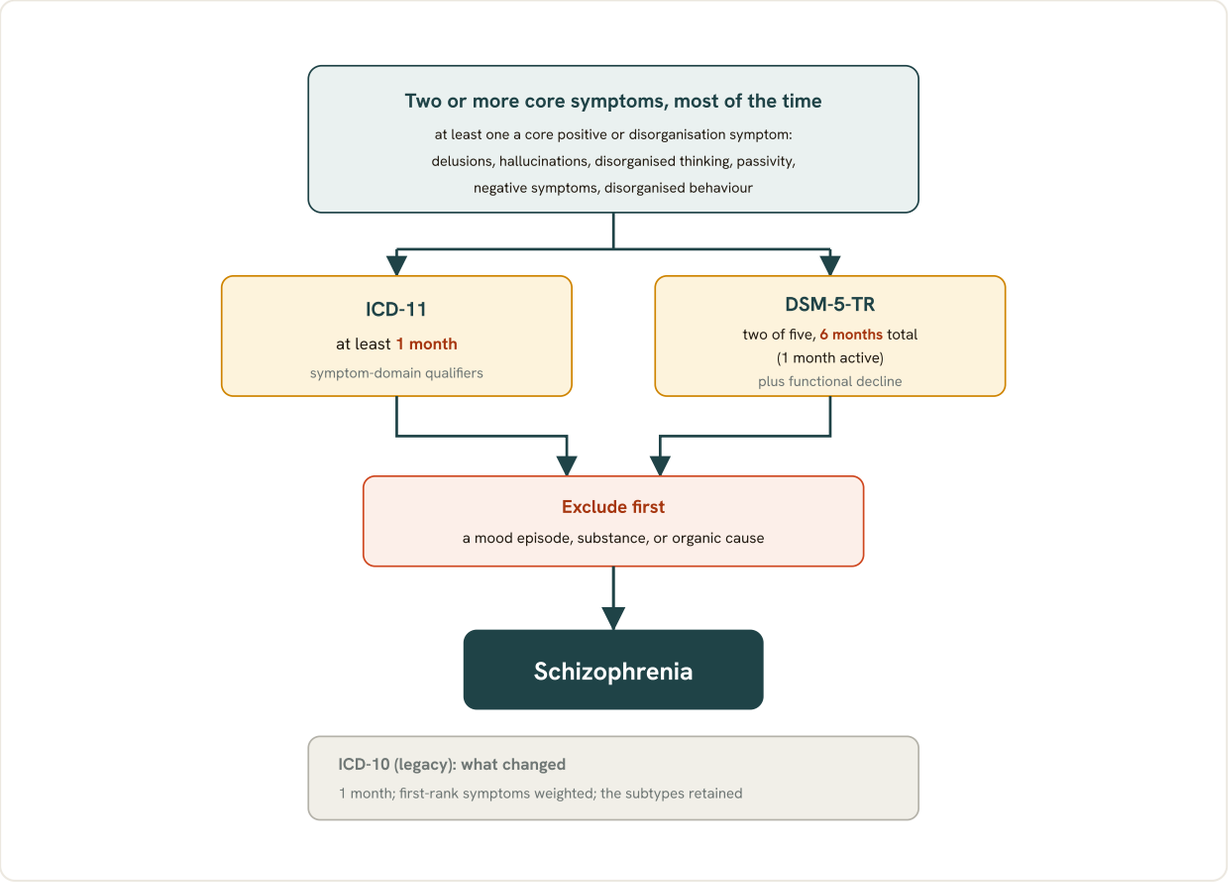


Fig 8.1 The diagnostic criteria as a decision map. Two or more core symptoms, at least one from the positive or disorganisation cluster, must persist for the required duration, ICD-11 asking one month and DSM-5-TR a six-month total with functional decline, and a mood, substance or organic cause must be excluded before the diagnosis is made. The legacy ICD-10 box records what the current systems changed.

1.1 The illness at a glance: one orientation before the detail

What kind of disorder this is. Schizophrenia is a severe, typically persistent disorder in which psychosis, a loss of contact with reality expressed as delusions, hallucinations and disorganisation, is coupled to a decline in functioning and, in most patients, an enduring deficit that outlasts the acute episodes. It presents in the second and third decades: the psychotic features usually emerge between the late teens and the mid-30s, with a peak in the early-to-mid 20s in men and the late 20s in women, and onset before adolescence is rare (Kaplan & Sadock 2024). The lifetime risk sits near **~1%** as the classic teaching figure, with rigorous population surveys giving a somewhat lower lifetime prevalence of about **0.3 to 0.7%** (DSM-5-TR 2022); the disorder is strongly familial, with a twin-study heritability of the order of **~80%** (Sullivan et al. 2003). The detailed epidemiology, the sex difference, the Indian figures and the WHO cross-cultural outcome finding are developed in the epidemiology topic and the genetic evidence in the genetics topic; twin, family and adoption study methods themselves belong to the Psychiatric Genetics notes.

~1%	~80%	late teens to mid-30s
LIFETIME RISK (CLASSIC FIGURE)	HERITABILITY (TWIN STUDIES)	TYPICAL ONSET WINDOW

The five-domain picture. The clinical phenomenon is not one thing but a spread across five symptom domains, and holding the domains from the start makes both the phenomenology band and the criteria map legible. A positive symptom is an addition to normal experience: delusions and hallucinations. A negative symptom is a subtraction from it: blunted affect, alogia, avolition, asociality and anhedonia. The cognitive domain is the impairment of attention, working memory, processing speed and executive function that carries much of the functional disability. The disorganisation domain is formal thought disorder and disorganised or bizarre behaviour. The affective domain is the mood disturbance, depression, dysphoria and, importantly, suicide risk, that runs through the course. These five recur as the spine of the whole chapter.

RULE **A syndrome, not a test.** Schizophrenia is diagnosed by recognising a constellation of signs and symptoms with functional decline over a required duration; there is no radiological, laboratory or psychometric test that confirms it, and no single symptom is pathognomonic.

TRAP **Diagnosing schizophrenia inside an untreated mood episode.** If delusions or hallucinations occur only during a depressive or manic episode, the diagnosis is a mood disorder with psychotic features, not schizophrenia; schizophrenia requires psychosis in the absence of a concurrent mood episode.

1.2 The criteria-map schema: the whole diagnosis on one decision tree

Why the criteria are the organising schema. Every clinical judgement in this chapter is a move on a single **criteria map**: does this presentation meet the symptom threshold, does it meet the duration threshold, and have the exclusions (mood, substance, medical) been cleared. Learn the map as a decision tree and the phenomenology, the classification and the differential all become branches of it rather than separate lists. The current **diagnostic criteria** come from two live systems that agree on the core and differ mainly on duration, with a third, ICD-10, now legacy.

ICD-11, run forward. Under ICD-11 (6A20), at least two of seven symptom groups must be present most of the time for a period of one month or more, and at least one of the two must be a core symptom, one of persistent delusions, persistent hallucinations, disorganised thinking (formal thought disorder), or experiences of influence, passivity or control (WHO ICD-11 CDDR 2024). The remaining three groups, negative symptoms, grossly disorganised behaviour and psychomotor (catatonic) disturbance, can supply the second symptom but cannot stand alone. The exclusion is that the picture is not due to another medical condition, a substance or a medication. Note the two features an examiner rewards: the qualifying-symptom rule (at least one core positive or disorganisation symptom) and the one-month duration.

DSM-5-TR, cross-mapped. Under DSM-5-TR (2022), Criterion A requires two of five symptoms, each present for a significant portion of a one-month period, and at least one must be delusions, hallucinations or disorganised speech; the other two options are grossly disorganised or catatonic behaviour and negative symptoms. The decisive difference is duration: DSM-5-TR adds Criterion B (functional decline) and Criterion C, a total illness duration of **at least 6 months** that must include that one month of active-phase symptoms, plus the mood (Criterion D), substance and medical (Criterion E) exclusions. So the two systems share the same symptom

core and the same one-month active-phase requirement; ICD-11 stops at one month, DSM-5-TR demands six months of total disturbance.

FEATURE	ICD-11 (6A20), CURRENT, PRIMARY	DSM-5-TR, CURRENT, CROSS-MAPPED
Symptoms required	At least two of seven groups, most of the time	**Criterion A: two of five symptoms**
Qualifying (core) symptom	At least one from delusions, hallucinations, disorganised thinking, or influence/passivity/control	**At least one from delusions, hallucinations, disorganised speech**
Active-phase duration	One month or more	**One month of Criterion A symptoms**
Total duration	Not separately required (one month suffices)	**At least 6 months of continuous signs (Criterion C)**
Functional decline	Impairment implied, not a separate criterion	**Criterion B, a required threshold**
Exclusions	Not substance/medication/medical condition	**Mood (D), substance and medical (E) ruled out**

The criteria map, ICD-11 run forward and DSM-5-TR cross-mapped; the single high-yield contrast is the duration threshold, one month versus six months, highlighted in the right column.

COMMON TRAP

Do not confuse the two duration figures. The one-month figure is the active-phase (florid) symptom requirement that both systems share; the six-month figure is DSM-5-TR's *total* illness duration including prodrome and residual. A florid picture of five weeks meets ICD-11 but a DSM-5-TR diagnosis at that point would be schizophreniform disorder, which converts to schizophrenia once the total disturbance reaches six months.

1.3 ICD-10 as legacy: what changed on the way to ICD-11

Why the older system still turns up. Many Indian examinations and case records still run on ICD-10, so it is flagged here as legacy rather than dropped. ICD-10 (F20) diagnosed schizophrenia on a list built around Schneiderian first-rank symptoms: one very clear first-rank or bizarre-delusion symptom, or two or more of a second group (other persistent hallucinations, thought disorder, catatonia, negative symptoms), present for most of the time during at least one month. ICD-11 made three examinable changes. It removed the privileged status of first-rank symptoms, so that thought insertion or a running commentary no longer carries diagnostic weight above other core positive symptoms. It replaced the historical subtypes (paranoid, hebephrenic, catatonic and the rest) with a dimensional set of symptom specifiers, on the grounds that the subtypes had poor reliability and predictive validity; that nosological change is developed in the classification band. The core one-month duration was retained. Where an exam paper is explicitly ICD-10, answer on ICD-10; where it is unmarked, lead with ICD-11 and note the DSM-5-TR six-month contrast.

TRAP **Calling first-rank symptoms pathognomonic.** First-rank symptoms are suggestive but not specific and not diagnostic; DSM-5 and ICD-11 both stripped them of special status, and they occur in mania and organic psychoses too. Their descriptive definitions are cross-referenced to the Psychometry, Assessment and Descriptive Psychopathology notes.

1.4 The master mnemonic: chaining the four bands of the chapter

The whole chapter on a single hook. This chapter runs in four bands, and one mnemonic chains them so that a single cue unpacks the entire note: *cause* (aetiology and neurobiology), *phenomenon* (clinical features and phenomenology), *criteria* (classification and the nosological change), and *course* (course, prognosis and outcome). Fix the four Cs in that order and every later topic slots onto its band; the criteria map you have just learned is the hinge in the middle, the schema the cause bands build toward and the course bands read forward from.

MNEMONIC

"CAUSE, PHENOMENON, CRITERIA, COURSE": the four bands, in reading order. Under phenomenon, the five domains are "P-N-C-D-A": Positive, Negative, Cognitive, Disorganisation, Affective.

Unpack it band by band. **Cause** is the aetiology climb: the dopamine and glutamate hypotheses, the neurodevelopmental and two-hit models, genetics and the imaging findings, no single lesion but a convergence. **Phenomenon** is the five-domain picture, held on **P-N-C-D-A**: a **P**ositive symptom (delusion, hallucination), a **N**egative symptom (the deficit), the **C**ognitive impairment, the **D**isorganisation (thought disorder, disorganised behaviour) and the **A**ffective disturbance. **Criteria** is the map itself, ICD-11 forward, DSM-5-TR cross-mapped, ICD-10 legacy, and the dropping of the subtypes. **Course** is the natural history: premorbid, prodrome, acute and residual phases, the good-versus-poor prognostic factors, and the outcome, suicide and the mortality gap. One seed, four bands, the whole chapter.

WORKED EXAMPLE

A 22-year-old man is brought in after six weeks of persecutory delusions and a running commentary of voices, with two months of prior social withdrawal and self-neglect. Walk the criteria map. Symptoms: two are present and one (delusions) is a core positive symptom, so the symptom threshold is met. Duration: the florid phase exceeds one month, so ICD-11 6A20 is met now. On DSM-5-TR, Criterion A and the one-month active phase are met, but total disturbance so far is roughly three-and-a-half months, short of the six-month Criterion C, so the DSM-5-TR label at this instant is schizophreniform disorder pending the six-month mark. Exclusions: confirm no concurrent mood episode and no substance or medical cause before the label is fixed. That single vignette exercises every branch of the map.

HOLD THIS

ICD-11 needs at least two symptoms, at least one a core positive or disorganisation symptom, for at least one month; DSM-5-TR needs the same one-month active phase but a six-month total duration, and both demand that psychosis occur outside a mood episode and outside a substance or medical cause.

GOOD TO REMEMBER

- **Schizophrenia:** chronic multifactorial psychotic disorder of the young adult, defined by a syndrome not a test; core criterion is psychosis plus functional decline over the required duration; the one discriminator is that no single symptom is pathognomonic, so it is a threshold-and-duration diagnosis.
- **ICD-11 (6A20):** at least two of seven symptom groups for one month or more, at least one a core symptom (delusions, hallucinations, disorganised thinking, or influence/passivity/control); discriminator is the one-month active-phase threshold with no separate total-duration rule.
- **DSM-5-TR:** Criterion A, two of five with at least one being delusions, hallucinations or disorganised speech; discriminator is Criterion C, a six-month total duration including one month of active-phase symptoms.
- **ICD-10 (legacy):** first-rank-weighted list, one clear first-rank symptom or two of a second group over one month; discriminator versus ICD-11 is that ICD-11 removed the special status of first-rank symptoms and dropped the subtypes.
- **Five symptom domains:** positive, negative, cognitive, disorganisation and affective; the map on which the whole phenomenology hangs; discriminator is that negative, cognitive and disorganisation symptoms, not the positive symptoms, carry most of the long-term disability.

Figure. The criteria map, the ICD-11-forward, DSM-5-TR-cross-mapped diagnostic decision tree with the ICD-10 legacy branch and the shared one-month versus DSM six-month duration gate, is drawn as Fig 8.1.

2 · Epidemiology: incidence, prevalence, onset and the mortality gap

The epidemiology of schizophrenia is a small set of numbers an examiner expects you to hold exactly, and to hold with their measure attached: a lifetime risk near one percent is meaningless unless you can say whether you mean point prevalence, lifetime prevalence, incidence or morbid risk, because each is a different denominator and each gives a different figure (Kaplan & Sadock 2024). This topic fixes the frequency measures, the age-and-sex pattern of onset, the Indian and cross-cultural picture, and the excess mortality that now defines the physical-health agenda for the disorder. The recurring exam trap is quoting a prevalence stripped of its year and source, so every figure below is tied to the study that produced it.

How to hold it. Anchor on three measures and their rough values, then let onset, the Indian data and the **mortality gap** attach to that spine. The descriptive definitions of the psychotic phenomena themselves belong to the Psychometry, Assessment and Descriptive Psychopathology notes; the twin, family and adoption evidence for familial risk belongs to the Psychiatric Genetics notes; and the WHO cross-cultural *outcome* finding and the cardiometabolic detail behind the mortality gap are developed in the course, prognosis and outcome topic, so this topic states them only as far as the epidemiology requires.

2.1 Three frequency measures, three different numbers

Why the measure decides the number. Prevalence is the proportion of a population that has the disorder at a point in time (point prevalence) or over a defined window (period or lifetime prevalence); incidence is the count of new, first-onset cases arising per unit population per year; and lifetime morbid risk is the probability that a person surviving through the entire age of risk

will develop the disorder. Because schizophrenia is chronic, prevalence pools accumulated surviving cases while incidence counts only new ones, so the two are not interchangeable, and morbid risk is higher than any cross-sectional prevalence because it projects across the whole lifespan. Confusing these is the single commonest epidemiology error in the disorder.

Prevalence, with its source. The most-cited systematic review of prevalence, drawing on studies from 46 countries published between 1965 and 2002, gave a median point prevalence of about **4.6 per 1,000** persons (roughly 0.46 percent), a period prevalence of 3.3 per 1,000, a lifetime prevalence of 4.0 per 1,000, and a lifetime morbid risk of about **7.2 per 1,000** (roughly 0.72 percent) (Saha et al. 2005). The Global Burden of Disease 2016 estimate, using a different Bayesian method across 195 countries, put the global age-standardised point prevalence at **0.28%**, and found it did not vary widely between countries (Kaplan & Sadock 2024). The classic teaching figure of a lifetime risk near **~1%** therefore sits at the upper edge of the rigorous survey estimates; the American Psychiatric Association guideline quotes a lifetime prevalence of approximately **0.7%** (McGrath et al. 2008, in APA 2020), which is the number to reach for when an examiner presses on the difference between the round teaching figure and the survey data.

RULE **State the measure before the number.** Lifetime risk near one percent, point prevalence near half a percent, and incidence near 15 per 100,000 per year are three different statements about three different denominators, not three versions of one figure.

TRAP **Quoting a prevalence without its year and source.** A bare "prevalence of schizophrenia is 1%" invites the follow-up you cannot then answer; tie the figure to Saha et al. 2005 or GBD 2016 (point prevalence about 0.3 to 0.5 percent) or to McGrath et al. 2008 (lifetime about 0.7 percent).

2.2 Incidence and the McGrath finding of real geographic variation

The incidence figure. First-onset incidence is the more informative measure for causal epidemiology because, unlike prevalence, it is not distorted by illness duration or differential mortality. A systematic review of studies published between 2002 and 2017 gave a median incidence of about 0.22 per 1,000 persons per year, and the Global Burden of Disease 2017 update gave an age-standardised incidence rate of roughly **15 per 100,000** per year (14.98 per 100,000 in 1990 and 14.39 per 100,000 in 2017), so the working figure to carry is an incidence of the order of **~15 per 100,000** per year (Kaplan & Sadock 2024). That is the number an examiner wants when they ask for incidence rather than prevalence.

Variation is real, not artefact. The older orthodoxy that schizophrenia occurs at a uniform rate everywhere was overturned by a systematic review that found genuine, several-fold variation in incidence, prevalence and mortality between sites and populations, argued to reflect real environmental and demographic differences rather than only differences in method (McGrath 2006; McGrath et al. 2008). The parsed reviews record incidence rising with urbanicity and a markedly raised rate in migrant and some ethnic-minority groups: pooled incidence rate ratios of about 2.3 for first-generation and 2.1 for second-generation migrants, and a near-ninefold excess in the African-Caribbean population of the United Kingdom (Kaplan & Sadock 2024). Hold the

headline as McGrath's: the incidence of schizophrenia has "surprisingly rich contours," and geographic variation is a substantive finding.

~1%	~0.7%	~0.3%	~15/100k/yr
LIFETIME RISK (CLASSIC FIGURE)	LIFETIME PREVALENCE (MCGRATH ET AL. 2008)	POINT PREVALENCE (GBD 2016, 0.28%)	INCIDENCE (GBD AGE-STANDARDISED)

2.3 Age of onset and the sex difference

The onset window. Schizophrenia is a disorder of the young adult: onset clusters in the late teens through the mid-30s, with a peak in early adulthood, and onset before adolescence or after the mid-40s is uncommon (Kaplan & Sadock 2024). This early-adulthood peak is one of the features that recurs across cultures and supports the view that the same disorder is being counted in different populations.

The sex difference. The age of onset shows a robust sex difference: onset is earlier in men, typically in the early-to-mid twenties, than in women, typically in the late twenties, and women show a characteristic second, smaller peak of onset in the peri-menopausal years that men do not (Hafner et al. 1998; Kaplan & Sadock 2024). Alongside the earlier male onset, men carry a modestly higher incidence than women (a male-to-female incidence rate ratio of the order of 1.3 to 1.4 in pooled data), and the female illness tends to run a somewhat more benign course, a pattern the parsed textbooks attribute in part to a putative protective effect of oestrogen (McGrath et al. 2008). The classic bedside summary is that onset is earlier and outcome poorer in men.

RULE **Earlier onset, poorer outcome in men.** Men present in the early-to-mid twenties with a modestly higher incidence and a worse average course; women present in the late twenties, carry a second peri-menopausal peak, and run a relatively more benign course.

2.4 The Indian picture and the cross-cultural frame

What the Indian survey shows. The National Mental Health Survey 2015-16, the reference community-epidemiology study for India, reported a lifetime prevalence of any mental disorder of 13.7 percent and a current prevalence of 10.6 percent, with a large treatment gap for severe mental disorders (Gururaj et al. 2016; Kaplan & Sadock 2024). The survey did publish a disorder-specific figure for schizophrenia and other non-affective psychoses, but the exact percentage is not confirmed in the parsed reference set, so it is flagged rather than quoted here to avoid reporting an unverified number.

INDIA

The National Mental Health Survey 2015-16 (Gururaj et al., NIMHANS) gives the national frame you should cite for any Indian prevalence claim: any mental disorder, lifetime 13.7 percent and current 10.6 percent, across 12 states, with a treatment gap for severe mental disorders reported in the region of 75 to 92 percent. The specific psychosis and schizophrenia prevalence from this survey is commonly quoted in Indian teaching but is not verifiable in the parsed sources here, so quote it only from the NMHS report itself, with the survey year attached.

The cross-cultural frame. No human community studied has been found to be free of schizophrenia, and the core clinical picture and the age-and-sex distribution of onset are broadly similar across cultures, which is the strongest argument that a single disorder is being diagnosed worldwide (Jablensky 2000; Kaplan & Sadock 2024). Against this backdrop of similar frequency and presentation, the WHO cross-cultural programme reported the counterintuitive finding that the *course and outcome* were, on average, better in patients from developing than from developed countries; that outcome finding, and the debate about it, is developed in the course, prognosis and outcome topic and is only cross-referenced here.

2.5 The mortality gap

The size of the gap. Schizophrenia carries a large excess mortality that is now treated as a core epidemiological fact rather than a footnote. People with the disorder die, on average, some **15 to 20 years** earlier than the general population, a reduction in life expectancy documented across care systems (Kaplan & Sadock 2024). Expressed as a standardised mortality ratio, all-cause mortality is roughly two-fold to four-fold that of the general population (APA 2020; Saha, Chant & McGrath 2007), and the differential mortality gap has, if anything, widened rather than closed over recent decades despite improving general-population life expectancy (Saha, Chant & McGrath 2007).

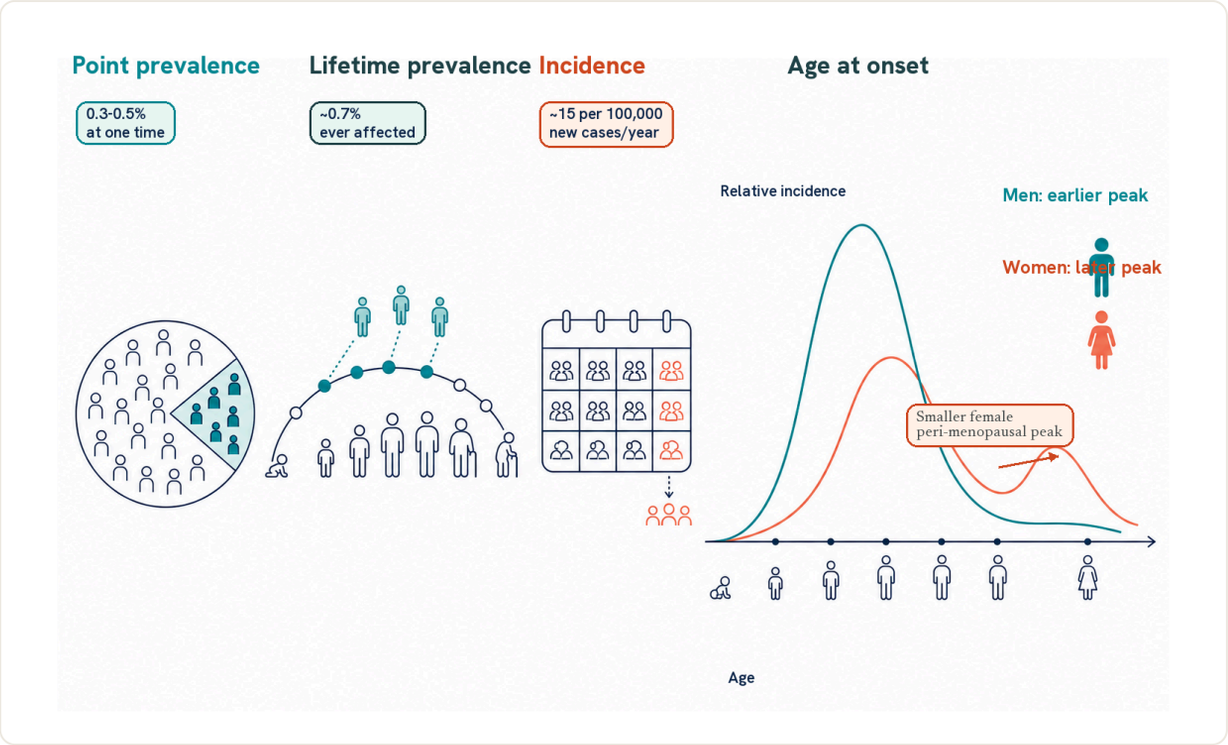


Fig 8.2 Schizophrenia epidemiology on one page. Point prevalence is about 0.3 to 0.5 per cent, lifetime prevalence about 0.7 per cent and incidence about 15 per 100,000 per year; onset peaks earlier in men, later in women, with a smaller female peri-menopausal second peak.

What drives it. Suicide accounts for a substantial share of the early excess deaths, particularly in the early years of illness, but the larger and growing part of the mortality gap is natural-cause death, dominated by cardiometabolic disease: cardiovascular disease, driven by smoking, obesity, dyslipidaemia and the metabolic effects of antipsychotic treatment, together with under-recognition and under-treatment of physical illness (Kaplan & Sadock 2024; APA 2020). The

cardiometabolic detail, and the management response to it, belong to the Schizophrenia: management, antipsychotics and adverse effects notes and are developed in the course, prognosis and outcome topic; the epidemiological headline to hold is the 15-to-20-year figure and its mostly cardiometabolic cause.

TRAP **Attributing the whole gap to suicide.** Suicide raises mortality most in the first years, but across the lifespan most of the excess death is natural-cause and cardiometabolic; the correct one-line cause of the mortality gap is cardiovascular disease, not suicide alone.

HOLD THIS

Lifetime risk near one percent, point prevalence near 0.3 to 0.5 percent, incidence near 15 per 100,000 per year with real geographic variation (McGrath); onset earlier in men (early-to-mid twenties) than women (late twenties, plus a peri-menopausal peak); and a mortality gap of 15 to 20 years that is mostly cardiometabolic.

GOOD TO REMEMBER

- **Point prevalence:** proportion of the population with schizophrenia at one time; central estimate about 0.3 to 0.5 percent (GBD 2016 point prevalence 0.28%; Saha et al. 2005 median 4.6 per 1,000); discriminator is that it pools all surviving chronic cases, so it exceeds incidence but is not the lifetime figure.
- **Lifetime prevalence and lifetime risk:** proportion ever affected / probability of developing the disorder across the lifespan; classic teaching figure about one percent, rigorous surveys about 0.7 percent (McGrath et al. 2008); discriminator is that the round 1 percent figure is the memorised anchor while 0.7 percent is the survey-derived value.
- **Incidence:** new first-onset cases per population per year; about 15 per 100,000 per year age-standardised (GBD); discriminator is that it varies genuinely by place and group (McGrath), higher with urbanicity and in migrants, so it is not uniform worldwide.
- **Age of onset and sex difference:** peak in early adulthood; earlier in men (early-to-mid twenties) than women (late twenties), women with a second peri-menopausal peak; discriminator is the modestly higher male incidence and the earlier, poorer-outcome male illness.
- **Mortality gap:** excess early death in schizophrenia; life expectancy reduced by 15 to 20 years, standardised mortality ratio about two-fold to four-fold; discriminator is that most of the gap is cardiometabolic natural-cause death, not suicide, and the gap has widened over time (Saha, Chant & McGrath 2007).

PEARL

The four numbers that carry every epidemiology viva on schizophrenia are: lifetime risk **~1%**, incidence **~15 per 100,000** per year, onset in the twenties (earlier in men), and a mortality gap of **15 to 20 years**. Attach a source to each and you have answered before the follow-up arrives.

Figure. The three frequency measures side by side, point prevalence against lifetime prevalence against incidence with their verified values and sources, plus the onset curve showing the earlier male peak, the later female peak and the female peri-menopausal second peak, is drawn as Fig 8.x.

3 · Genetics: heritability, twin and adoption data, CNVs and polygenic risk

Schizophrenia is among the most heritable of all common disorders, yet it obeys no Mendelian law. The examinable story is a layered one: a very high heritability established by family, twin and adoption designs, then a genetic architecture that is overwhelmingly **polygenic**, common and of small effect, studded with a handful of rare high-penetrance variants. **High heritability, but no single gene.** The commonest trap in vivas is to hunt for the schizophrenia gene when the correct answer is a distributed liability across thousands of loci plus a few large-effect exceptions (Sullivan et al. 2003, Owen et al. 2016).

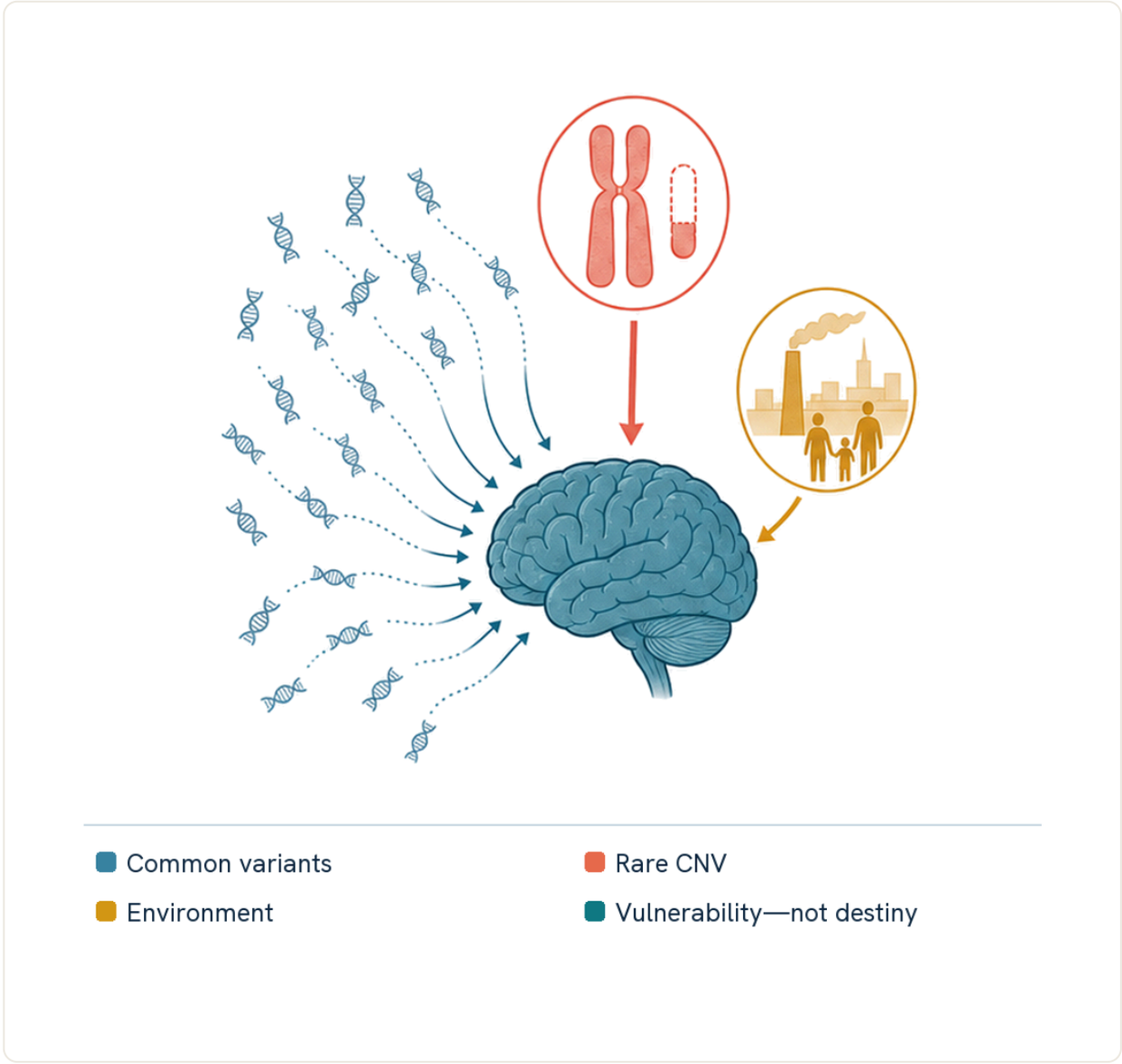


Fig 8.3 Polygenic liability in schizophrenia. Many common variants of small effect, occasional higher-impact copy-number variants and environmental exposures converge on neurodevelopmental vulnerability; none is individually deterministic.

The raw study designs, how family, twin and adoption methods actually separate genes from environment, are taught in the Psychiatric Genetics notes; here we apply them to schizophrenia and hold the numbers a resident must recite. The descriptive signs those relatives share (delusion, hallucination, first-rank symptom) are defined in the Psychometry, Assessment and Descriptive Psychopathology notes.

~80%	~40-50%	~10-15%	>100
HERITABILITY	MZ CONCORDANCE	DZ CONCORDANCE	GWAS RISK LOCI

3.1 Heritability: the strongest single risk factor is an affected relative

The headline figure. The heritability of schizophrenia is high, of the order of **~80%**; the Sullivan meta-analysis of twelve twin studies gave a point estimate of 0.81 for liability to schizophrenia (Sullivan et al. 2003). Heritability names the proportion of the variance in liability to the phenotype accounted for by additive genetic effects in that population, not the proportion of an individual's illness that is genetic. **What predicts risk.** Against a general-population lifetime risk of **~1%**, the single strongest risk factor a resident can name is having an affected **first-degree relative**: controlled family studies converge on an average relative risk near 9 to first-degree relatives (Tasman 2015). Population-register estimates run lower than twin estimates (about 64 percent in Lichtenstein et al. 2009), a discrepancy worth flagging but not fatal to the ~80 percent teaching figure.

RULE **Risk tracks genetic loading.** The more genes shared with an affected proband, the higher the risk: lowest in the general population, highest in the monozygotic co-twin and in the 22q11.2 deletion carrier.

3.2 Twin data: MZ versus DZ concordance

The pivotal comparison. Twin studies separate genes from environment by contrasting concordance in monozygotic (MZ) and dizygotic (DZ) pairs. For schizophrenia, MZ concordance is roughly **~40-50%** against DZ concordance of about **~10-15%** (Sullivan et al. 2003). A rough heritability estimate is twice the difference in concordance, which recovers the high figure above. **The two lessons in one datum.** MZ concordance well above DZ proves a large genetic contribution; MZ concordance well below 100 percent proves that genes are necessary but not sufficient, leaving room for environmental and stochastic (non-shared) influences. The twin method's assumptions (equal-environment, representativeness) are the province of the Psychiatric Genetics notes.

3.3 Adoption studies: separating genes from rearing

Why they matter. Twin and family studies cannot fully disentangle shared genes from shared rearing; adoption studies can, by studying children reared apart from their biological relatives. **Heston (1966).** The first adoption study of schizophrenia found significantly higher rates of schizophrenia in adults adopted away at birth from mothers with schizophrenia than in adoptees of unaffected parents, implying the excess risk is carried independently of the rearing environment (Heston 1966). **The Danish adoption studies.** Rosenthal, Wender and Kety extended this in a large Copenhagen and nationwide Danish sample, using adoptees' biological and adoptive relatives (and half-sibling designs to control the prenatal environment) to show that schizophrenia aggregated in the biological, not the adoptive, relatives (Kety et al. 1976, Rosenthal et al. 1971). Together they established, as close to unequivocally as this field allows, a substantial genetic component. The twin, family and adoption study methods themselves are taught in the Psychiatric Genetics notes.

WORKED EXAMPLE

A resident is asked why Heston's 1966 result cannot, by itself, prove the transmission is genetic rather than intrauterine. The answer: adopted-away offspring still shared the biological mother's prenatal environment. The half-sibling arm of the Danish adoption studies was designed precisely to control for that, and it still showed genetic aggregation.

3.4 Polygenic architecture: GWAS, small-effect common variants

The modern picture. After early linkage and single-**candidate gene** studies largely failed to replicate, well-powered genome-wide association studies (GWAS) reshaped the field. Large consortium GWAS have identified more than one hundred common genome-wide-significant risk loci (108 in the 2014 Psychiatric Genomics Consortium analysis, rising with sample size), each of individually tiny effect (Schizophrenia Working Group of the PGC 2014). **Common disease, common variant.** This is the polygenic model: susceptibility is spread across many common alleles of small effect that sum toward a threshold of liability. Common variants collectively explain a large share of heritability but no single one is diagnostic or necessary.

3.5 Polygenic risk score and the C4 / MHC signal

Aggregating the signal. The polygenic risk score (PRS) sums an individual's burden of risk alleles weighted by GWAS effect sizes. It shifts risk at the group level and is a powerful research tool, but its predictive value in any one patient is currently far too weak for clinical or diagnostic use. **The strongest single locus.** The most robust and largest common-variant signal sits in the major histocompatibility complex (MHC) region on chromosome 6. This was mechanistically resolved to structurally diverse alleles of the complement component 4 gene (C4): higher-expressing C4 alleles raise schizophrenia risk, plausibly through excessive complement-mediated synaptic pruning in adolescence (Sekar et al. 2016). This is the one common variant with a candidate mechanism worth naming in an exam.

TRAP **Never call any single gene causal.** C4, DISC1, NRG1 and the rest are risk contributors, not deterministic causes; treating one candidate gene as the cause of schizophrenia is a classic error.

3.6 Rare high-penetrance copy number variants and 22q11.2

The other end of the architecture. Alongside common small-effect variants sit rare copy number variants (**CNVs**): submicroscopic deletions or duplications, individually rare but of much larger effect and often arising de novo (Marshall et al. 2017). De novo cnv burden is enriched in schizophrenia, especially in sporadic cases, and several recurrent CNVs carry substantial risk. **The one to know: 22q11.2.** The recurrent microdeletion at 22q11.2, the basis of **velocardiofacial syndrome** (DiGeorge / 22q11.2 deletion syndrome), was the first de novo CNV described in schizophrenia (Karayiorgou et al. 1995). Up to about a third (around 25 to 30 percent) of deletion carriers develop a schizophrenia-spectrum psychosis by early adulthood, one of the highest known single-locus risks; conversely the deletion is found in roughly 1 to 2 percent of unselected schizophrenia cases (Murphy et al. 1999, Bassett & Chow 2008). Other high-risk CNVs include deletions at 1q21.1, 15q13.3 and NRXN1.

INDIA

22q11.2 deletion syndrome is under-recognised in Indian psychiatric practice; a young patient with psychosis plus congenital cardiac disease, cleft or velopharyngeal problems, hypocalcaemia, a nasal voice or learning difficulty warrants a low threshold for referral for genetic testing (FISH or microarray), where available.

3.7 Candidate genes and the shift to polygenic and CNV models

The historical layer. Before GWAS, the field pursued individual **candidate gene** hypotheses. The three most examined historical **risk gene** candidates were DISC1 (Disrupted-in-Schizophrenia 1), NRG1 (neuregulin 1) and DTNBP1 (dysbindin) (Owen et al. 2016). **Why they faded.** Most single candidate-gene associations failed robust replication in large samples; the field moved decisively to the two-tier model, common polygenic variation plus rare high-penetrance CNVs. Residents should present these three as historical candidates, not confirmed causal genes.

3.8 Gene-environment interaction

Genes are not destiny. Because MZ concordance is well under 100 percent, genetic liability interacts with environmental exposures rather than acting alone. Established environmental contributors (obstetric complications, cannabis use, urbanicity, migration) plausibly act on a genetically susceptible substrate, so that genetic loading raises the impact of a given exposure and vice versa. The dopamine and monoamine pathways through which these converge are covered in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes. The practical corollary: a positive family history sharpens vigilance for prodromal features but never fixes an individual's outcome.

HOLD THIS

Schizophrenia is ~80 percent heritable, MZ concordance ~40-50 percent versus DZ ~10-15 percent, driven by >100 common small-effect loci (polygenic, strongest signal C4/MHC) plus rare high-penetrance CNVs, above all the 22q11.2 deletion, in which about one third of carriers develop psychosis.

GOOD TO REMEMBER

- **Heritability ~80%:** proportion of population liability variance from additive genes (Sullivan 0.81); discriminator is that the single strongest risk factor is an affected first-degree relative (relative risk ~9), not any one gene.
- **Twin concordance:** MZ ~40-50% versus DZ ~10-15%; discriminator is that MZ well above DZ proves genes matter, while MZ well below 100% proves genes are necessary but not sufficient.
- **Heston (1966):** first schizophrenia adoption study, higher rates in adopted-away offspring of affected mothers; discriminator is that it separated genes from rearing but not from the prenatal environment.
- **Danish adoption studies (Kety, Rosenthal, Wender):** aggregation in biological not adoptive relatives; discriminator is the half-sibling design controlling the prenatal environment.
- **Polygenic / GWAS:** >100 common risk loci of small effect summed as a polygenic risk score; discriminator is that PRS shifts group risk but does not diagnose an individual.
- **C4 / MHC:** strongest single common-variant signal (chromosome 6); discriminator is the candidate mechanism of excess complement-mediated synaptic pruning (Sekar 2016).
- **22q11.2 deletion (velocardiofacial):** first de novo CNV in schizophrenia, high-penetrance; discriminator is that ~1/3 of carriers develop psychosis and it is found in ~1-2% of schizophrenia cases.
- **Candidate genes DISC1, NRG1, DTNBP1:** historical single-gene hypotheses; discriminator is that most failed robust replication, prompting the shift to polygenic + CNV models.

4 · The dopamine hypothesis and aberrant salience

No idea in schizophrenia is examined more often than the dopamine hypothesis, and none has been revised more radically. The examinable story is generational: an **original** hypothesis of global dopamine excess, argued backwards from drugs; a **pathway** refinement that localised the excess and explained why one drug helps positive but not negative symptoms; a **regional** hypothesis of striatal excess with prefrontal deficit; and finally aberrant salience, which converts a neurochemical fact into a phenomenological account of what a delusion actually is (Howes & Kapur 2009, Kapur 2003). **One molecule, four hypotheses, and a bridge to phenomenology.** The commonest viva error is to recite the original excess model as though it were current, when the field long ago moved to a regional, salience-based reading.

This topic applies the neurochemistry to schizophrenia and its symptoms; the mechanics of how the dopamine tracts run and how antipsychotics act on them are developed in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes, and the descriptive definitions of the delusion and the hallucination it explains are set out in the Psychometry, Assessment and Descriptive Psychopathology notes. Treatment itself, antipsychotics and their adverse effects, points forward to the Schizophrenia: management, antipsychotics and adverse effects notes.

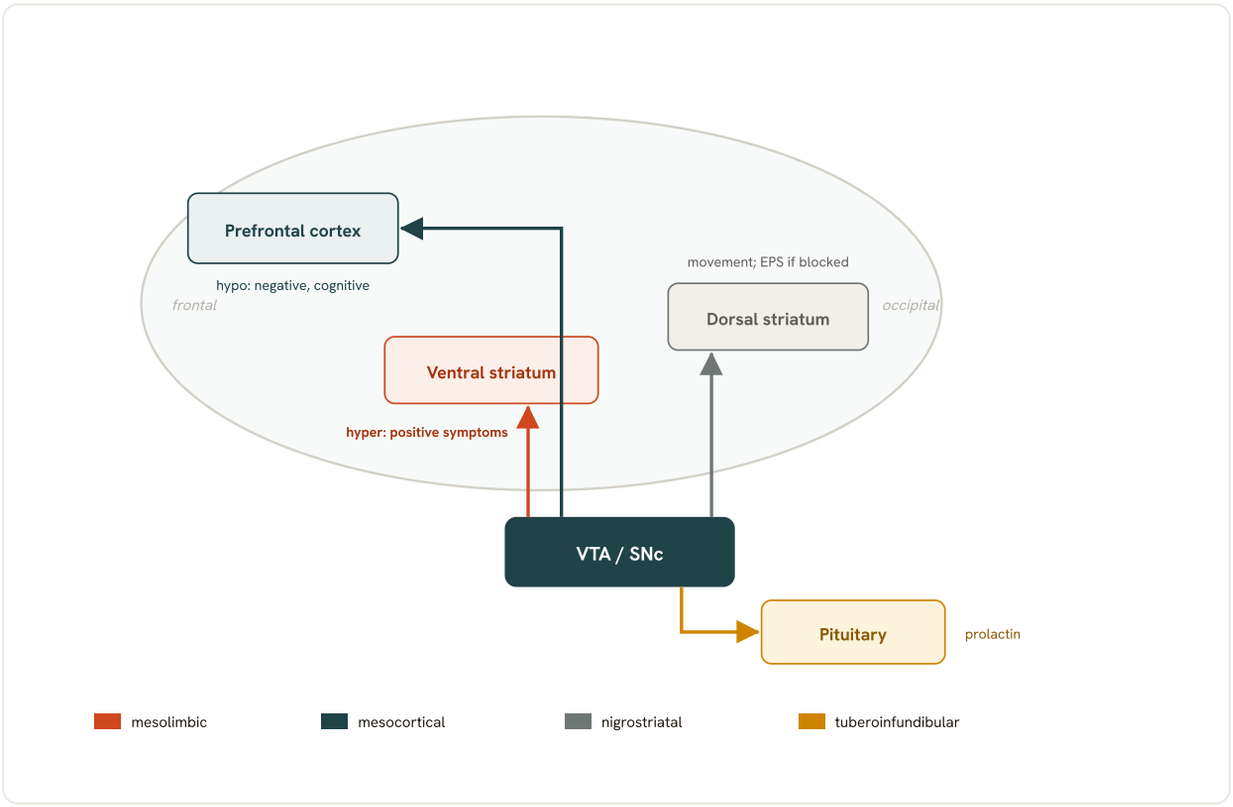


Fig 8.4 The four dopamine pathways on a schematic sagittal brain, colour-coded in the legend. The revised hypothesis is regional: the mesolimbic tract to the ventral striatum is overactive and drives the positive symptoms, while the mesocortical tract to the prefrontal cortex is underactive and underlies the negative and cognitive symptoms. The nigrostriatal and tuberoinfundibular tracts explain the movement and prolactin effects seen once dopamine is blocked.

4.1 The original hypothesis: dopamine excess and D2 overactivity

The claim. The original dopamine hypothesis held that psychosis arises from excess dopaminergic transmission, specifically overactivity at the dopamine D2 receptor (Kaplan & Sadock 2024). **The two pillars of evidence.** First, drugs that raise synaptic dopamine, above all amphetamine, can produce a paranoid psychosis in healthy people (**amphetamine psychosis**) and worsen established schizophrenia. Second, and more decisively, the clinical antipsychotic potency of the classical drugs correlates closely with their affinity for and blockade of the **D2 receptor**: the tighter a drug binds D2, the lower its effective dose (Seeman et al. 1976, Creese et al. 1976). **Why it was necessary but not sufficient.** The model explained why D2 blockade treats hallucinations and delusions, but never accounted for the negative and cognitive symptoms, and post-mortem D2 upregulation was confounded by prior antipsychotic exposure.

RULE **Potency tracks D2 affinity.** Antipsychotic clinical potency correlates with D2 receptor blockade, and dopamine-releasing drugs like amphetamine are psychotogenic, the twin observations that founded the hypothesis.

4.2 The four dopamine pathways

Localising the molecule. A global excess model could not stand once the anatomy was mapped: dopamine runs in four distinct dopamine pathways, and only some are dysregulated in schizophrenia while others explain the side effects of blocking dopamine indiscriminately (Stahl 2021). The four are the mesolimbic, the mesocortical, the nigrostriatal and the

tuberoinfundibular pathways. The projection anatomy and receptor pharmacology of each are drawn out in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; here we hold what each does and what its dysregulation produces.

PATHWAY	ROUTE	NORMAL FUNCTION	DYSREGULATION
Mesolimbic	VTA to ventral striatum / nucleus accumbens	Reward, salience, motivation	**Hyperactivity drives positive symptoms**
Mesocortical	VTA to prefrontal cortex	Cognition, executive function, affect	**Hypoactivity drives negative and cognitive symptoms**
Nigrostriatal	Substantia nigra to dorsal striatum	Motor control	D2 blockade here causes EPS and tardive dyskinesia
Tuberoinfundibular	Hypothalamus to anterior pituitary	Tonic inhibition of prolactin	D2 blockade here causes hyperprolactinaemia

The four dopamine pathways: only two carry the disease signal in schizophrenia; the other two explain the motor and endocrine costs of blocking dopamine non-selectively.

4.3 Mesolimbic hyperdopaminergia and the positive symptoms

The positive-symptom pathway. The core symptom correlation is that mesolimbic hyperdopaminergia, excess dopamine transmission in the mesolimbic projection to the ventral striatum, drives the positive symptoms of psychosis: delusions, hallucinations and thought disorder (Stahl 2021). Stahl frames this as the classic dopamine hypothesis of the positive symptoms of psychosis. **Why D2 blockade works.** Antipsychotics reduce positive symptoms precisely because they block D2 receptors in this overactive mesolimbic pathway, which is also why in-vivo PET and SPECT work shows elevated striatal dopamine synthesis and release in drug-naive patients and after amphetamine challenge (Kaplan & Sadock 2024). The raw descriptive definitions of these positive-symptom signs belong to the Psychometry, Assessment and Descriptive Psychopathology notes.

4.4 Mesocortical hypodopaminergia and the negative and cognitive symptoms

The corollary pathway. The mesocortical projection to the prefrontal cortex shows the opposite deficit: mesocortical hypodopaminergia, a deficient dopamine tone in the prefrontal cortex, underlies the negative symptoms (blunting, avolition, asociality) and the cognitive symptoms (Stahl 2021). Stahl frames this as the corollary to the classic hypothesis, mesocortical hypodopaminergia driving the cognitive, negative and affective symptoms. **The clinical sting.** Because these symptoms reflect too little dopamine in the cortex, D2 blockade cannot correct them and, by further reducing an already low mesocortical tone, may worsen them (the neuroleptic-induced deficit syndrome). This asymmetry, one pathway too high, the other too low, is the single most examinable feature of the pathway model.

TRAP **D2 blockade is not a cure-all.** Blocking D2 treats the positive symptoms but does not treat the negative or cognitive symptoms, which stem from mesocortical hypofunction, not mesolimbic excess.

4.5 The revised regional hypothesis: striatal excess, prefrontal deficit

The third generation. The revised regional hypothesis fused the pathway data into a single spatial statement: schizophrenia is characterised by **striatal hyperdopaminergia** together with **prefrontal hypodopaminergia**, rather than a uniform whole-brain excess (Davis et al. 1991, Howes & Kapur 2009). Davis, Kahn and colleagues first proposed this regional reformulation; Howes and Kapur then set it out as the definitive version, locating the abnormality at the level of presynaptic dopamine dysregulation in the striatum. **Why it matters.** The regional model reconciles the paradox of the pathway account: it explains simultaneously why raising dopamine (amphetamine) worsens positive symptoms, why blocking striatal D2 treats them, and why a prefrontal deficit leaves negative and cognitive symptoms untouched by D2 antagonism.

4.6 Aberrant salience: dopamine, meaning and the making of a delusion

Kapur's reframe. The fourth generation, aberrant salience, is the conceptual leap that links neurobiology to phenomenology (Kapur 2003). Kapur observed that mesolimbic dopamine normally assigns **salience**, converting a neutral mental representation into one that grabs the attention of the individual. **The mechanism.** In psychosis, dysregulated striatal dopamine fires independently of context and assigns undue salience to neutral, insignificant stimuli, thoughts and percepts: an unremarkable car, a passing glance or a stray idea becomes charged with unearned significance (the prodromal delusional mood). **Delusions as explanation.** Kapur's crucial move is that delusions and hallucinations are not the primary lesion but the patient's cognitive effort to explain that aberrant salience, a top-down narrative built to make sense of experiences that feel urgently meaningful (Kapur 2003, Kaplan & Sadock 2024). **Why it unifies the field.** This reframes psychosis as a disorder of salience: it recasts delusion formation as prediction error and salience misattribution, and it explains why antipsychotics dampen the conviction and preoccupation (they blunt the salience) without instantly erasing the belief itself.

PEARL

The aberrant salience model reframes the antipsychotic response phenomenologically: patients often report not that the delusion vanished but that it stopped mattering, that it receded and lost its grip. That is D2 blockade turning down the dopaminergic salience signal, exactly what the model predicts.

HOLD THIS

Mesolimbic (striatal) hyperdopaminergia drives the positive symptoms and is treated by D2 blockade; mesocortical (prefrontal) hypodopaminergia drives the negative and cognitive symptoms and is not; and aberrant salience (Kapur) explains delusions and hallucinations as the mind's effort to account for undue salience assigned by dysregulated striatal dopamine.

GOOD TO REMEMBER

- **Original dopamine hypothesis:** psychosis reflects dopamine excess / D2 overactivity; central claim rests on amphetamine psychosis plus the correlation of antipsychotic potency with D2 blockade; discriminator is that it never explained the negative or cognitive symptoms.
- **Mesolimbic pathway:** VTA to ventral striatum, subserves salience and reward; central claim is that mesolimbic hyperdopaminergia drives the positive symptoms; discriminator is that it is the pathway D2 blockade acts on to treat them.
- **Mesocortical pathway:** VTA to prefrontal cortex, subserves cognition and affect; central claim is that mesocortical hypodopaminergia drives the negative and cognitive symptoms; discriminator is that D2 blockade cannot treat and may worsen them.
- **Nigrostriatal pathway:** substantia nigra to dorsal striatum, subserves motor control; not primarily diseased in schizophrenia; discriminator is that blocking D2 here causes EPS and tardive dyskinesia.
- **Tuberoinfundibular pathway:** hypothalamus to pituitary, tonically inhibits prolactin; not primarily diseased in schizophrenia; discriminator is that blocking D2 here causes hyperprolactinaemia.
- **Revised regional hypothesis (Davis, Howes & Kapur):** striatal hyperdopaminergia with prefrontal hypodopaminergia, not a global excess; discriminator is the localisation to presynaptic striatal dopamine dysregulation.
- **Aberrant salience (Kapur 2003):** dysregulated striatal dopamine assigns undue salience to neutral stimuli; central claim is that delusions and hallucinations are the cognitive effort to explain that salience; discriminator is that it reframes psychosis as a disorder of salience and links neurobiology to phenomenology.

5 · Glutamate, GABA and the other transmitter systems

The dopamine hypothesis is the historical spine of schizophrenia neurochemistry, but on its own it fails a decisive test: amphetamine, which drives dopamine, reproduces only the positive symptoms, and antipsychotics that block **D2 receptors** barely touch the negative and cognitive burden that carries most of the long-term disability. This topic is the set of transmitter systems that step in where dopamine stops, and the examinable heart of it is the **glutamate hypothesis**. The dopamine and monoamine pathways themselves, and the neuroimaging methods behind these findings, belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes; here the systems are applied specifically to schizophrenia.

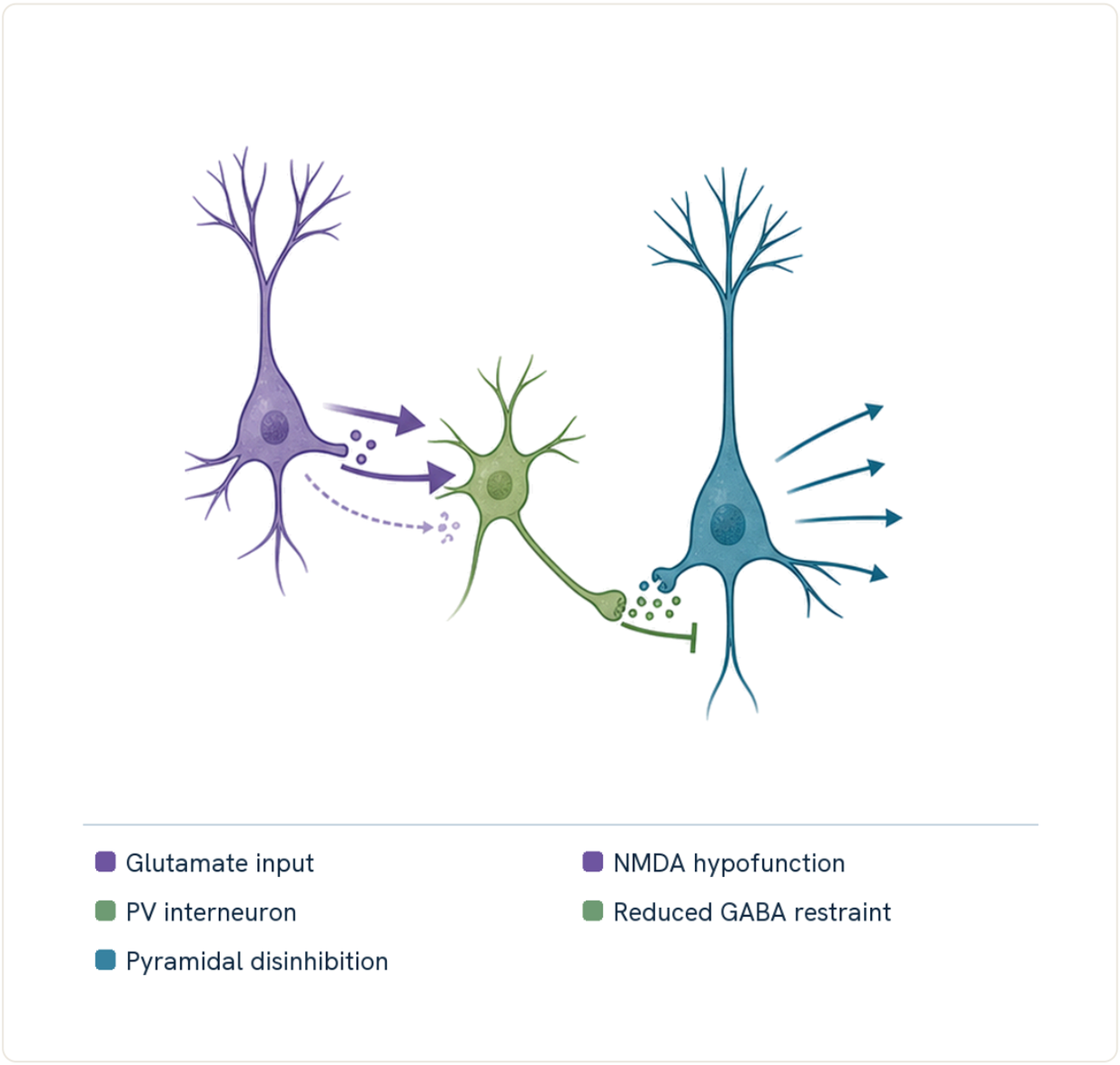


Fig 8.5 A simplified NMDA-GABA cortical microcircuit. Reduced NMDA drive to a parvalbumin interneuron weakens inhibitory restraint and leaves pyramidal output relatively disinhibited.

How to hold this. Anchor everything to one causal chain: an **NMDA receptor** that is underactive on inhibitory interneurons disinhibits downstream circuits, and from that single lesion the positive, negative and cognitive symptoms all follow, together with the GABA and dopamine changes seen in imaging. Then hang the other four systems (GABA, serotonin, acetylcholine, neuroinflammation) off that spine. The examiner's favourite move is to ask why the glutamate model beats a pure dopamine account, and the answer is always the same: the drug models. What antipsychotics reach forward into treatment, and the receptor-binding basis of the atypicals, is developed in the Schizophrenia: management, antipsychotics and adverse effects notes.

5.1 The glutamate hypothesis: NMDA receptor hypofunction as the core lesion

The central claim. The glutamate hypothesis holds that schizophrenia arises from underactivity of glutamatergic signalling at the NMDA receptor, the calcium-permeable ionotropic glutamate receptor gated jointly by glutamate and glycine and by voltage. The specific proposition is NMDA receptor hypofunction: the receptor is not fully blocked but functionally underactive, and critically the deficit is located on inhibitory neurons, not on the excitatory pyramidal cells

(Tasman 2015). Because glutamate is the brain's principal excitatory transmitter, a hypofunctioning NMDA receptor on an inhibitory interneuron removes a brake, and the net effect downstream is disinhibition and dysregulated cortical and subcortical firing rather than a simple loss of excitation.

Why hypofunction on interneurons, not pyramidal cells. The NMDA receptors that matter sit preferentially on GABAergic interneurons, in particular the fast-spiking parvalbumin cells (developed in 5.3). When their NMDA drive falls, they release less GABA, the pyramidal neurons they normally restrain fire excessively, and glutamate is released in an uncontrolled, noisy fashion in terminal regions. This reframes the illness as one of disinhibition and lost signal-to-noise, and it explains why a hypofunction hypothesis can paradoxically produce cortical hyperexcitability. Downstream, this same interneuron lesion dysregulates the mesolimbic and mesocortical dopamine systems, so the dopamine abnormalities are recast as a consequence of glutamatergic pathology rather than its cause (Tasman 2015).

HOLD THIS

The glutamate hypothesis is NMDA receptor hypofunction on GABAergic (parvalbumin) interneurons; the resulting disinhibition drives the positive, negative and cognitive symptoms and dysregulates dopamine downstream, which is why it explains what a pure dopamine account cannot.

5.2 The ketamine and PCP model: the strongest challenge to a pure dopamine account

The drug argument. The evidence that lifts NMDA hypofunction from hypothesis to leading model is pharmacological. The dissociative anaesthetics ketamine and phencyclidine are non-competitive NMDA-receptor antagonists that block the open channel, and in healthy volunteers a single subanaesthetic dose reproduces a strikingly complete schizophrenia-like state (Krystal et al. 1994). The point that wins exam marks is the breadth of what it reproduces. Phencyclidine (PCP, "angel dust") and ketamine produce positive symptoms (delusion-like ideas, hallucinations), negative symptoms (blunting, withdrawal) and cognitive impairment (deficits in working memory and executive function), and they even reproduce the electrophysiological endophenotypes of the illness, blunting mismatch negativity and P50 auditory gating after a single administration (Umbricht et al. 2000).

The contrast with amphetamine. Set the NMDA-antagonist psychosis against the classic dopamine-agonist psychosis. Amphetamine, which floods the synapse with dopamine, reproduces the positive symptoms and can precipitate a paranoid psychosis, but it does not reproduce the negative or cognitive syndrome. The dissociative anaesthetics do all three domains. That single dissociation is the strongest challenge to a purely dopaminergic account of schizophrenia: if dopamine excess were the whole story, a dopamine agonist should model the whole illness, and it does not (Kaplan & Sadock 2024). A further supporting strand is genetic: several risk genes converge on the NMDA receptor or glutamatergic transmission, and the metabotropic glutamate receptor gene GRM3 regulates glial glutamate transporters (Tasman 2015).

DRUG MODEL	ACTS ON	POSITIVE SYMPTOMS	NEGATIVE SYMPTOMS	COGNITIVE SYMPTOMS
Amphetamine	Dopamine release (agonist)	Yes	No	**No**
Ketamine / PCP (phencyclidine)	NMDA receptor block (antagonist)	Yes	Yes	**Yes, plus MMN and P50 gating deficits**
LSD / psilocybin	5-HT2A agonist	Mainly (visual) hallucinations	No	**No**

The three pharmacological psychosis models; the discriminator is that only the NMDA antagonists reproduce the negative and cognitive symptoms, which is why the ketamine model is the strongest evidence against a pure dopamine account.

RULE **The ketamine model does what dopamine cannot.** NMDA antagonists reproduce positive AND negative AND cognitive symptoms in healthy volunteers; amphetamine reproduces only positive symptoms, which is the single strongest argument that schizophrenia is more than a dopamine disorder.

TRAP **Treating glutamate and dopamine as rival hypotheses.** They are complementary, not competing: NMDA hypofunction on interneurons is upstream and dysregulates dopamine downstream, so the modern account is one integrated glutamate-dopamine circuit, not a contest between two theories.

5.3 GABA: the parvalbumin fast-spiking interneuron deficit

The GABAergic lesion. The inhibitory arm of the glutamate story is a specific and highly consistent GABA abnormality. Postmortem dorsolateral prefrontal cortex shows reduced expression of GAD67, the 67 kDa isoform of glutamic acid decarboxylase and the rate-limiting enzyme for GABA synthesis, and the deficit falls selectively on the parvalbumin interneuron, the fast-spiking cell that provides feedforward inhibition onto pyramidal neurons (Lewis et al. 2005; Lewis et al. 2012). Because NMDA antagonists reproduce exactly this parvalbumin-selective GABA change in animals, the field reads the GABA deficit as a downstream consequence of NMDA hypofunction rather than an independent lesion (Lewis & Gonzalez-Burgos 2006).

Why it matters for cognition: gamma oscillations. Parvalbumin fast-spiking cells are the pacemakers of gamma oscillations, the roughly 30 to 80 Hz synchrony that binds distributed cortical activity and underpins working memory and attention. Lose parvalbumin inhibition and gamma synchrony degrades, which maps neatly onto the cognitive impairment of schizophrenia and gives the negative-and-cognitive domain a concrete circuit mechanism. This is the mechanistic bridge from a molecular deficit to the functional disability, and it is why the GABA-parvalbumin story is asked alongside cognition.

5.4 Serotonin: the 5-HT2A receptor and the psychedelic model

The historical argument. A role for serotonin (5-hydroxytryptamine) was first proposed on the structural resemblance between serotonin and the hallucinogen LSD (Gaddum 1954). LSD, mescaline and psilocybin were later shown to be serotonin agonists, and their psychotomimetic effect is driven predominantly by agonism at the 5-HT2A receptor (Gresch et al. 2002). The

model is imperfect: psychedelics produce mainly visual hallucinations, whereas schizophrenic hallucinations are characteristically auditory, so this is a model of a fragment of the illness, not the whole.

Why it survives: the atypical antipsychotics. The serotonin hypothesis earns its keep through treatment. Excitatory 5-HT2A and inhibitory 5-HT1A receptors sit on cortical glutamatergic pyramidal cells and on GABAergic interneurons, so serotonin modulates the very glutamate circuits at the centre of the illness. Clozapine and the other second-generation ("atypical") agents combine potent 5-HT2A antagonism with relatively lower-potency D2 blockade, and it is this serotonin-dopamine profile, rather than D2 blockade alone, that is thought to underlie their broader effect and lower extrapyramidal burden. The receptor-binding pharmacology of the atypicals is developed in the Schizophrenia: management, antipsychotics and adverse effects notes.

5.5 Acetylcholine: nicotinic, muscarinic, and the smoking question

Two receptor families. Acetylcholine is implicated through both of its receptor classes: the ionotropic nicotinic receptor (nAChR) and the metabotropic muscarinic receptor (mAChR). Patients show abnormal expression of central nicotinic receptors, with the alpha-7 and alpha-4-beta-2 subtypes most implicated; the alpha-7 receptor is tied specifically to the P50 auditory sensory-gating deficit seen in patients and their first-degree relatives, which makes it an endophenotype marker as much as a treatment target (Tasman 2015). The muscarinic system is separately implicated, with reduced muscarinic receptor density reported in postmortem tissue.

Smoking as possible self-medication. People with schizophrenia smoke at a strikingly high rate, far above the general population, and one reading is **self-medication**: nicotine transiently normalises the alpha-7-dependent P50 sensory-gating deficit and may briefly sharpen attention, so heavy smoking may be an attempt to correct a cholinergic abnormality. This sets up the cholinergic and muscarinic treatment targets, an approach developed further in the cognition topic and in the Schizophrenia: management, antipsychotics and adverse effects notes; the recent arrival of muscarinic-agonist antipsychotics has made this system newly examinable.

> **PEARL**
>
> The alpha-7 nicotinic receptor is the thread that ties three exam facts together: the P50 auditory-gating deficit (an endophenotype found in unaffected relatives), the high smoking rate read as self-medication, and the cholinergic treatment target. One receptor, three questions.

5.6 Neuroinflammation: microglial activation and the kynurenine pathway

The immune strand. A newer body of work frames schizophrenia partly as a disorder of neuroinflammation. PET studies using TSPO ligands and postmortem work show microglial activation in the same regions that show grey-matter loss, and maternal immune activation in pregnancy is an established environmental risk factor, linking the immune hypothesis back to the neurodevelopmental account (Kaplan & Sadock 2024). Activated microglia are the resident

immune cells of the brain, and their over-activation is proposed to prune synapses excessively and to shift neurochemistry through inflammatory signalling.

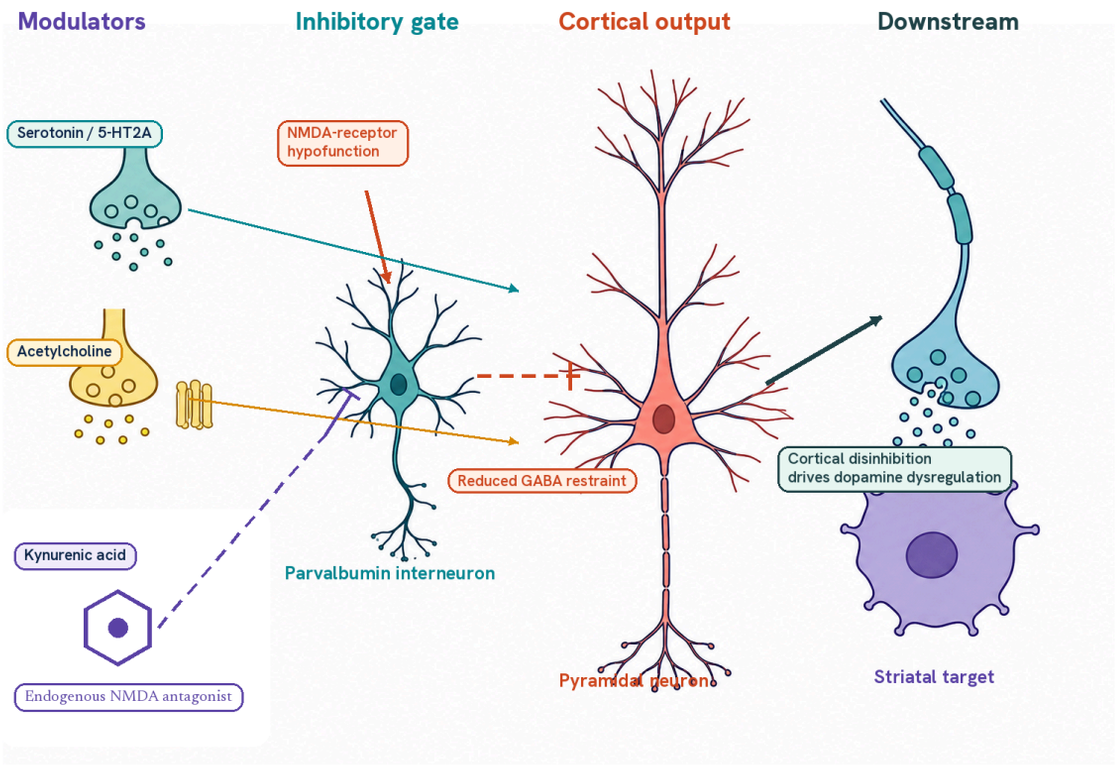


Fig 8.6 An integrated cortical circuit for schizophrenia. NMDA-receptor hypofunction on a parvalbumin interneuron reduces GABA restraint on a pyramidal neuron, producing cortical disinhibition and downstream dopamine dysregulation; serotonin, acetylcholine and kynurenic acid modulate the circuit.

The kynurenine link back to glutamate. The mechanistic bridge that makes neuroinflammation examinable alongside the glutamate hypothesis is the kynurenine pathway. Pro-inflammatory cytokines induce indoleamine 2,3-dioxygenase (IDO), which diverts tryptophan down the kynurenine pathway (Kaplan & Sadock 2024). One kynurenine metabolite, kynurenic acid, is an endogenous NMDA-receptor antagonist: raised brain kynurenic acid is reported in schizophrenia and would itself produce NMDA hypofunction. So the inflammatory strand does not sit apart from the glutamate hypothesis; through kynurenic acid it feeds directly into it, giving one plausible route by which an immune insult becomes an NMDA-hypofunction state.

COMMON TRAP

Do not present neuroinflammation as a fifth independent theory competing with dopamine and glutamate. Its examinable value is precisely that it converges on the glutamate hypothesis: cytokines to IDO to kynurenic acid to NMDA-receptor antagonism. State the convergence, not a list of rivals.

MNEMONIC

"GABA-SAN", the beyond-dopamine systems: Glutamate (NMDA), GABA, Serotonin, Acetylcholine, Neuroinflammation.

Glutamate: NMDA hypofunction on interneurons, argued from ketamine and PCP. **GABA**: parvalbumin fast-spiking cell deficit (low GAD67), degrades gamma oscillations and cognition. **S**erotonin: 5-HT2A and the LSD model, the basis of the atypicals. **A**cetylcholine: alpha-7 nicotinic (P50 gating, smoking self-medication) and muscarinic targets. **N**euroinflammation: microglial activation and kynurenic acid feeding back into NMDA hypofunction.

GOOD TO REMEMBER

- **Glutamate hypothesis:** schizophrenia as NMDA receptor hypofunction on inhibitory interneurons, causing disinhibition; central claim is that glutamate pathology is upstream of and dysregulates dopamine; the discriminator is that it explains negative and cognitive symptoms that dopamine alone cannot.
- **Ketamine / PCP (phencyclidine) model:** non-competitive NMDA antagonists reproduce a full schizophrenia-like state in healthy volunteers; core claim is that they reproduce positive, negative AND cognitive symptoms plus MMN/P50 deficits; the discriminator versus amphetamine is that amphetamine reproduces only positive symptoms.
- **GABA / parvalbumin deficit:** reduced GAD67 in DLPFC, selective to parvalbumin fast-spiking interneurons; central link is to gamma oscillations and cognition; the discriminator is that it is read as downstream of NMDA hypofunction, not an independent lesion.
- **Serotonin / 5-HT2A:** proposed from the LSD-serotonin structural similarity, psychedelic effect is 5-HT2A agonism; central relevance is that atypical antipsychotics are potent 5-HT2A antagonists; the discriminator is that psychedelics give mainly visual (not the auditory) hallucinations, so it models only a fragment.
- **Acetylcholine:** nicotinic (alpha-7, alpha-4-beta-2) and muscarinic abnormalities; central facts are the alpha-7 link to P50 gating and the high smoking rate read as self-medication; the discriminator is that alpha-7 ties the endophenotype, the smoking and the cholinergic treatment target together.
- **Neuroinflammation:** microglial activation (TSPO PET, maternal immune activation) and the kynurenine pathway; central claim is that inflammation raises kynurenic acid, an endogenous NMDA antagonist; the discriminator is that it converges on, rather than competes with, the glutamate hypothesis.

Figure. The integrated circuit, NMDA hypofunction on a parvalbumin interneuron disinhibiting a pyramidal cell, with dopamine dysregulation downstream and serotonin, acetylcholine and kynurenic acid as modulators feeding in, is drawn as Fig 8.x.

6 · The neurodevelopmental model and environmental risk

Schizophrenia is now framed as a disorder of **brain development** whose seed is sown long before the first psychotic symptom appears. The high heritability established by twin and adoption work (see "the Psychiatric Genetics notes") does not by itself explain onset: genes set a liability, but a cascade of early and later environmental hits determines who crosses the threshold and when. This topic organises that cascade into two explanatory frameworks, the **neurodevelopmental hypothesis** and the **two-hit** model, and then walks through the

individual risk exposures, early (obstetric, infective, seasonal) and late (cannabis, urban, migratory, familial), that examiners test one by one.

Why it matters. This is the single most heavily examined aetiology block in the schizophrenia paper. The favourite traps are causal ones: mistaking an association (low social class, urban residence) for a cause, and forgetting that most exposures act only on a genetically primed brain. Hold the odds ratios, the eponymous cohorts, and the two-hit logic, and you can answer almost any stem.

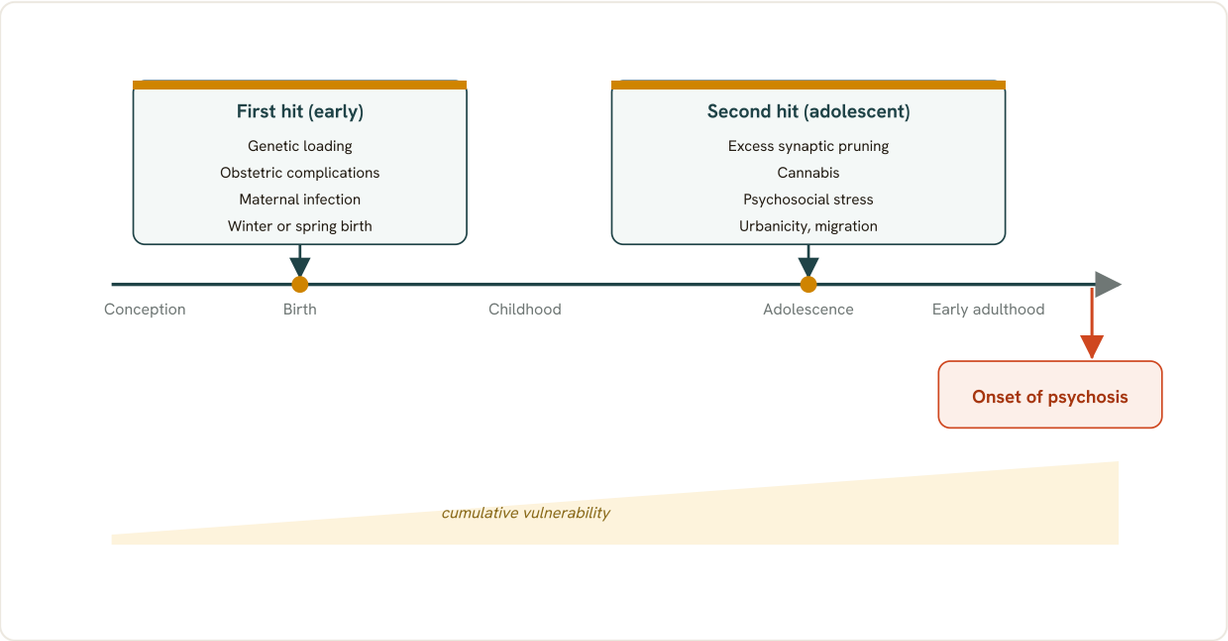


Fig 8.7 The neurodevelopmental two-hit model across the lifespan. An early first hit, genetic and prenatal, primes the vulnerability, which then accumulates until an adolescent second hit, synaptic and psychosocial, precipitates the onset of psychosis as the affected circuits mature. Neither hit alone is usually sufficient; the illness emerges from their convergence on a developing brain.

6.1 The neurodevelopmental hypothesis: an early static lesion

Core claim. The neurodevelopmental hypothesis (Weinberger 1987; Murray & Lewis 1987), also called the developmental hypothesis, proposes that schizophrenia originates in a fixed, early lesion of brain development (a disturbance of neuronal migration, connectivity and pruning arising in utero or early life) that lies clinically silent for years. The affected fronto-temporal and limbic circuits are not yet functionally loaded in childhood; only when they normally come online in late adolescence and early adulthood does the latent abnormality express itself as psychosis. This is why onset clusters in the late teens to twenties despite a lesion laid down before birth.

The gliosis argument. The strongest structural support is a negative finding: the modest brain changes of schizophrenia (ventricular enlargement, reduced cortical and hippocampal volume) occur *without* reactive gliosis, the astrocytic scarring that marks any acquired or degenerative lesion after roughly the second trimester. Absent gliosis points to an early developmental (organisational) origin rather than a neurodegenerative one, and it distinguishes schizophrenia from a dementing process. The neuroimaging and gliosis evidence is developed in "the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes".

RULE **Static, not progressive.** An early fixed lesion expressed at circuit maturation, and the absence of gliosis is the histological signature that it is developmental, not degenerative.

6.2 The two-hit model: first hit plus second hit

Central logic. The two-hit model (a "two hit" or two hit account) reconciles the early lesion with adolescent onset. The **first hit** is the early priming: genetic liability plus an early neurodevelopmental insult (obstetric, infective, nutritional) that leaves a vulnerable but compensated brain. The **second hit** arrives in adolescence, when physiological synaptic pruning strips cortical connections and psychosocial or substance stressors are superimposed; on an already-primed substrate this tips the system past threshold into frank psychosis.

Pruning as the trigger. Normal adolescent synaptic pruning, if excessive on a primed brain, is the mechanistic candidate for the second hit; complement C4 (implicated in microglial synaptic pruning) gives this a molecular anchor (Sekar et al 2016). The model explains both the premorbid trait markers of childhood and the sharp adolescent inflection.

HOLD THIS

Two-hit: hit one is genes plus early neurodevelopmental insult (a primed brain); hit two is adolescent synaptic pruning plus psychosocial or substance stress; onset is where the two meet.

6.3 Early risk: obstetric complications

What they are. An obstetric complication is any antenatal, perinatal or neonatal adverse event (antepartum haemorrhage, pre-eclampsia, gestational diabetes, hypoxia or asphyxia, low birth weight, Rhesus incompatibility, emergency section). Meta-analysis puts the pooled effect sizes generally below 2 (Cannon et al 2002), and the effect is amplified in those already carrying genetic liability (Nicodemus et al 2008), a clean gene-environment interaction. Fetal hypoxia is the leading proposed mechanism.

TRAP **Association, not necessarily cause.** An obstetric complication may be directly causal (hypoxia), or merely mark a pre-existing fetal abnormality, or reflect maternal characteristics, so do not report the odds ratio as proof of causation.

6.4 Early risk: maternal infection and malnutrition

Maternal infection. Second-trimester maternal infection is a candidate exposure, historically anchored to the 1957 influenza A2 pandemic, with later associations for toxoplasmosis, herpes simplex virus 2 and rubella. The evidence is inconsistent (a meta-analysis of the 1957 pandemic was negative, Selten et al 2010), and the modern reading is that maternal immune activation and inflammation, rather than a specific pathogen, prime the fetal brain (Cannon et al 2014).

Maternal malnutrition. Prenatal famine roughly doubles risk (odds ratio about 2), first shown in the Dutch Hunger Winter of 1944 and replicated in two Chinese famine cohorts; the proposed mechanism is epigenetic, with altered DNA methylation in exposed offspring (Kirkbride et al 2012).

6.5 Early risk: season of birth

The finding. A robust, replicated excess of winter and spring births exists among people who later develop schizophrenia, the season of birth effect. The excess is small (of the order of 5 to 10 per cent) but consistent across Northern Hemisphere studies, with the mirror pattern in the Southern Hemisphere. It is usually read as an indirect fingerprint of a seasonal early exposure, most plausibly second-trimester maternal viral infection or a nutritional or vitamin D factor, converging with 6.4.

> **PEARL**
> Season of birth is not itself a cause; it is a proxy that points to a seasonally varying prenatal exposure. Winter and spring births carry the excess in the Northern Hemisphere.

6.6 Later risk: cannabis as a component cause

The evidence. Prospective data make cannabis the best-established modifiable later exposure. The landmark Swedish conscript cohort found a relative risk of about 2.5 for schizophrenia in cannabis users, rising roughly sixfold in the heaviest users (Andreasson et al 1987); subsequent longitudinal studies give a pooled odds ratio of about 2, and cannabis use brings forward the age of onset (Large et al 2011). The risk is dose-dependent, greater with adolescent-onset use, and steepest with high-potency preparations (high delta-9-THC, low cannabidiol).

How to phrase it. Cannabis is neither necessary nor sufficient; it is a *component cause* that raises risk in the vulnerable, interacting with genotype (for example COMT, Caspi et al 2005). Cannabidiol content and route of onset matter, which is why high-potency and early-adolescent use dominate the risk.

RULE **Cannabis is a dose- and age-dependent component cause of psychosis.** Highest risk with heavy, adolescent-onset, high-potency use; it advances onset and interacts with genetic liability.

6.7 Later risk: urbanicity, migration and minority status

Urbanicity. Urbanicity shows a dose-response gradient: psychosis risk rises linearly with degree of urban birth and upbringing (odds ratio about 1.57; van Os et al 2003), independent of age, sex, education and family psychiatric history, and the urban effect is greater in those with a family history, again a gene-environment interaction.

Migration and minority status. Migration and ethnic-minority status carry a marked excess; in the UK AESOP first-onset study the relative risk for all psychoses was 6.7 in the Afro-Caribbean and 1.5 in the Asian population versus the white population (Fearon et al 2006), and the excess is often greatest in the second generation, arguing for social rather than purely biological mechanisms. Low ethnic density (being a small minority locally) more than doubles risk, pointing to social defeat, chronic discrimination and exclusion rather than selective migration alone.

INDIA

Indian teaching describes the "hemp insanity" or cannabis psychosis (Dhunjibhoy 1930) in heavy cannabis-using populations, where florid psychotic symptoms followed unusually heavy use and remitted with abstinence. Useful as an early Indian description of the cannabis-psychosis link, distinct from primary schizophrenia.

6.8 Later risk: childhood adversity and expressed emotion

Childhood adversity. Childhood trauma, abuse and neglect are dose-dependently associated with adult psychosis and form part of the **psychosocial risk** load that acts as a second hit on a primed brain.

Expressed emotion. Expressed emotion is a relapse (course) factor rather than an aetiological (onset) one. High-EE households (marked by critical comments, hostility and emotional over-involvement) strongly predict relapse after recovery from an acute episode (Brown et al 1972; Vaughn & Leff 1976; Leff & Vaughn 1985). This is the empirical basis for family intervention and psychoeducation to lower EE, covered in "the Schizophrenia: management, antipsychotics and adverse effects notes".

TRAP **Expressed emotion drives relapse, not onset.** High-EE families predict recurrence in an established illness; do not cite EE as a cause of the first episode.

6.9 Low socioeconomic status: social drift versus social causation

The observation. Schizophrenia is over-represented in the lowest socioeconomic groups and in deprived inner-city areas (Hollingshead & Redlich 1958; Faris & Dunham 1939). Two competing readings exist.

HYPOTHESIS	DIRECTION OF CAUSATION	KEY EVIDENCE
Social drift (drift hypothesis)	Illness leads to low SES	**Patients fall below their fathers' social status after onset (Goldberg & Morrison 1963); genetic liability itself contributes to the downward drift (Sariaslan et al 2016)**
Social causation	Low SES leads to illness	Patients more likely born into socially deprived households (Castle et al 1993); place of birth and early upbringing predict risk and cannot be explained purely as a consequence of illness

The low-SES association is best explained by social drift, though a residual social-causation (early-environment) contribution is supported by birth-cohort data.

The resolution. The social drift account (the drift hypothesis) carries most of the association: the prodrome and illness erode occupational and social standing, so patients drift down the social scale. Social causation retains a foothold because place of birth and early deprivation predict risk

independently of later drift. SES is therefore largely a consequence, with a smaller upstream contribution, not a primary cause.

TRAP **Low SES is mostly downstream.** Social drift explains the low-SES association without socioeconomic status itself causing the illness; reserve social causation for the birth and early-upbringing findings.

6.10 Synthesis: a lifespan risk architecture

Putting it together. The frameworks nest cleanly. Genes and early insults (the first hit) build a developmentally abnormal brain that is clinically silent (neurodevelopmental hypothesis, no gliosis); adolescent pruning plus psychosocial and substance stressors (the second hit) express it as psychosis (two-hit model). Each named exposure carries a modest odds ratio (around 2 for most) and repeatedly interacts with genetic liability, which is the through-line examiners want you to state explicitly.

<2 OR, OBSTETRIC COMPLICATIONS (CANNON 2002)	**2.5** RR, CANNABIS; ~6X HEAVY (ANDREASSON 1987)	**1.57** OR, URBANICITY (VAN OS 2003)	**6.7** RR, AFRO-CARIBBEAN PSYCHOSIS (AESOP 2006)

MNEMONIC

CoMMANDER SUC

Early hits: **Co**mplications (obstetric), **M**alnutrition, **M**aternal infection, **A**utumn/winter birth (season). Late hits: **N**o family (drift), **D**eprivation/urbanicity, **E**xpressed emotion, **R**acial-minority migration; plus **S**ubstance (cannabis), **U**rban, **C**hildhood adversity.

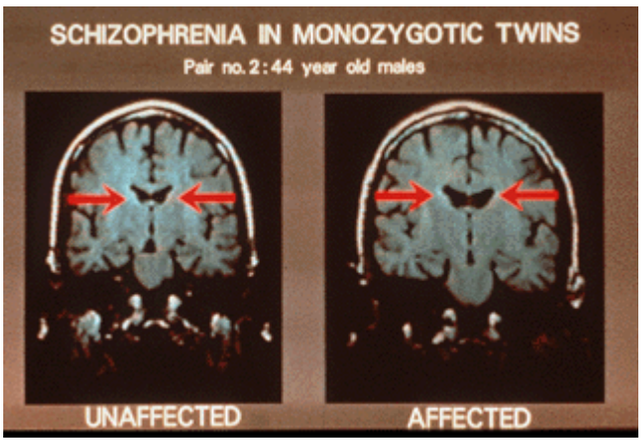
GOOD TO REMEMBER

- **Neurodevelopmental hypothesis (Weinberger; Murray & Lewis):** an early fixed lesion of brain development expressed at adolescent circuit maturation; discriminator is the absence of gliosis (developmental, not degenerative).
- **Two-hit model:** first hit = genes plus early neurodevelopmental insult; second hit = adolescent synaptic pruning plus psychosocial or substance stress; discriminator is that both are needed for onset.
- **Obstetric complications:** antenatal/perinatal adverse events (hypoxia the key mechanism); discriminator is pooled OR about 2, magnified by genetic liability.
- **Maternal malnutrition:** prenatal famine roughly doubles risk (Dutch Hunger Winter); discriminator is the proposed epigenetic (DNA-methylation) mechanism.
- **Season of birth:** winter and spring birth excess; discriminator is that it is a proxy for a seasonal prenatal exposure, not a cause in itself.
- **Cannabis:** dose- and age-dependent component cause (RR about 2.5, ~6x in heavy users, Andreasson 1987); discriminator is high-potency, adolescent-onset use and earlier age of psychosis onset.
- **Urbanicity:** linear dose-response with urban birth/upbringing (OR about 1.57); discriminator is the gene-environment interaction (stronger with family history).
- **Migration and minority status:** marked excess, greatest in second generation and at low ethnic density (AESOP RR 6.7 Afro-Caribbean); discriminator is social defeat, not selective migration.
- **Expressed emotion:** high-EE families (criticism, hostility, over-involvement) predict relapse; discriminator is that it is a course (relapse) factor, not an onset cause.
- **Social drift vs social causation:** low-SES association is mostly drift (illness lowers status, Goldberg & Morrison 1963; genetic liability contributes, Sariaslan 2016); discriminator is that residual social causation is supported only by place-of-birth and early-upbringing data.

7 · Structural neuroimaging and neuropathology

For a century schizophrenia was called a **functional** disorder precisely because Alzheimer and others could find no lesion, and the modern story of its neuroimaging and neuropathology is the story of that null hypothesis being overturned. The examinable spine is short and must be held cold: at the group level the brain in schizophrenia shows enlarged ventricles and a modest global and regional loss of tissue, present already at the first episode; the cellular substrate is reduced neuropil and dendritic spines with an altered cytoarchitecture; and, decisively, there is no gliosis and no neurodegeneration, which is the single fact that pushes the whole field toward a neurodevelopmental rather than a degenerative reading (Harrison 1999, Weinberger & Radulescu 2016). **Real changes, group-level only, and no scar.**

This topic applies the imaging and post-mortem findings to schizophrenia; the physics and technique of how a CT, the MRI sequences and PET actually work are developed in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes, and the descriptive definitions of the symptoms these changes are correlated with belong to the Psychometry, Assessment and Descriptive Psychopathology notes. The neurodevelopmental model that this evidence feeds, and the environmental hits behind it, sit in the aetiology material; here we hold the anatomy and the histology themselves.



Dr Daniel Weinberger, NIMH Clinical Brain Disorders Branch. Public domain (US Government).

Fig 8.8 Lateral ventricular enlargement in schizophrenia, shown in monozygotic twins discordant for the illness. The unaffected twin is on the left and the affected twin on the right, with the arrows marking the enlarged lateral ventricles. Because the twins are genetically identical, the difference cannot be genetic alone, which is why this image is the classic demonstration that structural change in schizophrenia is real and not wholly inherited.

7.1 Johnstone 1976: the landmark that reopened the question

The study that started it. In a landmark study, Johnstone and colleagues used the then-novel technique of computerized tomography and found significantly larger ventricles and more cortical atrophy in patients with schizophrenia than in controls (Johnstone et al. 1976). **Not the first, but the decisive one.** Lateral ventricular enlargement had actually been reported decades earlier using pneumoencephalography, but it was the Johnstone CT study that stimulated the renewed interest which the whole subsequent MRI literature grew out of (Kaplan & Sadock 2024). This is the exam-safe eponym for the birth of structural imaging in schizophrenia.

7.2 Ventricular enlargement: the most replicated structural finding

The single most robust result. Lateral (and third) **ventricular enlargement** is the most consistently replicated structural finding in schizophrenia, confirmed across hundreds of studies and, crucially, present in antipsychotic-naive patients, which argues it is not merely a drug effect (Haijma et al. 2013). **The number to hold.** A meta-analysis of brain volumes in over 18,000 subjects found that ventricular volume is increased by roughly a quarter to a third in schizophrenia relative to controls (Haijma et al. 2013). **The paired reductions.** The same meta-analysis found whole-brain volume decreased by about **2.6%** and intracranial volume reduced by about **2%**; that last figure is telling, because intracranial volume is fixed early in life, so a reduction in it points to a process that acted in childhood, before the illness declared itself.

~30%	~2.6%	~2%
VENTRICULAR VOLUME INCREASE	WHOLE-BRAIN VOLUME DECREASE	INTRACRANIAL VOLUME REDUCTION

RULE **Ventricular enlargement is the flagship.** Lateral ventricular enlargement is the most replicated structural finding in schizophrenia, seen even in antipsychotic-naive patients, so it is a disease signal and not just a consequence of treatment.

7.3 Grey matter loss: global, and regionally weighted to medial temporal and prefrontal cortex

The tissue that goes. Alongside the ventricles, there is a reduction in grey matter, both a modest global loss and a regionally weighted one: cortical grey matter is thinner overall, and the effect is greatest in the medial temporal structures and the prefrontal cortex (Haijma et al. 2013). The reduction is greater for grey matter than for white matter. Reporting conventions differ, so the term also appears as **gray matter** in the American literature; it is the same tissue and the same finding. **Where it bites hardest.** In that 18,000-subject meta-analysis the largest effect sizes were in the hippocampus and the thalamus, with the whole picture broadly similar in antipsychotic-naive and in medicated patients, again separating disease from drug.

7.4 Hippocampal and thalamic reduction: the strongest regional signal

The regions that carry the signal. Of all the structures examined, the hippocampal and thalamic volume reductions are the largest and most reproducible regional findings in schizophrenia, and they are present at the first episode (Haijma et al. 2013, Weinberger & Radulescu 2016). Smaller hippocampus and smaller thalamus sit at the top of the standard summary list of structural changes. **Why the hippocampus matters clinically.** Its involvement dovetails with the memory and declarative-learning deficits of the illness and with the aberrant-salience account of psychosis, giving a structural anchor for symptoms that are otherwise defined purely descriptively (cross-referenced to the Psychometry, Assessment and Descriptive Psychopathology notes).

7.5 Present at first episode, modestly progressive: the time course

Neither purely fixed nor frankly degenerative. Longitudinal work shows the time course is genuinely complex: some of the volume reductions are present before the onset of symptoms and track the genetic predisposition, others emerge at the first episode, and thereafter there is some further, modest loss of grey and white matter whose timing, magnitude and cause remain unclear (Weinberger & Radulescu 2016). **The confounder that muddies progression.** The extent to which any progressive reduction is the disease itself, versus antipsychotic exposure, smoking and other confounders, is unresolved (Fusar-Poli et al. 2013). The examinable phrase is that the changes are present at first episode and only modestly progressive, and that whatever progression exists is not neurotoxic or degenerative in the classic sense (Zipursky et al. 2013).

> **PEARL**
>
> The reduction in intracranial volume is the quiet giant of this evidence. Because the skull vault stops growing early in childhood, a shrunken intracranial volume cannot be explained by an adult-onset degeneration or by years of medication: it fingerprints a process that acted long before the first psychotic symptom, and it is one of the cleanest single arguments for a neurodevelopmental origin.

7.6 Functional imaging: hypofrontality on executive tasks

The functional counterpart. The first functional study (Ingvar & Franzen 1974) found decreased perfusion of the frontal cortex relative to posterior regions in chronic patients, a pattern christened hypofrontality: reduced frontal activation, classically elicited on executive and

word-generation tasks such as the Wisconsin Card Sorting Test and verbal fluency. **Confirmed, but conditional.** Many individual studies were negative, but hypofrontality was confirmed in meta-analysis (Hill et al. 2004), and the relationship is stronger when the phase of illness and symptom profile are taken into account, above all its link with psychomotor poverty and negative symptoms (Shorter Oxford, Semple & Smyth 2019). The technical basis of how cerebral blood flow, PET and BOLD fMRI actually measure this is set out in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

7.7 Functional imaging: reduced efficiency and aberrant connectivity

Not simply less, but less efficient. fMRI during working-memory tasks refines the crude hypofrontality picture: when patients are matched to controls for task performance, they require greater prefrontal activation to achieve the same output, indicating reduced cortical efficiency rather than a simple flat deficit (Callicott et al. 2003, Minzenberg et al. 2009). **The dysconnectivity turn.** The dominant contemporary functional framing is dysconnectivity: aberrant coordination between brain circuits and networks rather than a single hot or cold region (Stephan et al. 2009). This revives Bleuler's original idea of a failure of integration of mental functions, now recast as disturbed connectivity and abnormal neural oscillations, and it aligns with the white-matter and structural findings above.

7.8 Neuropathology: reduced neuropil, dendritic spines and altered cytoarchitecture

What the microscope adds. Post-mortem neuropathology was sought to explain the imaging at a cellular level, and the positive findings are consistent (Harrison 1999, Dorph-Petersen & Lewis 2011). Brain weight is decreased by about 2 to 3%. The core finding is reduced neuropil: reductions in markers of synapses and dendrites, with smaller neurons packed more densely, so that neuronal loss is minimal but the felt-work of connections between neurons is thinned. **The specific cells.** There are reductions in dendritic spine density, and in specific populations, notably the parvalbumin subclass of GABAergic interneurons and layer III pyramidal neurons (Lewis et al. 2005). **Altered cytoarchitecture.** An abnormal position or clustering of neurons, a disturbed cytoarchitecture, has been reported particularly in the entorhinal cortex and subcortical white matter, the kind of misplacement expected from disordered neuronal migration in fetal life rather than from any adult insult.

7.9 The absence of gliosis: the argument for neurodevelopment, not neurodegeneration

The negative finding that decides the question. The most examinable single fact of the whole topic is a negative one: there is an absence of gliosis and no evidence of any neurodegenerative process in the schizophrenic brain (Roberts et al. 1986, Harrison 1999). **Gliosis**, the reactive proliferation of astrocytes, is the brain's universal scar and appears whenever mature tissue is injured or degenerates. Its absence means the structural and cellular abnormalities did not arise from an insult to a formed adult brain. **Why this points to neurodevelopment.** Injuries occurring before roughly the end of the second trimester, while glia are still immature, heal without a glial scar; a lesion laid down that early therefore leaves reduced neuropil, malpositioned neurons and smaller structures but no gliosis. The finding thus argues that schizophrenia is a disorder of early brain development, and that whatever mild progression is

seen on serial MRI is not neurotoxic or degenerative (Weinberger 1987, Murray & Lewis 1987, Zipursky et al. 2013).

TRAP **Do not scan to diagnose.** Ventricular enlargement and grey matter loss are group-level statistical findings with wide overlap between patients and controls; they are not a diagnostic test, and a normal or an abnormal scan neither confirms nor excludes schizophrenia in an individual.

7.10 Excess adolescent synaptic pruning: linking the histology to onset

Why an early lesion declares itself in late adolescence. If the pathology is developmental, why does psychosis emerge only in the late teens and twenties? The influential answer is the excessive synaptic pruning hypothesis (Feinberg 1982): normal adolescence involves a large, programmed elimination of cortical synapses, and if that pruning is excessive or mistimed it could push an already vulnerable, synapse-poor cortex past a threshold, producing symptoms at exactly the age pruning peaks. **The modern genetic support.** This once-speculative idea gained hard support when the strongest common-variant genetic signal, at the MHC locus, was traced largely to the complement component 4 (C4) gene: risk alleles drive higher C4 expression and, at least in mice, more synaptic pruning (Sekar et al. 2016), converging with the post-mortem finding of reduced neuropil and giving a mechanism for the loss of synapses over adolescence.

WORKED EXAMPLE

A registrar presents a drug-naive man at his first episode whose MRI shows mildly enlarged lateral ventricles and reduced hippocampal volume, and is asked what this proves. The disciplined answer: it is consistent with schizophrenia at the group level and, being present at first episode and before treatment, argues the changes are neither purely a drug effect nor a late degeneration. It does not, on its own, diagnose him, because these are statistical findings with large patient-control overlap. The clinching conceptual point the examiner wants is that the underlying neuropathology shows an absence of gliosis, marking this as a neurodevelopmental and not a neurodegenerative disorder.

HOLD THIS

The brain in schizophrenia shows enlarged ventricles (the most replicated finding, ventricular volume up by roughly a quarter to a third) with reduced grey matter, hippocampus and thalamus, present at first episode and only modestly progressive; the histology is reduced neuropil, dendritic spines and altered cytoarchitecture with, crucially, an absence of gliosis, which marks the process as neurodevelopmental, not neurodegenerative.

GOOD TO REMEMBER

- **Ventricular enlargement:** enlargement of the lateral and third ventricles; the most consistently replicated structural finding, seen even in antipsychotic-naive patients; discriminator is the meta-analytic finding of ventricular enlargement of roughly a quarter to a third (Haijma et al. 2013).
- **Grey matter (gray matter) reduction:** global and regional cortical thinning, greater for grey than white matter; central claim is that loss is regionally weighted to medial temporal and prefrontal cortex; discriminator is that whole-brain volume falls about 2.6% and the effect is broadly equal in naive and medicated patients.
- **Hippocampal and thalamic reduction:** smaller hippocampus and thalamus; the largest and most reproducible regional volume losses; discriminator is that they carry the biggest effect sizes and are already present at the first episode.
- **Johnstone et al. 1976:** the landmark CT study showing larger ventricles and cortical atrophy; central claim is that it reopened schizophrenia as a brain disorder; discriminator is that it used computerized tomography and revived a finding first hinted at by pneumoencephalography.
- **Hypofrontality (Ingvar & Franzen 1974):** reduced frontal cerebral blood flow and activation on executive tasks; central claim is a functional prefrontal deficit; discriminator is that it is confirmed on meta-analysis (Hill et al. 2004) and is tied to psychomotor poverty and negative symptoms, and that it reflects reduced cortical efficiency, not simple inactivity.
- **Reduced neuropil and dendritic spines:** thinned synaptic and dendritic markers with smaller, densely packed neurons and loss of parvalbumin interneurons and layer III pyramidal cells; central claim is that connections, not neurons, are lost; discriminator is that neuronal loss is minimal and gliosis is absent.
- **Altered cytoarchitecture:** abnormal neuronal position and clustering, notably in entorhinal cortex and subcortical white matter; central claim is disordered neuronal migration; discriminator is that malposition without gliosis implicates a fetal, second-trimester developmental error.
- **Absence of gliosis:** no reactive astrocytic scarring and no neurodegenerative change; the pivotal negative finding; discriminator is that its absence excludes an adult degenerative process and is the core argument that schizophrenia is neurodevelopmental (Roberts et al. 1986, Weinberger 1987).
- **Excess synaptic pruning (Feinberg 1982):** excessive programmed elimination of cortical synapses in adolescence; central claim is that it explains the late-adolescent onset of an early lesion; discriminator is the modern C4 complement genetic support (Sekar et al. 2016) converging with the reduced-neuropil finding.

Clinical features and phenomenology

8 · The symptom domains and the dimensional models

The phenomenology of schizophrenia does not resolve into a single presentation, and the examiner rewards the resident who can organise it. The organising map is a set of semi-independent **symptom domains**: a patient is described by a **profile** across them, not by one label. This topic sets out the modern five domain map and then the historical dimensional and phenotype models, Crow's type I and type II and Liddle's three-syndrome scheme, that fed into it. The raw descriptive definitions of the individual signs, what a delusion, a hallucination, a first-rank symptom or formal thought disorder *is* as a phenomenon, are not re-derived here; they belong to the Psychometry, Assessment and Descriptive Psychopathology notes, and this chapter applies them to schizophrenia.

Why this is the payoff. The domains are the spine that the criteria map, the classification band and the differential all hang from, and the same domain vocabulary drives the reason both ICD-11 and DSM-5 dropped the classical subtypes in favour of a dimensional specifier approach. Fix the five domains and their representative signs first; the two eponymous models then read as historical attempts to compress the same variation into two or three biologically motivated syndromes (Kaplan & Sadock 2024).

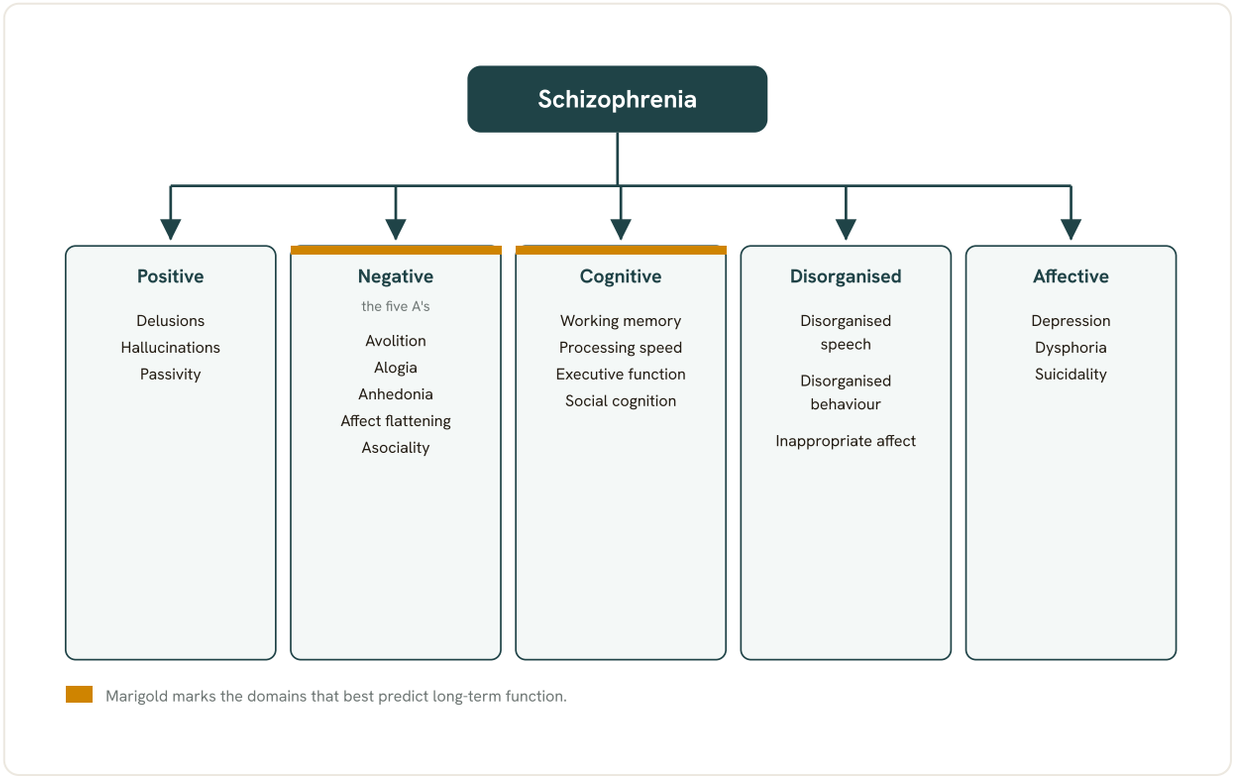


Fig 8.9 The five symptom domains of schizophrenia as one map. A patient is described by a profile across these semi-independent dimensions rather than by a single subtype. The negative and cognitive domains, marked in marigold, carry the greatest weight for long-term functional outcome even though the positive symptoms are the most visible.

8.1 The five-symptom-domain map: a profile, not a subtype

The map. Contemporary phenomenology describes schizophrenia across five semi-independent symptom domains, and a given patient carries a **profile** of varying weight across all five rather than belonging to one discrete category (Kaplan & Sadock 2024). Holding the five domain map converts a sprawling symptom list into a compact grid, and it is the grid the classification band builds on when it replaces subtypes with dimensional specifiers. The five are positive, negative, cognitive, disorganised, and affective (mood).

Positive. A positive symptom is an addition to normal experience: delusions and hallucinations are the representative signs, the florid features that most often bring the patient to attention and drive admission. They are the domain most responsive to dopamine-blocking treatment and the one the classic type I picture is built from.

Negative. A negative symptom is a subtraction from normal experience, the loss or diminution of a normal function. The representative signs cluster as blunted (flat) affect, alogia (poverty of speech), avolition, asociality and anhedonia, conventionally chained on the mnemonic below.

This domain carries much of the long-term disability and responds least well to antipsychotics. The distinction between primary (enduring, deficit) and secondary negative symptoms, and the deficit syndrome, is developed in the next topic.

Cognitive. The cognitive domain is the impairment of attention, processing speed, working memory, verbal learning and executive function. Deficits average about one standard deviation below expected performance, are present at the first episode, and are the strongest single predictor of functional outcome; executive function and attention may be the core deficits (Kaplan & Sadock 2024). Kraepelin's original *dementia praecox* foregrounded exactly this, then it was neglected for decades before contemporary studies restored it to the map.

Disorganised. The disorganisation domain is formal thought disorder (derailment, tangentiality, loosening of associations, incoherence) together with disorganised or bizarre behaviour and inappropriate affect. Factor-analytic work repeatedly pulls disorganisation out as its own factor distinct from the positive symptoms it was once bundled with, and it maps onto reduced dorsolateral prefrontal activity (Tasman 2024).

Affective (mood). The affective domain is the mood disturbance woven through the illness: depression, dysphoria, hopelessness and, decisively, suicide risk, plus the anxiety and demoralisation that accompany insight. It is not an epiphenomenon; it carries a large part of the mortality of the disorder and is easily missed when attention fixes on positive symptoms.

RULE **Describe the profile, not the subtype.** The five domains are semi-independent dimensions that vary in weight within and between patients; the correct clinical description is a profile across all five, and any one patient can score high on several at once.

TRAP **Reading a domain as a diagnosis.** A prominent negative-symptom picture is a point on the profile, not a "type II patient" filed away in a box; the domains coexist, and the affective and cognitive domains are the two most often forgotten because they are quieter than florid positive symptoms.

MNEMONIC

Domains "P-N-C-D-A"; negative symptoms "the 5 As"

The five domains read **P**ositive, **N**egative, **C**ognitive, **D**isorganised, **A**ffective. Within the negative domain, the representative signs are the **5 As**: **A**ffective blunting, **A**logia, **A**volition, **A**sociality, **A**nhedonia (with attentional impairment sometimes added as a sixth A, though attention properly belongs to the cognitive domain).

8.2 The domains as a table: representative signs and significance

The grid. The value of the map is that each domain has a short list of representative signs and a one-line clinical significance, which is what an examiner wants back when they ask you to "describe the symptom domains of schizophrenia."

DOMAIN	REPRESENTATIVE SIGNS	ONE-LINE SIGNIFICANCE
Positive	Delusions, hallucinations	**Florid, dopamine-responsive; drives admission; the type I core**
Negative	Blunted affect, alogia, avolition, asociality, anhedonia	**Enduring disability; poor drug response; the type II core**
Cognitive	Attention, working memory, processing speed, executive function	**Strongest predictor of functional outcome; present at first episode**
Disorganised	Formal thought disorder, disorganised behaviour, inappropriate affect	**Separates from positive on factor analysis; frontal-linked**
Affective (mood)	Depression, dysphoria, hopelessness, suicidality, anxiety	**Carries much of the mortality; the most-missed domain**

The five semi-independent symptom domains, each with its representative signs and the single fact to attach; the significance column is the discriminator an examiner rewards.

8.3 Crow's type I and type II: the two-syndrome phenotype model

The model. Crow (1985) proposed two syndromes of schizophrenia built from a combination of clinical and neurobiological features (Crow 1980, 1985). Type I is the positive-symptom syndrome: acute onset, delusions and hallucinations to the fore, preserved social functioning during remissions, a good response to antipsychotics, an underlying dopamine overactivity, potentially reversible, and no structural brain change. Type II is the negative-symptom syndrome: insidious onset, blunting and poverty to the fore, cognitive impairment, poor outcome and poor antipsychotic response, no clear dopamine overactivity but structural brain change, classically ventricular enlargement, and thought to be less reversible. The model was influential as an early re-focusing on the neurobiology of the disorder, but subsequent research did not strongly support the predicted biological subtypes and their correlations (Shorter Oxford Textbook of Psychiatry).

FEATURE	TYPE I	TYPE II
Dominant symptoms	Positive (delusions, hallucinations)	**Negative (blunting, poverty)**
Onset and course	Acute; potentially reversible	**Insidious; chronic, less reversible**
Cognition	Relatively preserved	**Cognitive impairment**
Antipsychotic response	Good	**Poor**
Proposed mechanism	Dopamine overactivity	**Structural change (ventricular enlargement)**
Structural brain change	Absent	**Present**

Crow's type I versus type II; the discriminating axis is positive-and-reversible-and-dopaminergic against negative-and-structural-and-treatment-resistant.

TRAP **Treating type I and type II as mutually exclusive boxes.** Crow himself allowed that a patient could show both, and most patients do; the two syndromes are poles of a dimension, not two disjoint categories, and a single patient commonly has positive and negative features together.

COMMON TRAP

Do not attach the dopamine hypothesis to schizophrenia as a whole through the Crow model. Crow tied dopamine overactivity specifically to the type I, positive-symptom, treatment-responsive picture and left the type II, negative-and-structural picture outside it. The dopamine and monoamine pathways themselves are cross-referenced to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

8.4 Liddle's three-syndrome model: the factor-analytic dimensions

The model. Liddle (1987) studied patients with chronic schizophrenia and, from the clustering of symptoms, described three overlapping clinical syndromes, a three-syndrome model that he linked to distinct neuropsychological deficits and to patterns of regional cerebral blood flow (Liddle 1987; Liddle et al. 1992). The three are reality distortion, the disorganisation syndrome, and psychomotor poverty, and they map cleanly onto the positive, disorganised and negative groupings of the modern domain map.

Reality distortion

Delusions and hallucinations; the positive-symptom cluster.

Disorganisation syndrome

Formal thought disorder, inappropriate affect and bizarre behaviour; the disorganised cluster.

Psychomotor poverty

Flat affect, poverty of speech and decreased spontaneous movement; the negative cluster.

The neurobiological linkage. The single most reproducible finding from the model is the link between psychomotor poverty, impaired performance on frontal-lobe tasks, and decreased frontal blood flow ("hypofrontality"); disorganisation was associated with abnormal activity in the anterior cingulate and prefrontal cortex, and reality distortion with medial temporal and cingulate activity (Liddle et al. 1992). The three-factor structure, positive, negative and disorganisation, is the finding factor-analytic studies most consistently recover and is the historical bridge to the modern domains (Tasman 2024). The neuroimaging principles themselves belong to the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

RULE **Liddle's three collapse into the domain map.** Reality distortion is the positive domain, the disorganisation syndrome is the disorganised domain, and psychomotor poverty is the negative domain; the modern five-domain map simply adds the cognitive and affective dimensions.

8.5 From dimensions to nosology: why the models matter for classification

The through-line. The dimensional models are not museum pieces. The observation that positive, negative and disorganisation vary semi-independently, and that classical categories (paranoid, hebephrenic, catatonic) had poor reliability, temporal instability and low predictive

validity, is precisely the argument that led both ICD-11 and DSM-5 to drop the schizophrenia subtypes and replace them with a set of dimensional symptom specifiers rated on severity (Tandon et al. 2013; Kaplan & Sadock 2024). That nosological-change point is developed in the classification band; here the point is that Crow and Liddle are the intellectual ancestors of the specifier approach, and the five-domain profile is what the specifiers operationalise. The subtypes were dropped because dimensions describe the same patients better than categories do.

What this leaves for exams. Where a paper is explicitly ICD-10, the subtypes still exist and may be asked; where it is unmarked, describe the domains and note the dimensional turn. The management implications, that positive symptoms respond to antipsychotics and negative and cognitive symptoms respond poorly, point forward to the Schizophrenia: management, antipsychotics and adverse effects notes.

HOLD THIS

Schizophrenia is a profile across five semi-independent domains (positive, negative, cognitive, disorganised, affective), not a subtype; Crow compressed this into positive-reversible-dopaminergic type I versus negative-structural-treatment-resistant type II, and Liddle into reality distortion, disorganisation syndrome and psychomotor poverty, and the same dimensional logic is why both ICD-11 and DSM-5 dropped the classical subtypes.

GOOD TO REMEMBER

- **Five symptom domains:** positive, negative, cognitive, disorganised, affective; each a semi-independent dimension; the discriminator is that a patient carries a profile across all five, not a single subtype.
- **Positive domain:** delusions and hallucinations; an addition to normal experience; discriminator is dopamine-responsiveness and its central place in the type I picture.
- **Negative domain:** the 5 As (affective blunting, alogia, avolition, asociality, anhedonia); a subtraction from normal experience; discriminator is that it carries long-term disability and responds least to antipsychotics.
- **Cognitive domain:** attention, working memory, processing speed, executive function; discriminator is that it is the strongest predictor of functional outcome and is present at first episode.
- **Disorganised domain:** formal thought disorder, disorganised behaviour, inappropriate affect; discriminator is that factor analysis separates it from the positive domain.
- **Affective domain:** depression, dysphoria, suicidality; discriminator is that it carries much of the mortality and is the most-missed domain.
- **Crow type I:** positive symptoms, acute, good antipsychotic response, reversible, dopamine overactivity, no structural change; discriminator against type II is reversibility with treatment.
- **Crow type II:** negative symptoms, insidious and chronic, cognitive impairment, poor response, structural change (ventricular enlargement); discriminator is that it is not mutually exclusive from type I, they coexist.
- **Liddle three-syndrome:** reality distortion (positive), disorganisation syndrome (disorganised), psychomotor poverty (negative); discriminator is the reproducible link of psychomotor poverty to hypofrontality and impaired frontal-lobe task performance.

9 · Positive symptoms: delusions, hallucinations and thought disorder

Why this matters. The **positive symptom** cluster is what most residents call to mind when they think of schizophrenia, and it is where examiners test whether you can distinguish a phenomenon from a diagnosis. A **positive symptom** is an added, distorted experience: a belief, a percept or a disorder of the flow of thought that is present in the illness but absent in health. The raw descriptive definitions of these phenomena, what a delusion, a hallucination or a formal thought disorder actually is, are owned by the Psychometry, Assessment and Descriptive Psychopathology notes; here we do not re-define them from scratch but apply them to schizophrenia and ask which forms are characteristic.

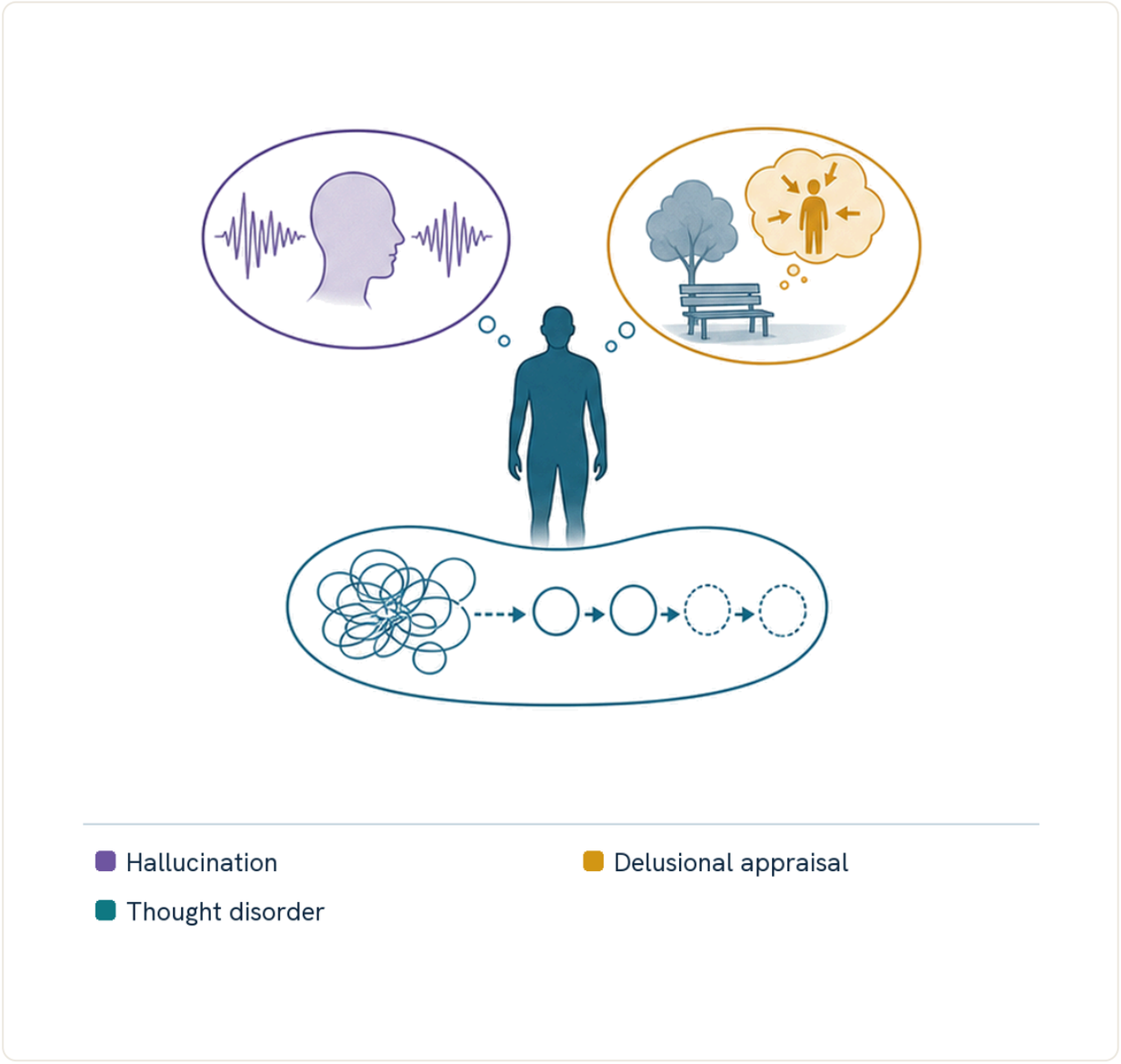


Fig 8.10 Three positive-symptom forms: perception without an external stimulus, fixed delusional interpretation of an event, and disruption of the form and sequence of thought or speech.

The governing principle for the whole topic is one line: no single positive symptom is specific to schizophrenia. Every delusion, every hallucination, every thread of disorganised speech can appear in mood disorder, in an organic state or in substance-induced psychosis. What matters in

the exam is the *form* that is characteristic, the company it keeps, and the differentials it should raise (Kaplan & Sadock 2024, Gelder et al. 2013).

9.1 Positive symptoms within the symptom domains

Both current classifications describe schizophrenia through symptom domains rather than a pathognomonic sign, and the positive domain sits alongside negative, cognitive, affective and psychomotor domains. The positive symptoms proper are **delusions, hallucinations, formal thought disorder** (inferred from disorganised speech) and grossly disorganised behaviour. ICD-11 requires at least two symptoms present most of the time for one month, with at least one drawn from its "core" list, and its items a) to d) are exactly the positive-symptom phenomena: persistent delusions, persistent hallucinations, disorganised thinking, and experiences of influence, passivity or control (ICD-11 CDDR 2024). DSM-5-TR cross-maps to the same phenomena but frames them under Criterion A and adds a six-month total duration.

RULE **No single positive symptom is specific to schizophrenia.** Diagnose on form, persistence and context, never on the presence of one delusion or one voice.

9.2 Delusions characteristic of schizophrenia: the themes

A delusion applied to schizophrenia keeps the descriptive definition from the Psychometry, Assessment and Descriptive Psychopathology notes, a fixed false belief held on inadequate grounds, unshakeable by reason and out of keeping with the person's background, and adds a characteristic set of themes. Persecutory content and delusions of reference are the most frequent, but themes alone carry little diagnostic weight; the attitude to them can help. In a depressive psychosis the patient accepts persecution as deserved punishment, whereas in schizophrenia he resents it as unwarranted (Gelder et al. 2013).

Persecutory delusion

Belief that people or organisations intend harm, are conspiring or spying; common but low specificity across psychoses.

Delusions of reference

Neutral events, remarks, articles or gestures are read as carrying a personal message about the patient; the referential form.

Grandiose delusion

Exaggerated belief in one's own importance, powers or identity; more typical of mania but occurs in schizophrenia.

Control and passivity delusion

Actions, impulses, sensations or thoughts are experienced as made or controlled by an outside agency; strongly suggestive of schizophrenia.

Bizarre delusion

Content that is culturally impossible and cannot derive from ordinary life (thoughts removed by radio waves); high weight in classification.

9.3 Control and passivity: the phenomena that point to schizophrenia

Among delusional themes, the passivity phenomena (delusions of control) carry the most diagnostic weight. Here the patient firmly believes that his movements, impulses, feelings or thoughts are brought about by an external agency rather than willed by himself (Gelder et al. 2013). The thought-possession delusions belong here: thought insertion (thoughts placed into the mind by others), thought withdrawal (thoughts removed, often with thought blocking) and thought broadcasting (unspoken thoughts known to others). These map directly to ICD-11 item d), experiences of influence, passivity or control, and to the classic Schneiderian first-rank symptoms whose descriptive definition is developed in the Psychometry, Assessment and Descriptive Psychopathology notes. Distinguish thought insertion from the obsessional patient, who is distressed by alien thoughts but never doubts they are his own.

9.4 Delusional mood and delusional perception: the onset phenomena

Two primary (autochthonous) experiences mark the onset of a delusional illness and are worth eliciting because they carry weight in the diagnosis of schizophrenia. Delusional mood (Wahnstimmung) is a strange, uncanny sense of foreboding that something sinister is about to happen; the world feels changed and charged with unspecified significance before any belief has crystallised. Delusional perception is a fully formed delusion arising directly from a normal, correctly perceived percept: the perception itself is normal, and it is the abnormal significance attached to it that is delusional (for example, a letter left on the desk is instantly known to mean that the patient must die). Note that delusional perception is a disorder of thought, not of perception (Gelder et al. 2013).

WORKED EXAMPLE

A young man says that over two weeks the streets began to feel "loaded", as if everyone knew something was coming; he could not say what (delusional mood). Then, seeing a red car turn the corner, he knew with total certainty and no reasoning that he had been chosen to save the city (delusional perception). The percept, a red car, was accurate; the sudden unquestionable meaning is the delusion. Both are primary phenomena and, taken with persistence over a month, weigh toward schizophrenia rather than a mood disorder.

9.5 Hallucinations: auditory hallucinations are the most characteristic

A hallucination applied to schizophrenia again takes its descriptive definition from the Psychometry, Assessment and Descriptive Psychopathology notes, a percept without an external stimulus, experienced as real and located in external space, and asks which modality and which content are characteristic. The answer is the auditory modality: the auditory hallucination, specifically voices, is the most characteristic hallucination of schizophrenia, and ICD-11 item b) notes hallucinations are "most commonly auditory" (ICD-11 CDDR 2024). Second-person voices that address the patient directly do not point to any one diagnosis; it is particular forms of the auditory hallucination that carry weight (Gelder et al. 2013).

Third-person voices

Voices referring to the patient as "he" or "she", discussing or arguing about him among themselves; characteristic of schizophrenia.

Running commentary

A voice giving a continuous commentary on the patient's actions as they happen; a Schneiderian first-rank form.

Thought echo

Hearing one's own thoughts spoken aloud, either as they are thought (Gedankenlautwerden) or repeated just after (echo de la pensee); characteristic.

TRAP **Treating any auditory hallucination as diagnostic.** A second-person voice, a derogatory voice or a single voice is not diagnostic; only the characteristic forms (third-person, running commentary, thought echo) carry weight, and even they are not pathognomonic.

9.6 Other modalities and the organic search

Hallucinations in modalities other than hearing are less common in schizophrenia and should lower your threshold for an organic workup. Visual hallucinations should always suggest the possibility of an organic disorder (delirium, temporal lobe epilepsy, drug intoxication or withdrawal, a space-occupying lesion), although they do occur in severe affective disorder and in schizophrenia; the content of a visual hallucination is of little diagnostic value (Gelder et al. 2013). Olfactory and gustatory hallucinations are infrequent and, when present, raise temporal lobe epilepsy and tumours of the olfactory pathway. Investigate the physical substrate before you settle on a primary psychotic disorder; the neuroimaging principles are set out in the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

TRAP **Prominent visual hallucinations should prompt an organic workup.** Vivid or predominant visual, olfactory or tactile hallucinations point away from uncomplicated schizophrenia and toward a delirium, epilepsy, intoxication or a lesion until proven otherwise.

9.7 Formal thought disorder: the positive form in schizophrenia

Formal thought disorder, sometimes shortened to thought disorder, is a disturbance not of the content of individual thoughts but of the form and linkage between them, and it is inferred from disorganised speech because thought itself cannot be observed. Its descriptive definition sits in the Psychometry, Assessment and Descriptive Psychopathology notes; here we apply the positive form to schizophrenia. The positive form is a loosening of the normal connections between ideas so that speech drifts, jumps or fragments. ICD-11 lists it as item c), disorganised thinking, giving tangentiality, loose associations, irrelevant speech and neologisms, with "word salad" as its severe end (ICD-11 CDDR 2024). The clinical assessment and grading of disorganised speech is developed in the disorganisation topic; here hold only that the positive form of formal thought disorder is a positive symptom.

Loosening of associations

Ideas slide from one to another without logical connection; the core positive formal thought disorder in schizophrenia.

Tangentiality

Replies veer off the point and never return to it; the answer is oblique to the question.

Neologism

A newly coined word or a familiar word used in a private idiosyncratic sense.

MNEMONIC

PDF for the positive triad

Perceptions gone wrong (hallucinations, auditory above all), **D**elusions (persecutory, referential, grandiose, control and passivity, bizarre), **F**ormal thought disorder (loosening, tangentiality, neologism). Three phenomena, one positive-symptom domain.

9.8 First-rank symptoms: a useful map, not a diagnostic test

Many of the characteristic positive phenomena above, thought echo, running commentary and third-person voices, thought insertion, withdrawal and broadcasting, passivity and delusional perception, are the Schneiderian first-rank symptoms (Schneider 1959). ICD-10 placed considerable weight on them; the phenomena themselves are defined in the Psychometry, Assessment and Descriptive Psychopathology notes. The examiner's point is that first-rank symptoms are neither necessary nor sufficient: they occur in roughly 10 to 20 percent of manic patients and in organic psychoses, and are absent in many people with schizophrenia. Treat them as a memory scaffold for the characteristic forms, not as a diagnostic test.

TRAP **Calling first-rank symptoms pathognomonic.** They are characteristic, not specific; present in mania and organic states, absent in many with schizophrenia. ICD-11 and DSM-5 no longer give them privileged diagnostic status.

9.9 Where the positive symptoms sit in the criteria and the differential

ICD-11 runs the positive symptoms forward as items a) to d) and needs at least one core symptom over one month; DSM-5-TR cross-maps the same phenomena under Criterion A and asks for six months total. A legacy ICD-10 box below shows what changed. In the differential, the same positive symptoms in a full mood episode point to a mood disorder with psychotic features, in a short-lived acute picture to an acute and transient psychotic disorder, and in an encapsulated non-bizarre belief to delusional disorder; those entities are developed in the Other psychotic disorders, delusional syndromes and catatonia notes. Management of the positive symptoms, antipsychotics and their adverse effects, belongs to the Schizophrenia: management, antipsychotics and adverse effects notes.

POSITIVE PHENOMENON	CHARACTERISTIC FORM IN SCHIZOPHRENIA	DISCRIMINATOR TO HOLD
Delusion	Persecutory, referential, control and passivity, bizarre	**Passivity and bizarre content weigh most; themes alone are low-specificity**
Auditory hallucination	Third-person, running commentary, thought echo	**Second-person or derogatory voices are not diagnostic**
Non-auditory hallucination	Uncommon; visual, olfactory, tactile	**Prominent visual hallucinations should prompt an organic workup**
Formal thought disorder	Loosening of associations, tangentiality, neologism	**Positive form; inferred from disorganised speech, graded in the disorganisation topic**

The positive-symptom phenomena, their characteristic schizophrenia form, and the single discriminator to carry into a viva.

INDIA

Where the exit examination and many Indian question banks still test ICD-10, the positive symptoms are examined through Schneider's first-rank symptoms and the ICD-10 group (a) to (d). Know both: run ICD-11 forward, but be able to reproduce the ICD-10 first-rank framing when the paper asks for it.

COMMON TRAP

Diagnosing schizophrenia on a florid positive picture that is unfolding inside an untreated manic or depressive episode. Mood-congruent grandiose or nihilistic delusions and even brief first-rank symptoms occur in mania; the positive symptoms must be assessed against the mood state and its timeline before the label is applied.

GOOD TO REMEMBER

- **Delusion in schizophrenia:** a fixed false belief out of keeping with background; characteristic themes are persecutory, referential, grandiose, control and passivity, and bizarre; the discriminator is that passivity and bizarre content weigh most while theme alone is low-specificity.
- **Delusional mood (Wahnstimmung):** an uncanny foreboding that something significant is about to happen, before any belief forms; a primary onset phenomenon weighing toward schizophrenia.
- **Delusional perception:** a full delusion arising from a normally perceived percept; the discriminator is that the perception is normal and only the attached meaning is delusional, and it is classed as a disorder of thought.
- **Passivity phenomena (delusions of control):** actions, impulses, feelings or thoughts felt as made by an outside agency, including thought insertion, withdrawal and broadcasting; the discriminator is the loss of the sense of ownership or agency, strongly suggestive of schizophrenia.
- **Auditory hallucination:** the most characteristic hallucination of schizophrenia; the discriminator forms are third-person voices commenting or arguing, running commentary and thought echo, whereas second-person voices are non-specific.
- **Formal thought disorder (positive form):** a disturbance of the linkage of thoughts inferred from disorganised speech; core forms are loosening of associations, tangentiality and neologism, with word salad at the severe end.
- **Schneiderian first-rank symptoms:** a map of characteristic positive phenomena (Schneider 1959); the discriminator is that they are neither necessary nor sufficient, occurring in 10 to 20 percent of manic patients and dropped from privileged status in ICD-11 and DSM-5.

GOOD TO REMEMBER

- **ICD-10 (legacy) positive-symptom framing:** weighted the first-rank symptoms heavily, grouping thought echo/insertion/withdrawal/broadcasting (a), passivity and delusional perception (b), third-person and running-commentary voices (c) and bizarre persistent delusions (d); one such symptom for one month sufficed.
- **What changed in ICD-11 and DSM-5:** first-rank symptoms lose their special diagnostic weight, no positive symptom is privileged as pathognomonic, and the emphasis shifts to at least two symptoms (one core) over the duration threshold with a dimensional symptom-domain description.

HOLD THIS

No positive symptom is specific to schizophrenia; the characteristic forms are third-person auditory hallucinations, thought echo and passivity phenomena, and prominent visual hallucinations should send you looking for an organic cause.

10 · Negative symptoms and the deficit syndrome

The negative symptoms are the quiet half of schizophrenia and the half that decides the patient's life. They are a subtraction from normal experience, and the examiner tests whether the resident can list the domains, separate **primary** from **secondary** forms, and recognise the validated deficit-syndrome subgroup. This topic applies the descriptive signs to schizophrenia; the raw phenomenological definitions of flat affect, poverty of speech and the rest belong to the Psychometry, Assessment and Descriptive Psychopathology notes and are not re-derived here.

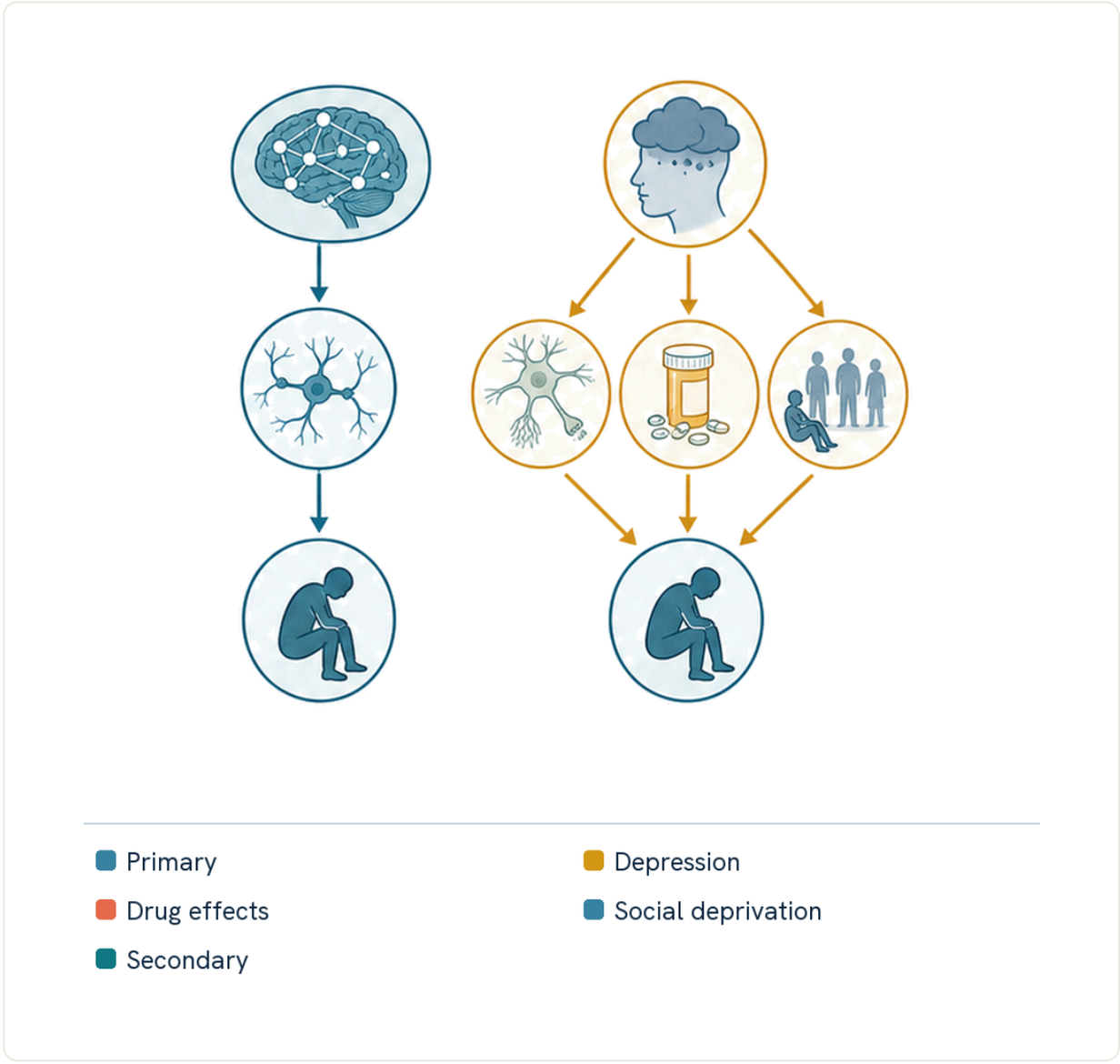


Fig 8.11 Primary and secondary negative symptoms. A direct illness-domain pathway must be distinguished from reduced motivation or expression secondary to depression, extrapyramidal effects, sedation or environmental deprivation.

Why this is the payoff. Negative symptoms predict short-term and long-term disability, social function and quality of life better than positive or disorganisation symptoms, they are more stable across time, and they respond least well to antipsychotics (Kaplan & Sadock 2024). The single most examinable move is to always split a negative-symptom picture into what the disease is doing and what a drug, a delusion or a depression is doing, because the treatable causes differ. Get that split right and the deficit syndrome, the assessment scales and the management pointers all follow.

10.1 What a negative symptom is

Definition. A negative symptom represents a loss or diminution of a normal mental function, and stands in contrast to a positive symptom, where a perception, cognition or behaviour is added to normal mental life (Kaplan & Sadock 2024). The concept is old: Kraepelin foregrounded emotional dullness and loss of the "mainsprings" of volition, and for Bleuler emotional deterioration stood at the forefront of the picture. Negative symptoms are not specific to

schizophrenia, mild forms appear in a minority of the general population, but the pattern of multiple enduring negative symptoms not due to medication or social effects is most characteristic of schizophrenia.

RULE **Negative symptoms drive disability.** The severity of negative symptoms predicts social function and long-term outcome better than positive or disorganisation symptoms, and they are the more stable dimension across time.

10.2 The five domains: the five A's

The five. The NIMH-MATRICS consensus conference (2005) fixed five negative-symptom domains: affective flattening (blunted affect), alogia, avolition, anhedonia and asociality (social withdrawal), memorised as the five A's (Kaplan & Sadock 2024). Each is a loss of a distinct function, and a patient carries a profile of varying weight across the five.

Affective flattening

A reduction in the intensity of emotional expression: deficits in facial expression, prosody, gesture and vocal production; near-absence is flat affect. More common in men, early onset and poor premorbid function.

Alogia

A decrease in the production of speech, the "negative thought disorder": increased response latency, short replies, long pauses and paucity of spontaneous speech. It is one of the commoner negative symptoms. Poverty of content with normal volume is a disorganisation sign, not alogia.

Avolition

A loss of will or drive, an inability to initiate and persist in goal-directed activity (neurological *abulia*). Impairs grooming, self-care, work and study, and is the single largest driver of negative-symptom disability. Closely related to apathy.

Anhedonia

A loss of the capacity to derive pleasure or interest from experiences, activities or relationships; likely the most persistent negative symptom. When part of a negative syndrome it is not a manifestation of depression.

Asociality

Passive or apathetic social withdrawal: indifference to relationships, reduced drive to socialise, decreased sexual and intimate interest; linked to theory-of-mind deficits.

MNEMONIC

The 5 A's

Affective flattening, **A**logia, **A**volition, **A**nhedonia, **A**sociality. Attentional impairment is sometimes offered as a sixth A, but attention belongs to the cognitive domain and is not a negative symptom proper.

10.3 The modern two-factor grouping

Two factors, not five islands. Repeated factor-analytic studies collapse the five domains into two correlated groups: an avolition-apathy (motivation-and-pleasure) factor made of avolition,

anhedonia and asociality, and a diminished expression factor made of affective flattening and alogia (Kaplan & Sadock 2024). The clinical logic is elegant: the avolition-apathy factor is elicited by interview (what the patient does and wants), whereas diminished expression is observed by the clinician (how the patient looks and speaks). This two-factor structure is exactly why DSM-5-TR names "diminished emotional expression or avolition" as the representative negative symptoms in its Criterion A.

FACTOR	COMPONENT DOMAINS	HOW IT IS CAPTURED
Avolition-apathy (motivation and pleasure)	Avolition, anhedonia, asociality	**Elicited by interview (internal drive and pleasure)**
Diminished expression	Affective flattening, alogia	**Observed by the clinician (behaviour and speech)**

The two-factor grouping of the five negative-symptom domains; the discriminator is interview-elicited motivation versus clinician-observed expression, and it underlies the DSM-5-TR pairing of avolition with diminished emotional expression.

10.4 Primary versus secondary negative symptoms

The split that changes management. A secondary negative symptom is a negative symptom produced by another, potentially removable cause: untreated positive symptoms (a suspicious, hallucinating patient withdraws), depression, extrapyramidal side effects of antipsychotics, or understimulation of an institutionalised or socially isolated patient (Tasman 2024). Secondary negative symptoms are potentially reversible when the driver is treated. A primary negative symptom is intrinsic to the disease process, is the least variable of the symptoms of schizophrenia, tends to persist throughout the illness course, and predicts future disability (Kaplan & Sadock 2024). The clinical task is to strip out every treatable secondary cause before concluding that what remains is primary and enduring.

SOURCE OF THE NEGATIVE SYMPTOM	MECHANISM	TREATABLE? / ACTION
Positive symptoms	Withdrawal driven by paranoia, hallucinations, preoccupation	**Yes; optimise antipsychotic for positive symptoms**
Depression	Depressive anhedonia, amotivation, psychomotor slowing	**Yes; treat the depressive episode**
Extrapyramidal side effects	Drug-induced parkinsonism mimicking blunting and avolition	**Yes; reduce dose, switch agent, or add anticholinergic (neuroleptic-induced deficit syndrome)**
Understimulation	Institutionalism, social isolation, poverty of environment	**Yes; enrich environment, rehabilitation**
Primary (intrinsic)	Core disease process, enduring	**Poor drug response; the residue after secondary causes are excluded**

The four treatable sources of secondary negative symptoms against the intrinsic primary form; the discriminator is reversibility, and each secondary cause has a different remedy, which is why they must be separated.

RULE **Always separate primary from secondary.** Exclude positive symptoms, depression, extrapyramidal side effects and understimulation first; only the residue is primary. The treatable causes differ, so the split dictates the treatment.

TRAP **Calling drug-induced parkinsonism or a depressive episode "primary negative symptoms."** Masked facies, bradykinesia and amotivation from an antipsychotic, or depressive anhedonia, are reversible mimics; labelling them primary abandons a treatable patient.

COMMON TRAP

The neuroleptic-induced deficit syndrome is the classic mimic: high-dose D2 blockade blunts affect and drive so closely that it looks like the disease's own negative symptoms (Stahl). A parkinsonian patient on a high antipsychotic dose who is flat and avolitional needs the dose questioned, not a "poor prognosis" label. Antipsychotics, their adverse effects and dosing are developed in the Schizophrenia: management, antipsychotics and adverse effects notes.

10.5 The deficit syndrome (Carpenter)

The validated subgroup. The deficit syndrome, defined by Carpenter and colleagues, is the presence of enduring **primary** negative symptoms that persist between episodes and during periods of clinical stability, not attributable to positive symptoms, depression, medication or understimulation (Carpenter et al. 1988; Kaplan & Sadock 2024). It is operationalised by the Schedule for the Deficit Syndrome, which requires at least two negative symptoms present in the preceding year, from restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose and diminished social drive. It is now generally accepted as a separate disease process within schizophrenia, not merely severe illness.

The distinct picture. Deficit-syndrome patients have a poorer prognosis for functional recovery, more insidious onset with progressive negative symptoms, worse premorbid function, lower quality of life and a poor response of the negative symptoms to medication or social-skills training. Notably they have no more delusions or hallucinations than non-deficit patients, less prominent dysphoria, and fewer suicidal ideas and attempts, a discriminating profile the examiner rewards. Where a formal deficit assessment is impractical, Buchanan's persistent negative symptoms criterion offers a pragmatic proxy: schizophrenia plus at least two negative symptoms for at least 12 months during clinical stability, not due to comorbidity or medication.

~15%	25 to 30%	≥2
DEFICIT SYNDROME, FIRST-EPISODE	DEFICIT SYNDROME, CHRONIC	NEGATIVE SYMPTOMS IN PAST YEAR (SDS)

A meta-analysis of 23 studies put the overall rate near 30 percent, with rates lower early in the illness and rising over the first five years (Kaplan & Sadock 2024). Roughly **~15%** of first-episode and **25 to 30%** of chronic patients meet deficit-syndrome criteria (Tasman 2024).

TRAP **Equating "deficit syndrome" with "severe schizophrenia."** It is a distinct, validated subgroup with its own course and a paradoxically *lower* suicide and dysphoria burden, not simply the worst end of a severity spectrum.

10.6 Assessment: the scales

The instruments. The first purpose-built scale was Andreasen's sans (Scale for the Assessment of Negative Symptoms), paired with the SAPS for positive symptoms; it covers affective flattening, alogia, avolition-apathy, anhedonia-asociality and attentional impairment (Andreasen 1982). In practice the negative subscale of the panss (Positive and Negative Syndrome Scale) became the research and trial standard, though its original three-subscale split (30 items: 7 positive, 7 negative, 16 general psychopathology) does not map cleanly onto the true five-factor structure (Kay et al. 1987). The newer second-generation scales, built directly on the MATRICS five-domain consensus, are the BNSS (Brief Negative Symptom Scale, Kirkpatrick 2011) and the CAINS (Clinical Assessment Interview for Negative Symptoms, Kring & Blanchard 2013); both separate the motivation-and-pleasure factor from diminished expression, and the BNSS was designed for both research and busy clinical settings.

SCALE	WHAT IT IS	ONE THING TO KNOW
SANS	Andreasen's dedicated negative-symptom scale (with SAPS)	**First purpose-built; five sub-scales including attention**
PANSS negative subscale	Negative arm of the 30-item PANSS	**Trial standard; original split predates the five-factor model**
BNSS	Brief Negative Symptom Scale (Kirkpatrick)	**MATRICS-based; separates the two factors; clinic-usable**
CAINS	Clinical Assessment Interview for Negative Symptoms	**MATRICS-based; motivation-and-pleasure vs expression**

The four assessment instruments; the discriminator is generation, SANS and the PANSS negative subscale are first-generation, while the BNSS and CAINS are second-generation, built on the two-factor MATRICS consensus.

HOLD THIS

Deficit syndrome = enduring PRIMARY negative symptoms (Carpenter), persisting between episodes and NOT due to positive symptoms, depression, extrapyramidal side effects or understimulation; that persistence between episodes is the whole discriminator.

GOOD TO REMEMBER

- **Negative symptom:** a loss or diminution of normal function (contrast the positive symptom, an addition); best single predictor of long-term social disability.
- **The five A's:** affective flattening, alogia, avolition, anhedonia, asociality; the MATRICS (2005) five negative-symptom domains.
- **Two-factor grouping:** avolition-apathy (avolition, anhedonia, asociality, interview-elicited) versus diminished expression (affective flattening, alogia, clinician-observed); the basis for DSM-5-TR "diminished emotional expression or avolition."
- **Secondary negative symptoms:** caused by positive symptoms, depression, extrapyramidal side effects or understimulation; potentially reversible; treat the driver.
- **Primary negative symptoms:** intrinsic, enduring, the least variable symptoms; poor drug response; the residue after secondary causes are excluded.
- **Deficit syndrome (Carpenter):** enduring primary negative symptoms persisting between episodes; a validated distinct subgroup, roughly 15 percent first-episode and 25 to 30 percent chronic; discriminator is persistence outside episodes and outside depression/extrapyramidal effects.
- **Scales:** SANS (Andreasen) and PANSS negative subscale (first-generation); BNSS and CAINS (second-generation, MATRICS-based, two-factor).

11 · Disorganisation: disorganised speech and behaviour

The **disorganisation** (disorganization) domain is the third arm of the phenomenology of schizophrenia, distinct from the positive and negative domains and repeatedly pulled out as its own factor on factor-analytic work. It has two observable faces: **disorganised speech** (disorganized speech), which is the clinically visible surface of formal thought disorder, and **disorganised behaviour** (disorganized behavior), the disturbance of goal-directed action together with inappropriate affect. Both are inferences drawn from what the examiner can watch and hear, which is exactly why they carry weight in an assessment.

Why this matters. The raw descriptive definitions of the signs, what formal thought disorder, a neologism or inappropriate affect *is* as a phenomenon, are not re-derived here; they belong to the Psychometry, Assessment and Descriptive Psychopathology notes, and this topic applies them to schizophrenia. The examiner rewards the resident who understands that we never observe thought directly: we observe speech and behaviour and infer a disorder of thought form from them. In ICD-11 this domain is written explicitly as "formal thought disorder (typically manifested as disorganized speech) and disorganized behaviour" (ICD-11 CDDR 2024), so the vocabulary of this topic is the vocabulary the criteria themselves use.

11.1 Disorganised speech is the observable face of formal thought disorder

The core principle. Formal thought disorder refers to an abnormality in the coherence and logical structure of thought, the "how" or mechanics of thinking rather than its content, which makes conversation difficult to follow or at times incomprehensible (Companion to Psychiatric Studies). We cannot inspect the form of thought directly, so disorganised speech (disorganized speech) is the clinical evidence from which formal thought disorder is inferred. This is why ICD-11 and DSM-5-TR both phrase the criterion as formal thought disorder "typically manifested as

disorganized speech" (ICD-11 CDDR 2024): the speech is the sign, the thought disorder is the construct.

RULE **Speech is the evidence, thought disorder is the inference.** Disorganised speech is the clinical evidence of formal thought disorder; you rate the disorder only from an actual sample of the patient's speech, never from a global impression.

TRAP **Labelling culturally normal or dialectal speech as thought-disordered.** Speech that is indirect, allusive, code-switched or dialectal in the patient's own linguistic culture, or fluent in a non-native second language, can look loose to an examiner outside that culture; that is a language and register phenomenon, not formal thought disorder.

11.2 Derailment and loosening of associations

The prototype. Derailment, historically loosening of associations and also called tangential or "knight's move" thinking, is the prototype of disorganised speech: the train of thought slips off its track onto an idea that is obliquely related or completely unrelated (Andreasen 1979). Individual derailments may be slight, so the speaker digresses only gradually from the original point, or the links may be plainly obscure. The meaning is typically lost across several sentences, which distinguishes it from incoherence, where the individual sentence itself is already meaningless. Bleuler's original "loosening of associations" was one of his four fundamental symptoms, so this sign sits at the historical centre of the concept of schizophrenia.

11.3 Tangentiality and circumstantiality: the pair to separate

The discriminator. Tangentiality is an oblique or irrelevant reply to a question in which the speaker never returns to the goal, whereas circumstantiality is speech that is very indirect and delayed in reaching its goal, loaded with tedious detail and parenthetical remarks, but which does eventually arrive at the point (Andreasen 1979). The single distinguishing feature is whether the goal idea is ultimately reached: circumstantial speech gets there by a long road, tangential speech never gets there at all. Circumstantiality is not specific to schizophrenia and is common in normal individuals, the obsessional, and organic states, so it carries far less diagnostic weight than derailment.

SIGN	WHAT HAPPENS	DISCRIMINATOR
Circumstantiality	Long, over-detailed, parenthetical route to the answer	**The goal idea is eventually reached**
Tangentiality	Oblique or irrelevant reply that veers away	**The goal idea is never reached**
Derailment	Train of thought slips track across sentences	**Meaning lost over several sentences; links obscure**
Incoherence (word salad)	Individual sentences themselves meaningless	**Breakdown at the single-sentence level**

The disorganised-speech spectrum ordered by severity; the examiner's favourite pair is circumstantiality versus tangentiality, separated by whether the point is ever reached.

11.4 Word salad, incoherence and clang associations

The severe end. Word salad (incoherence, schizophasia) is the severe pole: speech that is essentially incomprehensible, where the individual sentence itself has no meaning because grammar and syntax are ignored or cementing words are dropped (Companion to Psychiatric Studies; Andreasen 1979). Clang associations are a pattern in which word choice is governed by sound, rhyme or pun rather than meaning, so that a word similar in sound drags in a new thought. Clanging is classically emphasised in mania alongside flight of ideas, but it also appears in the disorganised speech of schizophrenia; its presence should therefore prompt a careful look for an affective picture, because diagnosing schizophrenia inside an untreated mood episode is a standard error. Flight of ideas and clang associations as mood-related thought-form disorders, and delusional mood, cross-reference to the Psychometry, Assessment and Descriptive Psychopathology notes.

11.5 Neologisms and word approximations

The invented word. A neologism is a newly formed word or phrase whose derivation cannot be understood, coined to express a concept for which the patient has no dictionary word (Andreasen 1979); classic examples are invented tokens such as "tarn-harn". The term is also loosely applied to existing words used in idiosyncratic ways. A related, milder variant is the word approximation (paraphasia), where an imprecise or old word is substituted for a familiar one, for instance a patient speaking of having "a menu three times a day" instead of three meals a day (Cameron 1938). Neologisms are often found in conjunction with incoherence, so their appearance signals the more severe end of the spectrum.

WORKED EXAMPLE

Asked how she was brought to hospital, a patient replied, "In a convestation, you fool" (Kaplan & Sadock 2024). "Convestation" is a neologism: an invented word with no recoverable dictionary meaning, embedded in speech that is otherwise grammatically intact, which locates the disturbance at the level of word formation rather than whole-discourse derailment.

11.6 Poverty of content of speech: the bridge to the negative domain

The empty message. Poverty of content of speech (alogia of content) is speech that is adequate in amount but conveys little information because it is vague, over-abstract, over-concrete, repetitive or stereotyped; the replies are long enough but the message is empty (Andreasen 1979). It must be separated from *poverty of speech* (reduced amount of speech), which is a negative symptom akin to avolition affecting the domain of speech (Companion to Psychiatric Studies). Poverty of content is conventionally grouped with the disorganisation domain because the disturbance is in the form and informativeness of the message, whereas poverty of speech, blunted affect and avolition belong to the negative domain; the two are easy to confuse and are separated by amount (poverty of speech) versus emptiness (poverty of content).

HOLD THIS
Disorganised speech is the observable evidence of formal thought disorder; you must quote an actual example of the patient's speech, and circumstantiality reaches its goal whereas tangentiality never does.

11.7 Disorganised behaviour: impaired goal-directed activity and bizarre acts

The behavioural face. Disorganised behaviour (disorganized behavior) in ICD-11 is "grossly disorganized behaviour that impedes goal-directed activity", behaviour that appears bizarre or purposeless, unpredictable, or with inappropriate emotional responses that interfere with the ability to organise behaviour (ICD-11 CDDR 2024). It ranges from difficulty performing everyday sequenced tasks and neglect of self-care through to overtly bizarre, purposeless acts. The defining feature is the breakdown of goal-directed activity: the behaviour is not organised toward an end. ICD-11 explicitly separates this from abnormal psychomotor and catatonic behaviour, which is rated in a distinct psychomotor domain, not here.

11.8 Inappropriate affect (incongruity of affect)

The mismatch. Inappropriate affect (incongruity of affect) is emotional expression that is discordant with the thought content or situation, for example laughing while describing a bereavement, and is grouped within the disorganisation picture rather than the negative domain. It is distinct from *blunted or flat affect*, which is a reduction in the range and intensity of emotional expression and is a negative symptom: incongruity is a mismatch of affect, blunting is a loss of affect. Incongruity of affect was, with thought disorder, one of the features Bleuler and later clinicians attached particular significance to as a fundamental disturbance of schizophrenia (Companion to Psychiatric Studies).

TRAP **Confusing inappropriate affect with blunted affect.** Inappropriate (incongruous) affect is a mismatch between emotion and context and sits in the disorganisation domain; blunted or flat affect is an absence of emotional expression and sits in the negative domain.

11.9 Catatonia: flagged here, developed elsewhere

The pointer. Catatonic phenomena, stupor, mutism, negativism, posturing, waxy flexibility, echolalia, echopraxia, stereotypies and excitement, form part of the broader disorganised and psychomotor picture and were historically Kraepelin's catatonic subtype. They are flagged here only as part of that picture; ICD-11 rates them in a separate psychomotor-symptoms domain and treats catatonia as its own entity that can be associated with schizophrenia or arise independently. Catatonia as an entity, its full sign list, its assessment scales and its management, is developed in the Other psychotic disorders, delusional syndromes and catatonia notes, not here. Its management, and the management of schizophrenia as a whole, points forward to the Schizophrenia: management, antipsychotics and adverse effects notes.

GOOD TO REMEMBER

- **Formal thought disorder:** disorder of the form or coherence of thought (the "how" of thinking), inferred from speech; discriminator is that it is the construct, and disorganised speech is its observable evidence.
- **Derailment / loosening of associations:** train of thought slips track onto obliquely or unrelated ideas (Andreasen 1979); discriminator is meaning lost over several sentences, and it was one of Bleuler's fundamental symptoms.
- **Tangentiality:** oblique reply that veers off; discriminator is the goal idea is *never* reached.
- **Circumstantiality:** over-detailed, delayed route to the answer; discriminator is the goal idea *is* eventually reached, and it is non-specific (common in normals and organic states).
- **Incoherence / word salad (schizophasia):** speech incomprehensible at the single-sentence level; discriminator is breakdown within the sentence, versus derailment across sentences.
- **Clang associations:** word choice governed by sound, rhyme or pun; discriminator is its classic link to mania, so it should prompt a search for a mood episode.
- **Neologism:** invented word whose derivation cannot be understood (Andreasen 1979); discriminator is a novel token with no dictionary meaning, versus the milder word approximation (paraphasia).
- **Poverty of content of speech:** adequate amount but empty message (Andreasen 1979); discriminator is amount preserved but informativeness lost, versus poverty of speech (reduced amount, a negative symptom).
- **Disorganised behaviour:** grossly disorganised, bizarre or purposeless behaviour impeding goal-directed activity (ICD-11 CDDR 2024); discriminator is the breakdown of goal direction, rated separately from catatonic psychomotor signs.
- **Inappropriate (incongruous) affect:** emotion discordant with context; discriminator is a mismatch of affect (disorganisation domain), versus blunted affect which is a loss of affect (negative domain).

MNEMONIC

Speech disorganisation "DDT-C-N-P": Derailment, Distractibility/Tangentiality, word-salad (incoherence), Circumstantiality, Neologism, Poverty-of-content

Run the disorganised-speech signs as **D**erailment (loosening of associations), **T**angentiality, word salad / incoherence, **C**lang and **C**ircumstantiality, **N**eologism (with word approximations), and **P**overty of content of speech; then add the two behavioural signs, disorganised behaviour and inappropriate affect.

INDIA

In a multilingual, code-switching setting, an examiner who does not share the patient's language or dialect can over-call formal thought disorder: allusive narration, proverb-heavy speech, or fluent code-switching between languages is a register phenomenon, not disorganised speech. Assess speech form in the language the patient is most fluent in, ideally with an interpreter who can flag what is culturally normal, before rating derailment or tangentiality.

12 · Schneider's first-rank symptoms and Bleuler's fundamental symptoms

Why this matters. Two great phenomenological frameworks shaped how a century of psychiatry decided who has schizophrenia, and examiners love to test whether you can keep them apart. **Eugen Bleuler** asked what lies at the *core* of the illness and answered with his fundamental symptoms, the four A's; **Kurt Schneider** asked which symptoms make the diagnosis *reliable* in the clinic and answered with his first-rank symptoms. The two men were solving different problems, and confusing their lists is the classic exam error. This topic applies both frameworks to schizophrenia and cross-references the raw descriptive definitions of the underlying phenomena, what a delusion, a hallucination or a passivity experience actually is, to the Psychometry, Assessment and Descriptive Psychopathology notes rather than re-defining them here.

The governing tension is one line: Schneider's symptoms are pragmatic diagnostic pointers with no claim to being the essence of the illness, whereas Bleuler's are a theory of what schizophrenia fundamentally *is*. Neither list survives as a diagnostic test in modern nosology, and that loss of status is itself high-yield (Kaplan & Sadock 2024, Gelder et al. 2013).

12.1 Two frameworks, two different questions

Bleuler (1911), renaming Kraepelin's dementia praecox as the "group of schizophrenias", was concerned with the psychological mechanism of the disorder and asked what feature was present in every case. His answer was a splitting or loss of harmonic coordination among thought, emotion and behaviour, captured in the fundamental symptoms. Kurt Schneider (1959), by contrast, made no claim about the essence of schizophrenia; he simply identified a group of symptoms of the first rank that, in the absence of coarse brain disease, made the diagnosis more reliable in everyday practice (Kaplan & Sadock 2024). Older texts write the term as either "first-rank" or "first rank", and both spellings refer to the same Schneiderian set. It is worth noting explicitly that, unlike Bleuler's fundamental symptoms, Schneider's symptoms were never supposed to have any central psychopathological role, merely that they were valuable in making the diagnosis (Gelder et al. 2013).

RULE **Bleuler asks what schizophrenia is; Schneider asks how to spot it reliably.** Fundamental symptoms are a theory of the core; first-rank symptoms are pragmatic diagnostic pointers.

12.2 Schneider's first-rank symptoms: the enumerated list

The Schneiderian first-rank symptoms are a defined set of eleven phenomena, and residents are expected to reproduce them. Their descriptive definitions belong to the Psychometry, Assessment and Descriptive Psychopathology notes; here we enumerate them as applied to schizophrenia (Schneider 1959, Kaplan & Sadock 2024). They fall into three natural families: special auditory hallucinations, disorders of the possession and control of thought, and made experiences of feeling, impulse and act, with delusional perception standing on its own. Somatic passivity and the made experiences together constitute the passivity phenomena, in which the patient experiences his own feelings, impulses or acts as imposed by an external agent.

Audible thoughts (thought echo)
Hearing one's own thoughts spoken aloud, as they are thought or echoed just after (Gedankenlautwerden).

Voices arguing or discussing (third person)
Two or more voices arguing or discussing the patient among themselves, referring to him as "he" or "she".

Voices commenting (running commentary)
A voice giving a continuous commentary on the patient's actions or thoughts as they happen.

Thought withdrawal
The sensation that thoughts are actively removed from the mind by an external agent.

Thought insertion
Thoughts experienced as placed into the mind by an outside agency, not the patient's own.

Thought broadcasting
The sense that one's thoughts escape and are experienced as real by others, made audible or known by telepathy.

Made feelings, impulses and acts
Feelings, impulses or volitional acts experienced as imposed and controlled by an external agent; the patient is a passive participant.

Somatic passivity
Bodily (tactile or visceral) sensations experienced as imposed on the patient by an outside agency.

Delusional perception
A normal percept to which a sudden, unquestionable and idiosyncratic delusional meaning is attached; a two-stage phenomenon.

12.3 The logic of the first-rank list

The list is easier to hold once its structure is clear. Three of the eleven are the special auditory hallucinations (audible thoughts, third-person voices, running commentary). Three are disorders of the possession of thought (thought withdrawal, thought insertion, thought broadcasting). Three are the made experiences of the will (made feelings, made impulses, made acts), which with somatic passivity form the passivity group where the boundary between self and outside agency has broken down. The last, delusional perception, is unique in being a two-stage event: a correctly perceived, normal percept followed instantly by an unshakeable delusional interpretation. This determination of what is part of the self and what is not, lost in passivity, is the thread that unifies most of the list.

WORKED EXAMPLE

A man reports that his own thoughts are spoken back to him a beat after he thinks them (thought echo), that "they lift the thoughts straight out of my head" mid-sentence (thought withdrawal), and that when he raised his arm to drink it was "not me, they moved it for me" (a made act, passivity). Seeing a traffic light turn green, he knew at once and without reasoning that he had been appointed to lead the city (delusional perception: the percept is accurate, only the attached meaning is delusional). Four first-rank symptoms are present, which raises strong suspicion of schizophrenia but, on their own, do not confirm it.

12.4 The modern caveat: first-rank symptoms are not pathognomonic

The single most tested point about Schneider is a corrective one: first-rank symptoms are not pathognomonic of schizophrenia. When first described, the presence of one first-rank symptom in the absence of intoxication, brain injury or clear affective illness was sometimes taken as sufficient for the diagnosis (Kaplan & Sadock 2024). This no longer holds. First-rank symptoms occur in mania, where Schneiderian symptoms have been reported in roughly 10 to 20 percent of manic patients, and in organic psychoses; and they are absent in many people who clearly have schizophrenia (Gelder et al. 2013). It has been clear for decades that no single hallucination or delusion, however carefully specified, confirms or excludes schizophrenia by itself. Nothing about a symptom being pathognomonic can be claimed for any item on the list.

RULE **First-rank symptoms raise suspicion of schizophrenia but are not diagnostic.** They point; they do not prove. Assess form, persistence and mood context before applying the label.

TRAP **Calling first-rank symptoms pathognomonic of schizophrenia.** They occur in mania and organic psychoses and are absent in many with schizophrenia; they are not pathognomonic, and DSM-5 and ICD-11 have removed their privileged diagnostic status.

12.5 Loss of special status in DSM-5 and ICD-11

Both current systems have stripped the first-rank symptoms of their special diagnostic weight. DSM-5-TR and ICD-11 eliminated the special diagnostic importance previously given to Schneiderian symptoms such as running-commentary hallucinations, two or more voices conversing, and bizarre delusions; delusions are now weighed equally toward the diagnosis regardless of their content, and no single symptom is privileged as sufficient (Kaplan & Sadock 2024). DSM-5 raised the symptom threshold from one core symptom to at least two of Criterion A, so that a lone first-rank symptom can no longer carry the diagnosis. The detail of the current criteria, and how ICD-11 runs its symptom items forward with DSM-5-TR cross-mapped and the legacy ICD-10 first-rank weighting, is developed in the criteria topic; the point to hold here is that the Schneiderian era of privileged first-rank symptoms has closed.

INDIA

Where the exit examination and many Indian question banks still test ICD-10, the first-rank symptoms retain their old prominence: ICD-10 weighted thought echo, insertion, withdrawal and broadcasting; passivity and delusional perception; and third-person and running-commentary voices, with one such symptom for one month sufficing. Reproduce the Schneiderian list when the paper asks for ICD-10, but know that ICD-11 and DSM-5 have dropped their special status.

12.6 Bleuler's fundamental symptoms: the four A's

Bleuler divided the symptoms of schizophrenia into fundamental (primary) and accessory (secondary). The fundamental symptoms, present in every case and forming the diagnostic core, are the four A's (Bleuler 1911, Kaplan & Sadock 2024). Their raw descriptive meanings, what loosening of associations or blunted affect actually is, sit in the Psychometry, Assessment and Descriptive Psychopathology notes; here we hold them as Bleuler's account of the essence of schizophrenia. He saw a splitting, a loss of harmonic coordination among thought, emotion and behaviour, as the hallmark, and the four A's are its expression.

Associations (loosening of associations)

Disturbed logical connection between ideas, so that the thread of thought loosens and drifts; Bleuler's central disturbance.

Affect (blunting and incongruity)

Flattening, shallowness or incongruity of emotional response; the outward emotion no longer matches the situation or the thought.

Ambivalence

The simultaneous holding of opposite feelings, wishes or ideas about the same object, without their resolution.

Autism

Withdrawal from external reality into a private inner world, with thought and behaviour dominated by inner life rather than shared reality.

MNEMONIC

The four A's

Associations (loosening), **A**ffect (blunted or incongruous), **A**mbivalence, **A**utism. All 4 A words begin with A and are Bleuler's fundamental symptoms; hallucinations and delusions are conspicuously not among them.

12.7 Bleuler's accessory symptoms and "the schizophrenias"

What most people, patients and clinicians alike, regard as the striking face of schizophrenia, Bleuler regarded as merely secondary. For him hallucinations, delusions, social withdrawal and diminished drive were accessory symptoms: real, often dramatic, but dependent on the individual's adaptive capacity and circumstances, and not the essence of the disorder (Kaplan & Sadock 2024). This inverts the modern intuition, and it is exactly the inversion examiners probe. Bleuler also reframed Kraepelin's single dementia praecox as a group, "the schizophrenias",

holding that these were several related conditions sharing the fundamental disturbance rather than one disease; and he saw the symptoms as lying on a continuum with normal behaviour, a breadth that later contributed to over-diagnosis until formal criteria narrowed the concept.

PEARL

The single cleanest contrast: for Bleuler, hallucinations and delusions are accessory (secondary); the fundamental symptoms are the four A's. For most clinicians and the public, hallucinations and delusions *are* schizophrenia. Holding this reversal straight is what the question is testing.

12.8 Schneider versus Bleuler: setting the two lists side by side

The two frameworks are complementary, not competing, and the table below keeps them apart. Note the near-total non-overlap: Schneider's list is built almost entirely from hallucinations, passivity and delusional perception, the very phenomena Bleuler called accessory; Bleuler's list is built from disturbances of association, affect, volition and relatedness, none of which appears among Schneider's first-rank symptoms. A patient can show florid first-rank symptoms with little of the four A's, or a chronic defect state rich in the four A's with no first-rank symptoms at all.

SCHNEIDER'S FIRST-RANK SYMPTOMS	FAMILY
Audible thoughts (thought echo)	Special auditory hallucination
Voices arguing or discussing in the third person	Special auditory hallucination
Voices commenting (running commentary)	Special auditory hallucination
Thought withdrawal	Disorder of possession of thought
Thought insertion	Disorder of possession of thought
Thought broadcasting	Disorder of possession of thought
Made feelings, made impulses, made acts (passivity)	Made experience of the will
Somatic passivity	Made bodily experience
Delusional perception	Two-stage delusional phenomenon

Schneider's first-rank symptoms grouped by family: three auditory, three thought-possession, the made experiences with somatic passivity, and delusional perception.

BLEULER'S FOUR A'S (FUNDAMENTAL)	NATURE OF THE DISTURBANCE
Loosening of associations	Disturbed linkage of ideas; Bleuler's central sign
Affect (blunting, incongruity)	Emotional response flattened or mismatched
Ambivalence	Opposite feelings or wishes held at once, unresolved
Autism	Withdrawal into a private inner world

Bleuler's four A's, the fundamental symptoms; hallucinations and delusions are accessory and deliberately absent from this list.

COMMON TRAP

Muddling the two lists, for example putting hallucinations or delusions among Bleuler's fundamental symptoms, or listing loosening of associations as a first-rank symptom. Bleuler's four A's contain no hallucination or delusion (those are accessory); Schneider's first-rank symptoms contain no loosening of associations, blunted affect, ambivalence or autism.

GOOD TO REMEMBER

- **Schneider's first-rank symptoms (Schneider 1959):** eleven pragmatic diagnostic pointers, audible thoughts, third-person and running-commentary voices, thought insertion/withdrawal/broadcasting, made feelings/impulses/acts and somatic passivity (passivity), and delusional perception; central claim is that they make the diagnosis reliable, not that they are its essence; the discriminator to hold is that they are not pathognomonic, occurring in roughly 10 to 20 percent of manic patients and in organic psychoses.
- **Delusional perception:** a first-rank symptom in which a normal, correctly perceived percept acquires a sudden unquestionable delusional meaning; the discriminator is that it is two-stage and the perception itself is normal, so it is a disorder of thought, not perception.
- **Passivity (made experiences and somatic passivity):** feelings, impulses, acts or bodily sensations experienced as imposed by an external agent; the discriminator is the loss of the sense of self versus outside agency, the thread uniting most first-rank symptoms.
- **Bleuler's fundamental symptoms (Bleuler 1911):** the four A's, loosening of associations, affect (blunting/incongruity), ambivalence and autism; central claim is that they are the primary core present in every case; the discriminator is that hallucinations and delusions are deliberately excluded from this list.
- **Bleuler's accessory symptoms:** hallucinations, delusions, social withdrawal and diminished drive; central claim is that they are secondary and depend on the person's adaptive capacity; the discriminator is that the modern intuition inverts Bleuler, treating these very symptoms as the face of schizophrenia.
- **"The schizophrenias":** Bleuler's reframing of Kraepelin's single dementia praecox as a group of related conditions sharing the fundamental disturbance; the discriminator is that it introduced both the name schizophrenia (splitting of psychic functions) and a continuum-with-normality view that later widened the diagnosis.

HOLD THIS

Bleuler's four A's (associations, affect, ambivalence, autism) are the fundamental core with hallucinations and delusions merely accessory; Schneider's first-rank symptoms are reliable diagnostic pointers that are not pathognomonic and have lost their special status in DSM-5 and ICD-11.

13 · Cognitive impairment, insight and cognition as a treatment target

Cognition is the part of schizophrenia the examiner most often rewards a resident for taking seriously, because it is the part that decides whether a patient works, lives independently and keeps relationships, yet it appears nowhere in the diagnostic criteria. Two threads run through this topic: the **cognitive impairment** of schizophrenia (its domains, its status as a core feature, its power over function), and the closely related clinical construct of **insight**. Both are separable from positive symptoms, both predict outcome, and both are now framed as things to measure and, where possible, to treat.

Why this is the payoff. Neurocognitive deficits explain work performance and independent living better than positive or negative symptoms do, they are present before onset and in unaffected relatives, and they are the aspect of the illness most tightly correlated with measurable brain dysfunction (Kaplan & Sadock 2024). Dopamine D2 antipsychotics abolish delusions and hallucinations but leave cognition essentially untouched, which is exactly why cognition has become a distinct **treatment target**. The single most examinable move is to hold two facts together: cognition predicts functional outcome, and the drugs that treat psychosis do not fix cognition.

13.1 The neurocognitive impairment of schizophrenia

Magnitude. Patients with schizophrenia perform, on average, one to two standard deviations below healthy controls across a broad range of neurocognition tests, and this cognitive impairment is broad, severe and present in most, if not all, patients (Harvey, in Kaplan & Sadock 2024). It is detectable in unmedicated first-episode patients at a magnitude close to that of established illness, so it is not an artefact of chronicity or of medication. Deficits are also strikingly similar across countries, educational systems and ethnic groups, which argues that they are intrinsic to the disease rather than a product of environment.

1 to 2 SD	~15%	<10%
BELOW CONTROLS ON COGNITION	RATED CLINICALLY "UNIMPAIRED"	VARIANCE SHARED WITH POSITIVE SYMPTOMS

About **~15%** of patients are rated "unimpaired" on clinical neuropsychological testing, but even these individuals perform well below what their premorbid level and parental education would predict, and monozygotic twins discordant for schizophrenia almost always show the affected twin performing worse than the unaffected co-twin (Kaplan & Sadock 2024). In other words, almost every patient is functioning below their own expected baseline.

13.2 The domains affected (the MATRICS seven)

Which functions. The Neurocognition Subcommittee of the MATRICS project (Measurement and Treatment Research to Improve Cognition in Schizophrenia) fixed seven separable domains as the core impaired functions, chosen because they are substantially impaired, distinct from one another and each linked to functional outcome (Green & Nuechterlein; Kaplan & Sadock 2024). These are the domains the MATRICS Consensus Cognitive Battery (MCCB) was built to measure.

Processing speed

Speed of simple information handling (digit symbol, symbol coding, Trail Making A). Often the single strongest discriminator between patients and controls; accounted for more variance than any other measure in the CATIE cognitive data.

Working memory

Holding and manipulating information "online" for seconds (digits backward, spatial span). Described by many authors as a core component of the impairment, tied to prefrontal circuitry and to employment outcome.

Attention / vigilance

Sustained attention over time, tested by the Continuous Performance Test. Moderately-to-severely impaired; underlies difficulty following conversations, instructions and treatment.

Verbal learning and memory

Learning and retaining word lists or stories. Deficit is greater in learning than in retention; unlike Alzheimer disease, patients do not show rapid forgetting of what they did learn.

Visual learning and memory

Learning and reproducing visual material. Fewer sensitive tests exist; correlations with outcome are more modest and mixed.

Reasoning and problem-solving

"Executive function," classically the Wisconsin Card Sorting Test, on which patients perseverate like frontal-lobe patients; drove the frontal-hypoactivation hypothesis.

Social cognition

Theory of mind and facial-affect / social-cue perception. Impaired and, on recent evidence, more strongly tied to social functioning than general neurocognition, largely mediating the link between general cognition and social deficits.

MNEMONIC

Speedy Workers Attend, Verbally and Visually Reasoning Socially

The seven MATRICS domains: **Speed** of processing, **Working** memory, **Attention**/vigilance, **Verbal** learning and memory, **Visual** learning and memory, **Reasoning** and problem-solving, **Social** cognition.

13.3 Cognition as a core feature: the cognitive hypothesis

Core, not consequence. The claim that cognition is a **core feature** of schizophrenia, the framing sometimes called the cognitive hypothesis of schizophrenia, rests on three lines of evidence (Kaplan & Sadock 2024). First, the deficits precede psychosis: in follow-back and high-risk cohorts, low verbal, nonverbal and mathematical test scores are present in childhood and adolescence in those destined to develop the illness, and are prominent during the prodrome. Second, they are heritable and familial: first-degree relatives, including unaffected co-twins, are impaired on cognitive measures (small-to-medium effect sizes), consistent with cognition as an endophenotype. Third, and decisively, they are separable from symptoms: the variance shared between neurocognition and positive symptoms is typically less than **10%**, and when psychosis remits with treatment, cognition does not change with it. Kraepelin and Bleuler both placed cognitive deterioration at the centre of the illness over a century ago.

RULE **Cognition predicts function best.** Neurocognitive deficits explain community functioning, independent living and employment better than positive or negative symptoms, and predict functional status years later.

13.4 Functional impact

Why it matters clinically. The functional impact of cognition is the reason the topic exists. Across the three outcomes most studied, community (social and occupational) function, performance of simulated interpersonal and living skills, and success in psychosocial rehabilitation, every key MATRICS domain shows a significant, medium-sized relationship to outcome (Kaplan & Sadock 2024). Processing speed and verbal memory predict work behaviour and competitive employment; patients in full-time competitive work outperform the unemployed on working memory, attention, problem-solving and episodic memory, with part-time workers in between. Crucially, in patients whose function worsens over time, change in cognition predicts the change while change in negative symptoms does not, another line of evidence that cognition, not symptom fluctuation, carries the disability.

WORKED EXAMPLE

A 26-year-old with stabilised schizophrenia has no delusions or hallucinations on his current antipsychotic, yet cannot hold a supermarket shelf-stacking job: he loses track of instructions mid-task and works too slowly to keep pace. His positive symptoms are controlled; his working memory and processing speed are not. The exam-correct formulation is that residual neurocognitive impairment, not residual psychosis, is driving the occupational failure, which is why cognitive remediation and workplace support, addressed in the Schizophrenia: management, antipsychotics and adverse effects notes, matter more here than a further antipsychotic dose change.

13.5 Why cognition became a treatment target

The gap D2 blockade leaves. Antipsychotics have a pronounced effect on psychotic symptoms but there is currently little pharmacological relief for the neurocognitive impairment of schizophrenia (Kaplan & Sadock 2024). The NIMH CATIE trial compared four second-generation drugs and a first-generation comparator (perphenazine) under randomised, double-blind conditions: cognitive scores improved a little in every arm with none distinguishable from another, and even that small gain was interpreted as practice and expectation effects rather than true drug benefit. High-dose first-generation drugs, and the anticholinergics used to manage their extrapyramidal effects, can actively worsen cognition. The conclusion the examiner wants is blunt: dopamine D2 antipsychotics do not restore cognition, so cognition has to be pursued as a separate, **cognition-targeting** objective.

TRAP **Assuming D2 antipsychotics restore cognition.** They do not. Second-generation drugs give minimal-to-no cognitive benefit over first-generation ones in rigorous trials (CATIE), and high-dose D2 blockade plus anticholinergics can make cognition worse.

The two routes. Because pharmacology alone has failed, the field pursues two complementary strategies. The non-pharmacological route is cognitive remediation therapy: structured strategy-teaching and compensatory training that, in meta-analysis, produces moderate gains in cognitive performance and improves functional outcome when combined with psychosocial rehabilitation (Wykes et al. 2011; Kaplan & Sadock 2024). Its likely mechanism is experience-dependent neuroplasticity, which is why remediation may be a necessary substrate for any pro-cognitive

drug to show effect. The detail of remediation as a therapy, and the drugs below as licensed products, belongs to the Schizophrenia: management, antipsychotics and adverse effects notes; here they are covered only as the rationale for cognition-as-target.

13.6 The muscarinic route: xanomeline and KarXT

A non-dopaminergic mechanism. The most important recent **pro-cognitive** and antipsychotic strategy is the muscarinic agonist route. Xanomeline is a central muscarinic M1/M4 agonist: M4 agonism reduces dopamine cell firing in the ventral tegmental area (theoretically reducing positive symptoms), while M1 agonism increases prefrontal dopamine and is the arm thought most relevant to improving cognition (Stahl 2021). Given alone, xanomeline causes peripheral cholinergic side effects (nausea, vomiting, sweating). It is therefore combined with trospium, a peripherally-restricted anticholinergic that does not cross the blood-brain barrier and blocks the peripheral muscarinic side effects while leaving the central agonism intact. This combination is KarXT (xanomeline-trospium, marketed as Cobenfy).

State the mechanism accurately. The examinable point is mechanistic: unlike every previously approved antipsychotic, KarXT does not directly bind dopamine receptors; its therapeutic effect is mediated through direct agonism of muscarinic acetylcholine receptors (M1 and M4) rather than D2 blockade (Maudsley 15th ed.). A post-hoc analysis of a phase-2 trial reported a signal for benefit on cognitive impairment, particularly in patients who were cognitively impaired at baseline (Sauder et al. 2022), but this is a signal, not established pro-cognitive efficacy, and should be stated as such.

> **COMMON TRAP**
>
> Do not overclaim KarXT as a proven cognition drug or misstate its mechanism. What is verified: xanomeline is a central M1/M4 muscarinic agonist; it acts without direct dopamine-receptor binding; trospium is added purely to block peripheral cholinergic side effects; the primary approved indication is for schizophrenia symptoms, with the cognitive benefit reported so far as a post-hoc signal (Maudsley 15th ed.; Sauder et al. 2022). Licensing and dosing detail live in the Schizophrenia: management, antipsychotics and adverse effects notes.

13.7 Insight as a multidimensional construct

What insight is. In psychopathology, insight is awareness of a morbid change in oneself and a correct attitude to that change, including, where appropriate, recognition that it signifies a mental disorder (Shorter Oxford 2018). It is not simply present or absent, and it is not the same as agreeing with the doctor. The old idea that insight cleanly separates psychosis (absent) from neurosis (present) is no longer held; the "lack of insight" in psychosis is better understood as impaired reality testing. The descriptive definitions of the underlying phenomena that insight is directed at (delusion, hallucination) belong to the Psychometry, Assessment and Descriptive Psychopathology notes.

The three dimensions. The standard model (David 1990) treats insight as three separable, graded components, which map directly onto the classic staged questions (Shorter Oxford 2018): awareness that the phenomena are occurring, relabelling of those phenomena as abnormal or

pathological rather than normal or externally caused, and acceptance of the need for treatment, that is, treatment adherence. Insight is commonly impaired in schizophrenia, is influenced by cultural and cognitive factors, and each dimension can be present to a different degree in the same patient.

DIMENSION (DAVID 1990)	THE CLINICAL QUESTION	WHAT IT PREDICTS
Awareness of illness	Does the patient recognise that a change/phenomenon is occurring?	**Engagement with assessment**
Relabelling of symptoms as pathological	Does the patient attribute it to mental illness rather than to normal life or external cause?	**Acceptance of the clinical frame**
Treatment adherence	Does the patient accept the need for treatment and take it?	**Relapse risk and outcome**

The three-dimensional structure of insight (David 1990); the discriminator is that the three dimensions dissociate, a patient can be aware of an experience yet not relabel it as illness, or relabel it yet still refuse treatment.

Measurement and clinical weight. Insight is quantified by structured scales, notably the Schedule for the Assessment of Insight (SAI, David 1990) and its expanded version (SAI-E), and the Scale to assess Unawareness of Mental Disorder (SUMD, Amador). Poor insight predicts poorer treatment adherence and worse outcome, and is one of the mechanisms linking illness to non-adherence and relapse. Insight relates only weakly to general intelligence but overlaps with executive function, tying it back to the cognitive theme of this topic.

HOLD THIS

Cognition, not positive symptoms, predicts real-world function in schizophrenia; D2 antipsychotics fix psychosis but not cognition, which is why cognition is now a separate treatment target pursued by cognitive remediation and the muscarinic M1/M4 route (xanomeline-trospium, KarXT), a mechanism that acts without direct dopamine-receptor blockade.

GOOD TO REMEMBER

- **Cognitive impairment:** broad neurocognitive deficit ~1 to 2 SD below controls, present pre-onset and in unaffected relatives; core feature though absent from ICD-11/DSM-5-TR criteria; discriminator is that it is separable from and does not track positive symptoms.
- **MATRICS seven domains:** processing speed, working memory, attention/vigilance, verbal learning and memory, visual learning and memory, reasoning and problem-solving, social cognition; the number to know is seven, measured by the MCCB.
- **Processing speed:** often the single strongest cognitive discriminator between patients and controls (digit symbol; CATIE data).
- **Working memory:** a core component tied to prefrontal circuitry; predicts employment and job tenure.
- **Cognitive hypothesis:** central claim that cognition is core, predating onset, familial and separable from symptoms, and the strongest predictor of functional impact; discriminator is that cognition beats positive AND negative symptoms at predicting function.
- **Treatment target:** D2 antipsychotics do not restore cognition (CATIE), so cognition is pursued separately via cognitive remediation therapy (moderate effect, better with rehabilitation) and pharmacology.
- **Xanomeline / KarXT:** central muscarinic M1/M4 agonist (xanomeline) plus peripherally-restricted trospium (KarXT, Cobenfy); acts via muscarinic receptors, NOT direct D2 blockade; cognitive benefit reported so far as a post-hoc signal (Sauder 2022), not established.
- **Insight:** multidimensional (David 1990), awareness of illness, relabelling of symptoms as pathological, treatment adherence; measured by the SAI; commonly impaired and predictive of adherence and outcome; discriminator is that the three dimensions dissociate.

14 · Prodrome, the at-risk mental state and first-episode psychosis

Schizophrenia rarely announces itself with a florid first hallucination. In most patients there is a slow slide of months to years in which function erodes, personality flattens and odd experiences creep in before any frank psychotic symptom crosses threshold. Recognising this window, the **prodrome** and the operationalised **at-risk mental state**, matters because it is the seam where prevention, early intervention and a great deal of contemporary research live. It is also a favourite examiner trap: the whole clinical challenge is to identify risk without over-treating a state that, in most people, will never become schizophrenia.

Exam framing. Expect to be asked to define the prodrome, list the three at-risk (**ultra-high-risk**) subgroups, quote a **transition** rate, and, above all, to state the guideline position on antipsychotics in a high-risk state. Get the last point right and you separate yourself from the candidate who manages an at-risk state as though it were established illness.

14.1 The prodrome: non-specific decline, then attenuated symptoms

Definition. The prodrome is the period of disturbance preceding frank psychosis, typically evolving over months to years, in which non-specific changes appear first and attenuated (subthreshold) psychotic features follow. It is a *retrospective* concept in its classic sense: a prodrome is only certain once psychosis has actually declared, which is why prospective work reframed it as an "at-risk" state (see 14.3). Early features are famously non-specific, depressed mood, anxiety, sleep disturbance, irritability, social withdrawal, falling academic or occupational

performance, and reduced concentration, overlapping heavily with depression and normal adolescence (Yung & McGorry 1996).

Attenuated phase. As the prodrome matures, attenuated psychotic phenomena emerge: ideas of reference, magical or odd beliefs, perceptual distortions and suspiciousness, held with relatively preserved insight and below the intensity, frequency or conviction that would qualify as a delusion or hallucination proper. For the descriptive definitions of what a delusion, a hallucination or formal thought disorder actually *is* as a phenomenon, cross-reference the Psychometry, Assessment and Descriptive Psychopathology notes; here the point is only that these signs appear in a muted, subthreshold form.

TRAP **Prodrome is not a diagnosis.** Non-specific decline plus low mood in a teenager is far more often depression or adjustment than an emerging psychosis; the prodrome is confirmed only in hindsight.

14.2 Basic symptoms: the earliest self-experienced disturbances

Concept. The basic symptoms approach (Huber; Schultze-Lutter) describes the earliest, subtle, self-perceived disturbances of thought, perception, language and attention, for example thought interference, thought pressure, disturbances of receptive speech, and visual perceptual changes, experienced with full insight and often preceding attenuated psychotic symptoms. Cognitive-perceptive basic symptoms (COPER) and a cognitive-disturbances cluster (COGDIS) form one arm of contemporary **clinical high risk** criteria alongside the ultra-high-risk paradigm (Schultze-Lutter 2015).

14.3 The at-risk mental state and the ultra-high-risk criteria

Prospective identification is operationalised through the at-risk mental state (**arms**), assessed on the Comprehensive Assessment of At-Risk Mental States (CAARMS), and the closely equivalent ultra-high-risk (**uhr**) criteria of the Structured Interview for Psychosis-risk Syndromes (SIPS). To meet an ultra high risk / at-risk mental state one must fall into at least one of three **arms** (Yung et al. 2003, 2008):

GROUP	WHAT DEFINES IT	KEY QUALIFIER
Attenuated psychotic symptoms (APS)	Subthreshold positive symptoms present in the past year: below the intensity, frequency or duration of frank psychosis	**The commonest and largest entry route**
Brief limited intermittent psychotic symptoms (BLIPS / BIPS)	Frank psychotic symptoms that resolve spontaneously within a short window (CAARMS: less than 1 week) without treatment	**Highest short-term transition of the three**
Trait-plus-state (genetic risk and deterioration, GRD)	Schizotypal personality disorder or a first-degree relative with psychosis (trait), *plus* a marked decline in functioning (state) over the past year	**Risk comes from vulnerability + functional drop, not current symptoms**

The three ultra-high-risk / at-risk mental state subgroups. Meeting any one arm qualifies; BLIPS carries the highest short-term transition, GRD the lowest.

Terminology. "At-risk mental state", "ultra-high-risk" and "clinical high risk" (**chr**) are used near-synonymously; CHR is the umbrella term now favoured in North American and European literature, encompassing both the ultra high risk positive-symptom paradigm and the basic-symptom paradigm. The state is a help-seeking, symptomatic status, not a benign trait label.

RULE **Three arms, one qualifies.** Attenuated psychotic symptoms, brief limited intermittent psychotic symptoms, or trait-plus-state (genetic risk plus functional decline): any single arm meets the at-risk mental state.

14.4 Attenuated psychosis syndrome: the DSM-5 condition for further study

What it is. DSM-5 (and DSM-5-TR) placed attenuated psychosis syndrome among the conditions for further study, not in the main text, precisely to flag risk without minting a premature disorder (Fusar-Poli & Heckers). It describes at least one attenuated positive symptom (delusions, hallucinations or disorganised speech) that is present at least weekly for the past month, has begun or worsened in the past year, causes distress or disability, and, crucially, is held with *relatively intact reality testing*, that is, below the threshold for frank psychosis. It maps closely onto the attenuated psychotic symptoms arm of the ultra-high-risk criteria.

Its deliberate relegation to "for further study" reflects the core tension of this whole area: most who meet it will not transition, so naming it a disorder risks stigma and over-treatment (see 14.6). It is a research and staging construct, not a licence to prescribe.

14.5 Transition to psychosis: the numbers

Rate. Across ultra-high-risk cohorts, **transition** to a frank psychotic disorder accumulates with follow-up: about **18%** at 6 months, **22%** at 1 year, **29%** at 2 years and **36%** at 3 years, the risk rising steadily across that window. Early single-cohort studies reported higher short-term figures (about **37%** at 12 months) than the pooled one-year estimate of **22%**, partly because broader ascertainment and earlier detection dilute the sample (Fusar-Poli et al. 2012; New Oxford Textbook of Psychiatry 2020).

~22%	~36%	~1/3
POOLED TRANSITION AT 1 YEAR	POOLED TRANSITION BY 3 YEARS	RECOVER, ~1/3 STABLE SUBTHRESHOLD

Gradient. Transition is not uniform across the three arms: it is highest with brief limited intermittent psychotic symptoms and with more intense, frequent or persistent attenuated symptoms, and lowest in the trait-plus-state (genetic risk plus deterioration) group. Put simply, the closer the presentation already sits to frank psychosis, the higher the conversion. A useful rule of thumb from at-risk follow-up: roughly one-third convert to a psychotic disorder, one-third remain stably subthreshold, and one-third improve or fully recover (Kaplan & Sadock 2024). Importantly, when transition occurs the outcome is a spectrum, schizophrenia, schizoaffective, bipolar or psychotic depression, not schizophrenia alone.

TRAP **Do not quote a single "conversion to schizophrenia" figure.** At-risk states convert to a range of psychoses, and most at-risk individuals never transition at all.

14.6 Board steer: antipsychotics in the prodrome and at-risk state

This is the highest-yield point in the topic. Guidelines do **not routinely** recommend antipsychotics for a clinical-high-risk / at-risk state with the aim of preventing transition (NICE CG178; EPA guidance, Schmidt et al. 2015). The rationale is a simple risk-benefit calculation: because only a minority actually transition, most at-risk individuals treated with an antipsychotic would be exposed to weight gain, metabolic harm, sedation and extrapyramidal effects for no benefit, and the evidence that antipsychotics prevent (rather than merely delay) transition is weak.

What is preferred instead. The recommended stance is to offer cognitive behavioural therapy (individual CBT, for which the evidence in this group is strongest), active monitoring / regular review of mental state, and to *treat the comorbidity that is actually present*: depression, anxiety and substance use. Antipsychotics are reserved for frank psychosis, or for a severe, rapidly deteriorating or dangerous picture where the clinical situation itself, not a preventive rationale, warrants them. For the drugs themselves, their adverse-effect profiles and the management of established illness, cross-reference the Schizophrenia: management, antipsychotics and adverse effects notes.

RULE **No antipsychotic to prevent transition.** In a clinical-high-risk patient, offer CBT, active monitoring and treatment of comorbid depression, anxiety and substance use; reserve antipsychotics for frank psychosis or a severe, deteriorating picture.

TRAP **Managing an at-risk state as schizophrenia.** Starting a maintenance antipsychotic in an at-risk mental state purely to prevent transition medicalises a group most of whom will never develop psychosis.

14.7 First-episode psychosis and the duration of untreated psychosis

Definition. First-episode psychosis (**fep**) denotes the first frank psychotic episode, before diagnosis is stabilised: it is a syndromal, not a nosological, label, because the eventual diagnosis (schizophrenia, schizoaffective disorder, bipolar disorder, psychotic depression, substance-induced or organic psychosis) is often not yet clear. It is the target of dedicated early-intervention services (for example the EPPIC model), which combine low-dose antipsychotics with psychosocial and vocational support.

DUP. The interval between the onset of frank psychotic symptoms and the start of adequate antipsychotic treatment is the duration of untreated psychosis (DUP). A longer DUP is associated with poorer symptomatic and functional outcome and slower, less complete remission, which is the central argument for early detection and rapid treatment in first-episode psychosis (first episode psychosis) services. For how DUP and first-episode outcome fit into the natural history and prognosis of the illness, cross-reference the course topic within these notes. First-episode

patients are notably antipsychotic-sensitive, so the treatment principle is "low and slow"; the drug detail belongs in the Schizophrenia: management, antipsychotics and adverse effects notes.

DUP ↑	Low & slow
WORSE OUTCOME, SLOWER REMISSION	FEP ANTIPSYCHOTIC SENSITIVITY

14.8 Endophenotypes: heritable markers between genotype and phenotype

Concept. An endophenotype (intermediate phenotype; Gottesman & Gould 2003) is a heritable, quantifiable, state-independent trait marker lying on the causal pathway *between* genotype and the clinical phenotype, more proximal to gene action than the diagnosis itself and therefore more tractable for genetic and progression research. The classic Gottesman criteria: the marker is associated with the illness in the population, is heritable, is state-independent (present whether or not the person is currently ill), co-segregates with illness within families, and is found in unaffected relatives at higher rates than in the general population.

Candidate markers in schizophrenia. Well-studied examples include smooth-pursuit eye-movement abnormality (impaired pursuit gain with catch-up saccades), the P50 sensory-gating deficit (failure to suppress the P50 auditory evoked response to the second of paired clicks), prepulse inhibition deficits (reduced attenuation of the startle response by a preceding weak stimulus), and working-memory (and broader neurocognitive) deficits. These are found in patients and, at intermediate frequency, in their unaffected relatives, and are studied as markers of vulnerability and of progression across the at-risk to first-episode continuum (Kaplan & Sadock 2024). For the underlying twin, family and adoption methods that make a trait "heritable", cross-reference the Psychiatric Genetics notes.

HOLD THIS

Do not start an antipsychotic in a clinical-high-risk / at-risk mental state purely to prevent transition: only about 22 percent transition by 1 year and about 36 percent by 3 years, so offer CBT, active monitoring and treatment of comorbid depression, anxiety and substance use, and reserve antipsychotics for frank psychosis or a severe, deteriorating picture.

MNEMONIC

A-B-T for the three arms

Attenuated psychotic symptoms, **B**rief limited intermittent psychotic symptoms, **T**rait-plus-state (genetic risk plus deterioration). Any one arm meets the ultra-high-risk / at-risk mental state.

GOOD TO REMEMBER

- **Prodrome:** the disturbance preceding frank psychosis, non-specific decline first then attenuated symptoms; core point is that it is confirmed retrospectively, so prospective work uses the at-risk mental state instead.
- **At-risk mental state / ultra-high-risk / clinical high risk:** an operationalised help-seeking risk status; the discriminator is that it needs only ONE of three arms (attenuated psychotic symptoms, brief limited intermittent psychotic symptoms, or trait-plus-state).
- **BLIPS (brief limited intermittent psychotic symptoms):** frank psychotic symptoms that remit spontaneously within about a week; discriminator is that it carries the HIGHEST short-term transition of the three arms.
- **Trait-plus-state (GRD):** genetic risk (schizotypal PD or first-degree relative with psychosis) PLUS a marked functional decline over the past year; discriminator is that risk comes from vulnerability + drop, with no current subthreshold symptoms required.
- **Attenuated psychosis syndrome:** DSM-5 condition for further study, at least one attenuated positive symptom, weekly for a month, with relatively intact reality testing; discriminator is its deliberate placement OUTSIDE the main manual to avoid over-diagnosis.
- **Transition to psychosis:** pooled about 22 percent at 1 year and about 36 percent by 3 years, higher with more intense attenuated symptoms and with BLIPS; discriminator is that conversion is to a SPECTRUM of psychoses, not schizophrenia alone.
- **First-episode psychosis (FEP):** the first frank psychotic episode, diagnosis not yet stabilised; discriminator is that a longer duration of untreated psychosis predicts worse outcome, the rationale for early intervention.
- **Endophenotype:** a heritable, state-independent, quantifiable trait marker between genotype and phenotype (smooth-pursuit eye-movement abnormality, P50 sensory-gating deficit, prepulse-inhibition and working-memory deficits); discriminator is that it must appear in unaffected relatives, not just in patients.

PEARL

The single best "positive" predictor of transition is not any biomarker but the clinical severity of the presenting attenuated symptoms plus a steep functional decline; this is why staging models weight symptom intensity and function so heavily, and why active monitoring (not medication) is the default at-risk intervention.

Classification, subtypes and nosological change

15 · The diagnostic criteria: ICD-11, DSM-5-TR and the legacy ICD-10

Why this matters. A resident is expected to reproduce the operational criteria for schizophrenia from both current systems, and to know precisely what changed when **ICD-11** and **DSM-5-TR** replaced their predecessors. Examiners test three things: the two duration thresholds, the symptom set with its "at least two" rule, and the nosological shift away from subtypes and from privileged first-rank symptoms toward a dimensional, specifier-based description. This topic runs the criteria forward, cross-maps them, and closes with a labelled legacy box for ICD-10, which many Indian question banks still use.

The raw descriptive definitions of the underlying phenomena, what a delusion, a hallucination, formal thought disorder or a first-rank symptom actually is, belong to the Psychometry,

Assessment and Descriptive Psychopathology notes; here we apply and enumerate them within the operational criteria (Kaplan & Sadock 2024, Gaebel 2020). Management, antipsychotics and adverse effects are developed in the Schizophrenia: management, antipsychotics and adverse effects notes and are not taught here.

15.1 ICD-11: the core symptom set and the "at least two" rule

The current ICD-11 requirement is at least two of a defined set of core symptoms, present most of the time for at least one month (Gaebel 2020, Kaplan & Sadock 2024). The seven symptom groups are persistent delusions, persistent hallucinations, disorganised thinking (formal thought disorder), experiences of influence, passivity or control, negative symptoms, grossly disorganised behaviour, and psychomotor disturbance. Critically, at least one of the two must come from the first four groups, the core positive or disorganisation cluster, so a picture built only from negative symptoms and psychomotor disturbance does not meet the threshold. ICD-11 does not impose a separate functional-decline criterion in the way DSM-5-TR does, resting the diagnosis on the symptom set and the duration instead.

Persistent delusions

Fixed false beliefs, weighed equally toward the diagnosis regardless of bizarreness or content (core positive; one of the first four).

Persistent hallucinations

Perceptions without a stimulus, most often auditory (core positive; one of the first four).

Disorganised thinking

Formal thought disorder inferred from disorganised speech, from tangentiality to word salad (disorganisation; one of the first four).

Experiences of influence, passivity or control

The old Schneiderian passivity and thought-interference phenomena, now one item among several (one of the first four).

Negative symptoms

Blunted affect, alogia, avolition, asociality, anhedonia (not among the first four).

Grossly disorganised behaviour

Purposeless, bizarre or context-inappropriate behaviour impairing goal-directed activity.

Psychomotor disturbance

Catatonic phenomena: stupor, posturing, waxy flexibility, excitement, mutism.

RULE **ICD-11 needs two core symptoms for one month, and at least one must be a core positive or disorganisation symptom.** Negative and psychomotor items alone cannot carry the diagnosis.

15.2 ICD-11 symptom-domain qualifiers and course specifiers

Having replaced subtypes, ICD-11 asks the clinician to rate a set of symptom-domain qualifiers describing the cross-sectional profile of the current episode, plus course specifiers describing the longitudinal pattern (Gaebel 2020). Each domain qualifier is rated as present or absent and, where relevant, by severity, so that two patients with the same diagnosis can be described dimensionally rather than forced into one categorical box. The six symptom domains are positive

symptoms, negative symptoms, depressive mood symptoms, manic mood symptoms, psychomotor symptoms, and cognitive symptoms. The course specifiers capture stage and pattern: first episode, multiple episodes, or continuous, each further qualified as currently symptomatic, in partial remission, or in full remission.

Symptom-domain qualifiers

Six ratable domains, positive, negative, depressive, manic, psychomotor, cognitive, describing the current cross-sectional profile.

Course specifiers

First episode / multiple episodes / continuous, each as currently symptomatic, partial remission or full remission.

15.3 ICD-11 and the abolition of subtypes

The single most examined nosological point is the abolition of subtypes: ICD-11 deleted the classical paranoid, hebephrenic, catatonic, undifferentiated, residual and simple subtypes that ICD-10 had retained (Gaebel 2020). The stated grounds were their poor inter-rater reliability, their marked temporal instability, so that a patient labelled paranoid at one admission was frequently hebephrenic or undifferentiated at the next, and their low predictive validity for course, treatment response or outcome. In their place ICD-11 substitutes the symptom-domain qualifiers and course specifiers of the preceding subtopic, a dimensional description intended to capture the same clinical variation with far better reliability. Catatonia is now coded separately rather than as a schizophrenia subtype; its detail belongs to the Other psychotic disorders, delusional syndromes and catatonia notes.

> **PEARL**
>
> The subtypes fell for the same three reasons in both systems: poor reliability, temporal instability, and low predictive validity. Whenever an examiner asks why paranoid, hebephrenic and catatonic schizophrenia disappeared, those three phrases are the answer, and the replacement is a dimensional symptom-domain and course-specifier scheme.

15.4 DSM-5-TR Criterion A: two of five active-phase symptoms

The DSM-5 family defines the active-phase symptoms in Criterion A, which requires two of five symptoms, each present for a significant portion of a one-month period (or less if successfully treated), with at least one being a core positive symptom (American Psychiatric Association 2022, Kaplan & Sadock 2024). The five are delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour, and negative symptoms. The "at least one core positive" constraint means the qualifying pair must include one of delusions, hallucinations or disorganised speech; a diagnosis cannot rest on, for example, catatonic behaviour plus negative symptoms alone.

1. Delusions

A qualifying core positive symptom (any content, weighed equally).

2. Hallucinations

A qualifying core positive symptom.

3. Disorganised speech

The observable index of formal thought disorder; a qualifying core positive symptom.

4. Grossly disorganised or catatonic behaviour

Not counted as a core positive symptom for the "at least one" rule.

5. Negative symptoms

Diminished emotional expression or avolition; not a core positive symptom.

RULE **DSM-5-TR Criterion A is two of five, and the pair must include at least one core positive symptom.** Core positives are delusions, hallucinations or disorganised speech.

15.5 DSM-5-TR: the six-month duration, dysfunction and the exclusions

DSM-5-TR wraps Criterion A in three further requirements. First, a total six month duration: continuous signs of disturbance for at least six months, of which at least one month must be active-phase (Criterion A) symptoms, the remainder being prodromal or residual phases. This is the pivotal contrast with ICD-11's single month, and it is why an illness of five months meeting Criterion A is coded as schizophreniform disorder, not schizophrenia, until it crosses six months. Second, social or occupational dysfunction: functioning in work, relationships or self-care is markedly below the level achieved before onset. Third, the exclusion criteria (American Psychiatric Association 2022).

Six-month duration

Continuous disturbance for at least six months including at least one month of active Criterion A symptoms.

Functional criterion

Marked decline in work, interpersonal relations or self-care below the premorbid level.

Schizoaffective and mood exclusion

Excluded if a major depressive or manic episode has been present for the majority of the total active and residual illness, or if mood episodes are absent only briefly.

Substance and medical exclusion

The disturbance must not be attributable to a substance or another medical condition.

COMMON TRAP

Applying the schizophrenia label during an untreated mood episode. If a full depressive or manic syndrome is present alongside the psychosis, the mood-disorder exclusion must be worked through first: psychotic symptoms confined to mood episodes point to a mood disorder with psychotic features or to schizoaffective disorder, not to schizophrenia. Treat and re-assess the mood before committing to the diagnosis.

TRAP **Diagnosing schizophrenia inside an untreated mood episode without applying the exclusion.** Mood-congruent psychosis confined to depressive or manic episodes is a mood or schizoaffective disorder until proven otherwise.

15.6 What changed from DSM-IV: threshold, subtypes and first-rank de-prioritisation

Three changes from DSM-IV are high-yield (American Psychiatric Association 2022, Kaplan & Sadock 2024). First, the raised threshold and de-prioritisation of first-rank symptoms: DSM-IV allowed a single Criterion A symptom to suffice if it was a bizarre delusion or a Schneiderian hallucination (a running commentary, or two or more voices conversing). DSM-5 abolished this special weighting, so that two symptoms are always required and no bizarre delusion or first-rank hallucination counts double; this de-prioritization reflects evidence that first-rank symptoms are neither pathognomonic nor of superior diagnostic value. Second, subtype removal: the paranoid, disorganised, catatonic, undifferentiated and residual subtypes were deleted for the same reliability, stability and validity failings that led ICD-11 to drop its own subtypes. Third, DSM-5 introduced dimensional severity ratings across eight domains and moved catatonia to a cross-cutting specifier.

WORKED EXAMPLE

A 24-year-old has four months of persistent persecutory delusions and running-commentary auditory hallucinations, with a clear decline in work and self-care and no mood episode or substance cause. Under ICD-11 he already meets schizophrenia: two core symptoms, both from the first four, beyond one month. Under DSM-5-TR he meets Criterion A (two of five, including core positives) but the total illness is under six months, so the correct DSM-5-TR label is schizophreniform disorder; it converts to schizophrenia only once continuous disturbance reaches six months. The one lone running-commentary voice that would have sufficed under DSM-IV no longer carries the diagnosis by itself.

15.7 The legacy ICD-10 criteria: what changed

Because the exit examination and many Indian question banks still test ICD-10, its criteria remain worth holding, framed as a legacy standard against which to see what changed. ICD-10 required symptoms for at least one month, the same threshold ICD-11 retains, but differed in two decisive ways: it gave first-rank symptoms special weight, so that one clear first-rank symptom (thought echo, insertion, withdrawal or broadcasting; passivity or delusional perception; third-person or running-commentary voices) for one month sufficed for the diagnosis; and it retained the full list of subtypes (paranoid, hebephrenic, catatonic, undifferentiated, post-schizophrenic depression, residual, simple). The two current systems have removed both features.

INDIA

For an ICD-10 answer, reproduce the first-rank weighting and the subtype list; for a modern answer, state that ICD-11 keeps the one-month threshold but abolished subtypes and stripped first-rank symptoms of their special status, and that DSM-5-TR requires six months total. Where a paper is silent, note which system you are using.

15.8 The three systems side by side

The comparison below sets the current and legacy criteria against each other across the five axes examiners probe: duration, the core symptom rule, the status of first-rank symptoms, subtypes, and the functional criterion. It maps directly onto the criteria map (Fig 8.1).

AXIS	ICD-11	DSM-5-TR	ICD-10 (LEGACY)
Minimum duration	**1 month of symptoms**	**6 months total (>=1 month active)**	1 month of symptoms
Core symptom rule	>=2 of seven groups, >=1 from the first four (positive/disorganisation)	**Criterion A: 2 of 5, >=1 core positive**	1 first-rank OR 2 of a lower-rank set for 1 month
First-rank symptoms	De-prioritised; one item among several, no special weight	De-prioritised; no single symptom sufficient	**Special weight; one alone can suffice**
Subtypes	**Abolished; replaced by domain qualifiers + course specifiers**	**Removed; replaced by dimensional severity ratings**	**Retained (paranoid, hebephrenic, catatonic, etc.)**
Functional criterion	Not a separate mandatory criterion	**Required: marked social/occupational decline**	Not a separate mandatory criterion
Mood / substance exclusion	Present	Present (schizoaffective, mood, substance, medical)	Present

Criteria comparison: ICD-11 versus DSM-5-TR versus the legacy ICD-10 across duration, core symptoms, first-rank status, subtypes and the functional criterion; the pivotal contrast is one month (ICD-11, ICD-10) against six months total (DSM-5-TR).

GOOD TO REMEMBER

- **ICD-11 schizophrenia:** at least two of seven core symptoms with at least one from the first four (positive or disorganisation cluster), present for at least one month; central change is the abolition of subtypes for symptom-domain qualifiers plus course specifiers; the discriminator is the one-month duration and the "one from the first four" rule.
- **DSM-5-TR schizophrenia:** Criterion A two of five (>=1 core positive), plus six months total duration with at least one month active, social or occupational dysfunction, and the mood and substance/medical exclusions; the discriminator is the six-month total duration, distinguishing it from schizophreniform disorder (under six months).
- **Criterion A (DSM-5-TR):** delusions, hallucinations, disorganised speech, grossly disorganised or catatonic behaviour, negative symptoms; central rule is two of five with at least one core positive; the discriminator is that no single symptom, first-rank or bizarre, now suffices.
- **Symptom-domain qualifiers and course specifiers (ICD-11):** six ratable domains (positive, negative, depressive, manic, psychomotor, cognitive) and a course axis (first / multiple episodes / continuous, each symptomatic / partial / full remission); central claim is dimensional description replacing subtypes; the discriminator is that these are rated per-episode, not fixed categories.
- **Abolition of subtypes (both systems):** paranoid, hebephrenic/disorganised, catatonic, undifferentiated, residual and simple subtypes deleted; central reason is poor reliability, temporal instability and low predictive validity; the discriminator is that ICD-10 alone still retains them.
- **Legacy ICD-10:** one-month duration, but first-rank symptoms carried special weight (one alone could suffice) and the classical subtypes were retained; the discriminator, what changed, is that both current systems keep the month but drop first-rank privilege and subtypes.

HOLD THIS

ICD-11 needs at least two core symptoms (one from the first four) for one month; DSM-5-TR needs Criterion A two of five plus a six-month total duration with dysfunction and the exclusions; both abolished subtypes and de-prioritised first-rank symptoms, while legacy ICD-10 kept the month, the subtypes and the first-rank weighting.

16 · History and the abolition of the subtypes

The classification of schizophrenia is the most historically loaded topic in the whole chapter, and the modern examiner tests two things: whether you can trace the **historical evolution** from Kraepelin through Bleuler to Schneider, and whether you know that both current systems have deleted the classical subtypes. The disorder has been renamed and re-carved twice, from a unitary deteriorating dementia to a group of syndromes to a symptom-domain construct, and each turn left a residue that still surfaces in short-answer questions. Reading the history forward makes sense of why the ICD-10 subtypes existed at all and why they were retired.

How to use this page. Fix the three-name lineage first, because a single line on each of Kraepelin, Bleuler and Schneider answers most history questions. Then hold the six ICD-10 subtypes as a list you can reproduce, with simple schizophrenia as the odd, controversial one. Finally, learn the abolition argument as a four-point causal chain, because the shift from categorical subtypes to a dimensional specifier model is the single highest-yield nosology point in the chapter and the one most likely to be marked wrong. The descriptive definitions of the individual signs, what a delusion, a hallucination or formal thought disorder *is* as a phenomenon, are not re-derived here; they belong to the Psychometry, Assessment and Descriptive Psychopathology notes.

16.1 Kraepelin and dementia praecox: the unitary deteriorating illness

The founding separation. Emil Kraepelin, across the successive editions of his textbook, drew the great divide of modern psychiatric nosology: he separated two major primary psychotic illnesses, dementia praecox and manic-depressive insanity, using long-term course and outcome as the defining feature rather than any cross-sectional symptom (Kaplan & Sadock 2024). Dementia praecox, a term he borrowed from Morel meaning a dementia of the young, was conceived as a single, unitary illness with an early-adult onset and a characteristically *poor, deteriorating* outcome, set against manic-depressive insanity with its better, episodic, remitting prognosis (Companion to Psychiatric Studies). This prognosis-based dichotomy, deterioration versus recovery, is the Kraepelinian principle examiners want named.

What he folded into it. Kraepelin unified into dementia praecox three older descriptive syndromes that had been described separately: hebephrenia (Hecker 1871), catatonia (Kahlbaum 1874), and his own dementia paranoides, treating them as manifestations of one disorder with a common early onset and poor outcome (Companion to Psychiatric Studies). Those three descriptive strands are the ancestors of the later paranoid, hebephrenic and catatonic subtypes, which is why the subtype scheme reads as a fossil of nineteenth-century syndrome-spotting.

RULE **Kraepelin split psychosis by course, not by symptom.** Dementia praecox versus manic-depressive insanity was a prognosis-based dichotomy, poor deteriorating outcome versus better episodic outcome, and that longitudinal logic still underlies the schizophrenia/mood divide today.

16.2 Bleuler and the schizophrenias: a group, splitting, and the four A's

The renaming. Eugen Bleuler renamed dementia praecox **schizophrenia** in 1908, and, crucially, pluralised the concept: his 1911 monograph was titled *Dementia Praecox or the Group of Schizophrenias*, deliberately calling it "**the schizophrenias**", a *group* of related disorders rather than one disease (Bleuler 1911). He challenged Kraepelin on two counts: the outcome need not be a relentless dementia, so the prognosis was better and more variable than Kraepelin allowed, and the core disturbance was not memory loss but a *splitting* (schizo-) of the mind (-phrenia), a loosening of the associative threads between thought, emotion and volition.

Fundamental versus accessory symptoms. Bleuler distinguished the *fundamental* symptoms, which he held to be pathognomonic and always present, from the *accessory* symptoms (delusions and hallucinations), which he considered secondary and non-specific because they also occur in other disorders. The fundamental symptoms are memorised as the four A's.

MNEMONIC

THE FOUR A's: Association (loosening), Affect (blunted or incongruous), Ambivalence, Autism.

Bleuler's fundamental symptoms: loosening of **A**ssociations (the primary "splitting", disconnected thought), disturbance of **A**ffect (flattened or incongruous emotion), **A**mbivalence (simultaneous contradictory impulses or feelings), and **A**utism (withdrawal into an inner private world, detachment from reality). The accessory symptoms he demoted, delusions and hallucinations, are the very features the four A's are contrasted against. A common exam trap is to list delusions among the four A's; they are accessory, not fundamental.

16.3 Schneider and the symptom emphasis: first-rank symptoms

The pendulum swings back to cross-section. Where Kraepelin defined by course and Bleuler by an inferred core disturbance, Kurt Schneider defined by readily elicited cross-sectional symptoms. He proposed a set of first-rank symptoms, audible thoughts, voices arguing or commenting, thought withdrawal, insertion and broadcasting, made feelings, impulses and acts, somatic passivity and delusional perception, whose presence in the absence of organic disease he held to be strongly suggestive of schizophrenia (Kaplan & Sadock 2024). His contribution was pragmatic and reliability-driven: symptoms a clinician could observe and agree on, which is why first-rank symptoms dominated ICD-10. Their descriptive definitions as phenomena are cross-referenced to the Psychometry, Assessment and Descriptive Psychopathology notes; the point here is only the historical role. First-rank symptoms were later shown to be neither specific nor pathognomonic and were stripped of their privileged diagnostic weight in both ICD-11 and DSM-5.

FIGURE	NAMED THE DISORDER	DEFINING PRINCIPLE	PROGNOSTIC VIEW
Kraepelin (1890s)	Dementia praecox (from Morel)	**Longitudinal course and outcome; a unitary deteriorating illness**	Poor, deteriorating; separated from manic-depressive insanity
Bleuler (1908 to 1911)	The schizophrenias (a group)	**Splitting of psychic functions; four fundamental symptoms (four A's)**	Better and more variable than Kraepelin allowed
Schneider (1959)	(retained "schizophrenia")	**Cross-sectional first-rank symptoms, chosen for reliability**	Not a prognostic scheme; a diagnostic-symptom emphasis

The historical evolution on one row each: the discriminator is the defining principle, course (Kraepelin) to inferred core disturbance (Bleuler) to observable symptom (Schneider).

GOOD TO REMEMBER

- **Kraepelin:** coined the modern concept of dementia praecox as a unitary illness of the young with a deteriorating course; core claim is prognosis-based separation from manic-depressive insanity; discriminator is that he defined by long-term course, not symptom.
- **Dementia praecox:** Kraepelin's unitary, early-onset, poor-outcome psychosis that folded in hebephrenia (Hecker), catatonia (Kahlbaum) and dementia paranoides; discriminator is the poor deteriorating prognosis versus manic-depressive insanity.
- **Bleuler:** renamed it "the schizophrenias", a group with a better and more variable prognosis, with the core lesion a splitting of psychic functions; discriminator is the four fundamental symptoms (four A's: Association, Affect, Ambivalence, Autism), with delusions and hallucinations demoted to accessory.
- **Schneider:** defined schizophrenia by reliable cross-sectional first-rank symptoms; discriminator is that these were later found non-specific and lost their special diagnostic status in ICD-11 and DSM-5.

16.4 The ICD-10 subtypes: the six-way scheme

The legacy categorical scheme. ICD-10 (F20) carved schizophrenia into categorical clinical subtypes, assigned on the predominant symptom picture at presentation. Because many Indian examinations and case records still run on ICD-10, the list must be reproducible. The main types are paranoid (F20.0), hebephrenic (F20.1), catatonic (F20.2), undifferentiated (F20.3), residual (F20.5) and simple schizophrenia (F20.6), with post-schizophrenic depression (F20.4) sitting alongside as a course category rather than a symptom subtype.

Paranoid (F20.0)

Dominated by relatively stable, often systematised delusions (persecution, reference, grandeur, control, jealousy) and hallucinations, usually persecutory; affect, volition and speech relatively preserved. The commonest subtype, later and more insidious onset, least personality deterioration.

Hebephrenic (F20.1)

The disorganised subtype: prominent thought disorder and disorganisation, shallow, inappropriate or fatuous affect, mannerisms, aimless disinhibited behaviour, fragmentary delusions and hallucinations. Early onset (teens to early twenties), poor prognosis, one of the worst outcomes.

Catatonic (F20.2)

Dominated by psychomotor disturbance: stupor, mutism, negativism, rigidity, posturing, waxy flexibility, excitement or command automatism. Catatonia as an entity is cross-referenced to the Other psychotic disorders, delusional syndromes and catatonia notes.

Undifferentiated (F20.3)

Meets the general criteria for schizophrenia but fits no single subtype cleanly, or shows features of more than one without one predominating. A very common category, which is precisely part of the problem.

Residual (F20.5)

A chronic stage: enduring, prominent negative symptoms (social withdrawal, blunted affect, poverty of speech, psychomotor slowing) following at least one clear psychotic episode, with the florid positive symptoms now attenuated.

Simple schizophrenia (F20.6)

An insidious, progressive decline in functioning with negative symptoms and behavioural oddities but *without* a preceding florid psychotic episode (see 16.5).

16.5 Simple schizophrenia (simplex): the concept and the controversy

What it claims to be. **Simple schizophrenia**, the **simplex** form, describes an insidious but progressive decline, loss of drive and interest, aimlessness, social withdrawal, self-neglect and a shallow, odd affect, developing over years in the absence of frank delusions, hallucinations or any clear-cut psychotic episode. It is, in effect, a purely negative-symptom deteriorating course without positive psychosis, arriving at a residual-like state without ever passing through an acute one.

Why it is contentious. Simple schizophrenia is the most controversial subtype, and the **controversy** is a favourite exam point. Because it lacks the positive symptoms that make schizophrenia recognisable and reliably diagnosable, the diagnosis rests almost entirely on inferred decline, which is hard to distinguish from schizoid or schizotypal personality, an insidious depressive or negative-symptom prodrome, or simple demoralisation. Its inter-rater reliability is poor and its boundaries ill-defined; for this reason DSM never accepted it as a formal diagnosis (it appeared only as a research proposal, simple deteriorative disorder, in a DSM appendix), even while ICD-10 retained it.

> **COMMON TRAP**
>
> Do not equate simple schizophrenia with residual schizophrenia. Both are negative-symptom, deteriorated pictures, but residual schizophrenia *requires* a documented prior florid psychotic episode, whereas simple schizophrenia is defined by never having had one. The presence or absence of a past acute psychotic episode is the discriminator.

16.6 Why both systems abolished the subtypes

The nosological change. This is the currency point. Both DSM-5 (2013, unchanged in DSM-5-TR 2022) and ICD-11 (2019) achieved the **abolition of subtypes**: the classical categorical subtypes were deleted from both systems (Kaplan & Sadock 2024). The **subtype removal** rested

on a convergent, four-part evidence base, and reproducing the four reasons is what earns the mark.

WORKED EXAMPLE

Consider a patient labelled "paranoid schizophrenia" at first presentation who, over five years, loses the systematised delusions and settles into a withdrawn, blunted, amotivated state. On the old scheme the label would have to migrate from paranoid to residual, and had they been disorganised in between, to hebephrenic. The subtype changes while the patient does not have a different *disease*, illustrating the temporal instability that helped sink the scheme: a "subtype" that reclassifies the same person over time is not carving a real category.

1. **Poor inter-rater reliability.** Different clinicians assigned different subtypes to the same patient; the categories were not reliably distinguishable, especially at the boundaries (simple, undifferentiated).
2. **Temporal instability within a patient.** The subtype a given patient met changed across the course of their illness, so the label was not a stable trait of the person but a snapshot of the current cross-section (Linscott et al. 2010).
3. **Low predictive validity.** The subtypes had a weak relationship to biological variables, to treatment response and to long-term outcome, so knowing the subtype did not usefully predict prognosis or guide management (Kaplan & Sadock 2024).
4. **Most patients fell into undifferentiated.** A large share of real presentations did not fit any single clean subtype and defaulted to undifferentiated, which drains a classification of its point.

What replaced them. In place of categorical subtypes, both systems adopted a dimensional approach: the same patient is now described by rating the *severity* of a set of symptom domains and specifiers (for example positive, negative, cognitive, disorganisation, and mood symptoms in DSM-5's dimensional assessment; and course specifiers such as first-episode, multiple-episode, continuous). The clinical reality that a patient is "more negative-symptom-predominant" is captured as a position on continua rather than forced into a box. This categorical-to-dimensional shift is the high-yield nosology statement of the topic.

RULE **Subtypes out, dimensions in.** The schizophrenia subtypes were dropped from both DSM-5 and ICD-11 for poor reliability, temporal instability and low predictive validity, and replaced by a dimensional symptom-domain and specifier approach.

TRAP **Recording "paranoid schizophrenia" as a current formal subtype.** "Paranoid schizophrenia" is not a valid DSM-5-TR or ICD-11 subtype; both systems abolished the subtypes. It survives only as legacy ICD-10 terminology, and using it as a formal current diagnosis is a marked error.

HOLD THIS

Both DSM-5 (2013) and ICD-11 (2019) deleted the schizophrenia subtypes, paranoid, hebephrenic, catatonic, undifferentiated, residual and simple, because they showed poor inter-rater reliability, temporal instability within a patient, and low predictive validity, replacing them with a dimensional symptom-domain and specifier assessment.

GOOD TO REMEMBER

- **ICD-10 subtypes:** paranoid (delusions/hallucinations, best-preserved, commonest), hebephrenic (disorganised, early-onset, worst prognosis), catatonic (psychomotor), undifferentiated (fits none cleanly), residual (chronic negative state after a prior episode), simple (insidious negative decline, no florid episode); discriminator to memorise is that paranoid is the commonest and best-preserved while hebephrenic carries the worst prognosis, and that ICD-11 abolished the subtypes altogether.
- **Simple schizophrenia (simplex):** insidious progressive negative-symptom decline without a frank psychotic episode; central claim is deterioration without positive psychosis; discriminator and source of controversy is the absence of any acute episode, which makes it unreliable and led DSM to reject it as a formal diagnosis.
- **Abolition of subtypes:** both DSM-5 and ICD-11 removed all subtypes; central reasons are poor reliability, temporal instability, low predictive validity, and most patients being undifferentiated; discriminator is the replacement by a dimensional symptom-domain and specifier model.
- **Dimensional model:** rates severity across symptom domains (positive, negative, cognitive, disorganisation, affective) plus course specifiers; central claim is that schizophrenia is better described on continua than in categories; discriminator is that it is the direct successor to the deleted subtypes.

17 · The schizophrenia spectrum and the dimensional debate

Why this matters. Schizophrenia does not sit alone. It is the anchor of a **spectrum** of related psychotic conditions and, on a wider view, the severe end of a **psychosis continuum** that reaches down into the general population. Examiners use this topic to test whether a resident can hold two ideas at once: that our manuals still make a **categorical** diagnosis, and that the underlying phenomena are almost certainly **dimensional**. The high-yield payoff is being able to name the spectrum neighbours, place them by their boundary rule, and then explain how ICD-11 and DSM-5 fuse a categorical label with dimensional specifiers.

Two scope notes. First, the neighbouring disorders are named here only as the boundary of the spectrum around schizophrenia; each as a full diagnostic entity, with its own criteria and management, is developed in the Other psychotic disorders, delusional syndromes and catatonia notes, and the work of separating each from schizophrenia is done in the differential topic. Second, the raw descriptive definitions of the underlying phenomena, what a delusion, a hallucination, formal thought disorder or a first-rank symptom actually is, belong to the Psychometry, Assessment and Descriptive Psychopathology notes; here those signs are applied, not redefined (Kaplan & Sadock 2024).

17.1 What the schizophrenia spectrum is

The schizophrenia spectrum is the family of disorders sharing psychotic phenomenology and, to varying degrees, a genetic and neurodevelopmental relationship with schizophrenia, grouped

together in DSM-5-TR as the "Schizophrenia Spectrum and Other Psychotic Disorders" chapter and in ICD-11 as the "Schizophrenia or other primary psychotic disorders" grouping (American Psychiatric Association 2022, Gaebel 2020). The organising idea is that these conditions differ from schizophrenia not in kind but along measurable axes: the severity and breadth of psychotic symptoms, the duration for which they persist, and how far they are loaded with mood symptoms. Schizophrenia occupies the position of a full, sustained, mood-free psychotic syndrome; its neighbours sit at defined distances from it along those axes.

RULE **The spectrum is a continuum of severity, duration and mood-loading, not a set of unrelated boxes.** Each neighbour of schizophrenia is defined by where it sits on one of those three axes.

17.2 The boundary neighbours: how each is placed on the spectrum

Five conditions form the immediate spectrum boundary around schizophrenia. Each is best remembered by the single axis that separates it from schizophrenia. Schizotypal disorder marks the attenuated, personality-level lower boundary: enduring odd beliefs, perceptual distortions and eccentric behaviour that never reach frank, sustained psychosis (ICD-11 places it within the spectrum; DSM-5 lists schizotypal personality disorder in this chapter but also among the personality disorders). Schizophreniform disorder is a pure duration boundary: it is schizophrenia-like psychosis of less than the six-month total DSM-5 threshold, converting to schizophrenia if it persists. Brief psychotic disorder is the shortest-duration boundary: psychosis lasting more than a day but remitting within one month, with full return to premorbid function. Schizoaffective disorder is the mood boundary: a concurrent mood-plus-psychosis picture in which a mood episode and Criterion-A psychosis coincide, yet psychosis also occurs for at least two weeks without prominent mood symptoms. Delusional disorder is the circumscribed-content, preserved-function boundary: sustained delusions without the fuller symptom set or the functional collapse of schizophrenia.

SPECTRUM NEIGHBOUR	BOUNDARY AXIS	DISCRIMINATOR FROM SCHIZOPHRENIA
Schizotypal disorder	Severity (attenuated)	**Odd/eccentric but no frank, sustained psychosis**
Brief psychotic disorder	Duration (shortest)	**Psychosis >1 day, remits within 1 month, full recovery**
Schizophreniform disorder	Duration (intermediate)	**Full picture but total illness <6 months (DSM-5)**
Schizoaffective disorder	Mood-loading	**Mood episode concurrent with psychosis, plus >=2 weeks of psychosis without prominent mood**
Delusional disorder	Severity/breadth	**Circumscribed delusions, function otherwise preserved**

The five spectrum neighbours placed by their single defining boundary axis; each is developed as a full entity in the Other psychotic disorders, delusional syndromes and catatonia notes.

TRAP **Confusing schizophreniform with schizoaffective disorder.** Schizophreniform is a duration boundary (a full picture that has simply not lasted six months); schizoaffective is a mood-plus-psychosis boundary (a concurrent mood episode). One is about the clock, the other about mood.

17.3 The categorical model and its limits

The categorical model treats schizophrenia as a discrete disease entity, present or absent by criteria, qualitatively distinct from health and from other disorders. This is the working assumption of every operational manual and it has real virtues: it communicates in one word, guides treatment thresholds, and organises services. Its weakness is that nature has stubbornly refused to draw the lines the categories require. There is no biological test, no pathognomonic sign, no discontinuity in the distribution of symptoms that marks a clean boundary between schizophrenia and health or between schizophrenia and its neighbours. The categories carve a continuous landscape at conventional, and to some degree arbitrary, thresholds, which is why the same patient can shift diagnostic label across episodes and why comorbidity between "distinct" spectrum entities is so high (Kaplan & Sadock 2024).

17.4 The dimensional model and the psychosis continuum

The dimensional alternative holds that psychotic experience is distributed continuously in the population and that clinical psychosis is the severe, persistent, impairing tail of that distribution rather than a categorically separate state. This is the psychosis continuum: psychotic phenomena "lay on a continuum from mild subthreshold psychotic phenomena to frank and florid psychosis," with no discrete demarcation "other than severity, breadth, and persistence" (Kaplan & Sadock 2024). On this view the final categorical diagnosis is the endpoint of a longitudinal pathway, from asymptomatic, to subthreshold psychotic experiences, to infrequent frank symptoms, to persistent psychosis, with the transition governed by an accumulating interplay of genetic and environmental load. Subthreshold symptoms are read as indicators of proneness to psychosis, not as a disease in themselves.

PEARL

The continuum is the reason the same three axes recur everywhere: severity, persistence (duration), and mood-loading. They define the spectrum neighbours in 17.2 and they define the psychosis continuum here. Hold "severity, duration, mood" as the master key to the whole topic.

17.5 Psychotic-like experiences in the general population

The empirical engine of the dimensional case is that psychotic-like experiences (PLEs, also called psychotic experiences) are common in people who carry no psychiatric diagnosis and never seek care: isolated ideas of reference, magical thinking, unusual perceptual experiences, fleeting hallucination-like phenomena. Prevalence estimates vary widely with the instrument used, but converge on the message that these experiences are far commoner than psychotic disorders. The WHO World Mental Health Survey across 18 countries reported a mean lifetime psychotic-experience rate of **5.8%**, higher in high-income (6.8%) than low- and low-middle-income (3.2%) countries; a replication of the US National Comorbidity Survey found **9.1%** reporting at least one such experience, and the WHO World Health Survey across 52 countries found **12.5%**

endorsing at least one over the past year (Kaplan & Sadock 2024, McGrath 2015). The great majority of these individuals meet no diagnostic criteria and remain stable; only a modest proportion ever convert to a psychotic illness.

~5.8%	~9.1%	~12.5%
LIFETIME PE, WHO WMH (18 COUNTRIES)	>=1 PE, US NCS REPLICATION	>=1 PE PAST YEAR, WHO WORLD HEALTH SURVEY

COMMON TRAP

Reading a high general-population rate of psychotic-like experiences as a high rate of schizophrenia. The two are separated by an order of magnitude: schizophrenia lifetime risk is about one percent, while psychotic experiences run to several percent or more. The whole point of the continuum is that most people with a psychotic experience never develop a psychotic disorder; the experience marks proneness, not disease.

17.6 The extended psychosis phenotype and the proneness-persistence-impairment model

Van Os and colleagues formalised the continuum into the extended psychosis phenotype: the observable spread of psychotic experience from transient, non-clinical phenomena in the general population, through the attenuated and at-risk states, to full clinical psychosis, all seen as expressions of the same underlying liability (van Os & Linscott 2012). Their meta-analysis proposed the proneness-persistence-impairment model: subclinical psychotic experiences are common and mostly transitory (proneness); in a minority they persist rather than fade (persistence), driven by the accumulation of environmental and genetic risk; and only when persistence is joined by distress and functional impairment does the experience become clinically relevant and liable to cross into disorder (van Os 2009). The model reframes the diagnostic threshold as a point on a graded liability rather than a natural kind.

WORKED EXAMPLE

A 19-year-old with no illness reports occasional sensed presences and the feeling that song lyrics carry personal messages, without conviction, distress or dysfunction. This is a psychotic-like experience on the proneness end of the extended phenotype; base rates say it will most likely remit and never become a disorder. Contrast a 19-year-old whose similar experiences have hardened over a year into held delusions, daily voices, withdrawal and failing studies: persistence plus impairment has moved him along the continuum toward the clinical, categorical diagnosis. Same phenomenology, different position on severity, persistence and impairment.

17.7 How ICD-11 and DSM-5 blend categorical diagnosis with dimensional specifiers

The manuals did not choose between the two models; they blended them. Both retain a categorical diagnosis of schizophrenia made by threshold criteria, but both bolt on a dimensional layer that describes the individual patient beyond the label. DSM-5 introduced the Clinician-Rated Dimensions of Psychosis Symptom Severity, an eight-item scale rating hallucinations, delusions, disorganised speech, abnormal psychomotor behaviour, negative symptoms and the three associated domains of impaired cognition, depression and mania, each on a 0 to 4 scale

(American Psychiatric Association 2022). ICD-11 does the parallel thing through its six symptom-domain qualifiers, positive, negative, depressive, manic, psychomotor and cognitive, rated per episode, plus course specifiers (Gaebel 2020). Both did this in the same move that abolished the classical subtypes: the paranoid, hebephrenic and catatonic subtypes were dropped for poor reliability, temporal instability and low predictive validity, and a dimensional symptom-domain description was put in their place. The result is a hybrid: a categorical diagnosis carrying a dimensional profile.

INDIA

Where the exit examination or a question bank still uses ICD-10, remember that the dimensional specifier layer is a feature of ICD-11 and DSM-5, not of ICD-10, which retained the subtypes and offered no symptom-domain rating. For a modern answer, state the blend explicitly: categorical diagnosis plus dimensional specifiers, subtypes abolished. Note which system you are answering in.

GOOD TO REMEMBER

- **Schizophrenia spectrum:** the DSM-5 "Schizophrenia Spectrum and Other Psychotic Disorders" / ICD-11 "primary psychotic disorders" family sharing psychotic phenomenology with schizophrenia; central claim is that its members differ by degree along severity, duration and mood-loading; discriminator is that schizophrenia is the full, sustained, mood-free anchor.
- **Schizotypal disorder:** attenuated, enduring odd beliefs and perceptual distortions; central claim is a personality-level, subclinical psychosis phenotype genetically linked to schizophrenia; discriminator is that it never reaches frank, sustained psychosis.
- **Schizophreniform disorder:** a schizophrenia-like picture; central claim is that it is a duration boundary; discriminator is total illness under six months (DSM-5), converting to schizophrenia if it persists.
- **Brief psychotic disorder:** acute psychosis; central claim is the shortest-duration boundary; discriminator is onset over a day, remission within one month, and full return to premorbid function.
- **Schizoaffective disorder:** concurrent mood-plus-psychosis; central claim is the mood boundary; discriminator is a mood episode concurrent with Criterion-A psychosis plus at least two weeks of psychosis without prominent mood symptoms.
- **Delusional disorder:** sustained circumscribed delusions; central claim is a narrow, function-preserving boundary; discriminator is intact functioning outside the delusional theme without the fuller schizophrenia syndrome.
- **Psychosis continuum:** psychosis distributed continuously from subthreshold experiences to florid illness; central claim is no discrete demarcation other than severity, breadth and persistence; discriminator is that most population-level psychotic experiences never become disorder.
- **Extended psychosis phenotype (van Os & Linscott 2012):** the population-to-clinic spread of psychotic experience as one liability; central claim is the proneness-persistence-impairment model; discriminator is that clinical relevance requires persistence plus impairment, not the experience alone.
- **Categorical-dimensional blend (ICD-11 / DSM-5):** a threshold diagnosis carrying a symptom-domain rating; central claim is that both manuals kept the category but added dimensional specifiers and dropped subtypes; discriminator is that the dimensional layer is absent from legacy ICD-10.

HOLD THIS

Schizophrenia is the anchor of a spectrum whose neighbours are placed by severity (schizotypal, delusional), duration (brief, schizophreniform) and mood-loading (schizoaffective), and the severe end of a psychosis continuum on which psychotic-like experiences run to several percent of the healthy population; ICD-11 and DSM-5 keep a categorical diagnosis but add dimensional symptom-domain specifiers and abolish the subtypes.

18 · Discriminate: schizophrenia versus its mimics

Why this matters. Schizophrenia is a diagnosis of pattern and of exclusion. The whole point of the classification band is that it hands you a decision procedure: before the label is allowed to settle, every psychosis that could be mistaken for it must be walked past and ruled out. Examiners test this as a **differential diagnosis**, and they reward the candidate who can name, for each mimic, the single discriminator that separates it from schizophrenia rather than reciting six full criteria sets. This topic builds one interleaved **differential** decision tree, one discriminator per rival, and closes on the mandatory organic and substance workup of a first episode.

The raw descriptive definitions of the phenomena being weighed, what a delusion, a hallucination or formal thought disorder actually is, belong to the Psychometry, Assessment and Descriptive Psychopathology notes; here we only sort the disorders. The other psychotic disorders as entities in their own right, with their full criteria, belong to the Other psychotic disorders, delusional syndromes and catatonia notes; they appear below only as points on the differential diagnosis tree. Nothing about treatment is taught here (Kaplan & Sadock 2024, American Psychiatric Association 2022).

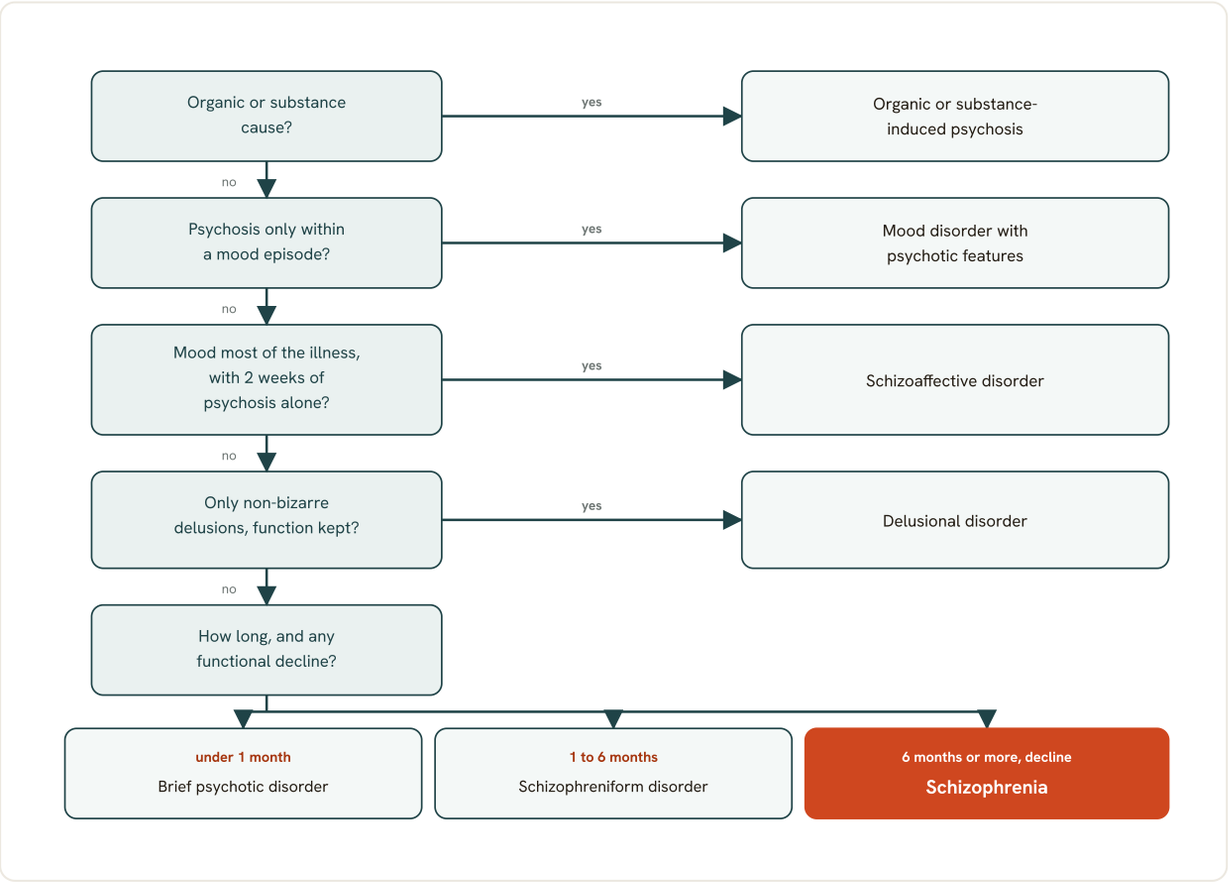


Fig 8.12 The differential decision tree that separates schizophrenia from its mimics. Working down from a first episode of psychosis, each question turns on a single discriminator: rule out an organic or substance cause first, then a mood-confined psychosis, then schizoaffective disorder, then a preserved-function delusional disorder, and finally sort the remainder by duration and decline. Only the six-month picture with functional decline is schizophrenia.

18.1 The order of operations: organic and substance first, then mood, then time

The differential is not a flat list; it has an order. First strip out the psychoses that are not primary at all, the organic and substance-induced ones, because missing them is the most dangerous error and the cause is treatable. Next apply the mood exclusion: a psychosis confined to a mood episode is a mood disorder, and one that overlaps a mood illness in a defined way is schizoaffective. Only once both of those are cleared does the picture become a *primary, non-affective* psychosis, at which point the remaining discriminator is time: less than one month is brief psychotic disorder, one to six months is schizophreniform, and six months or more (with dysfunction) is schizophrenia. Delusional disorder sits to the side as the picture built from non-bizarre delusions alone. This ordering is the tree in Fig 8.6.

RULE **Exclude secondary causes, then mood, then read the clock.** Organic and substance-induced psychosis are ruled out first, the mood exclusion next, and duration decides among the remaining primary non-affective psychoses.

18.2 Mood disorder with psychotic features: psychosis lives inside the mood episode

The first affective rival is a mood disorder with psychotic features, a major depressive or manic episode severe enough to carry delusions or hallucinations. The single discriminator is *temporal confinement*: the psychotic symptoms are present **only** during the mood episode and remit when

the mood resolves, never standing alone in euthymia (American Psychiatric Association 2022). A supporting clue, not a rule, is that the content is often **mood-congruent**: nihilistic, guilt-laden or poverty delusions in depression; grandiose or special-powers delusions in mania. In schizophrenia, by contrast, psychosis persists across mood states and outside any full mood episode.

RULE **Psychosis confined to mood episodes is a mood disorder, not schizophrenia.** If it is only ever present when the patient is depressed or manic, and it clears when the mood clears, the diagnosis is a mood disorder with psychotic features.

18.3 Schizoaffective disorder: the two rules that box it in

Schizoaffective disorder is the overlap zone, and it is defined by two rules that must both hold (DSM-5-TR Criteria B and C; American Psychiatric Association 2022). First, at some point in the lifetime illness there is a period of at least two weeks of delusions or hallucinations *in the absence* of a major mood episode; this is what separates it downward from a pure mood disorder with psychotic features, in which psychosis never outlives the mood. Second, symptoms meeting criteria for a major mood episode are present for the majority of the total duration of the active and residual illness; this is what separates it upward from schizophrenia, in which mood episodes, if they occur at all, are present only for a *minority* of the illness. Schizoaffective therefore sits precisely between the two: enough standalone psychosis to exclude a mood disorder, enough mood to exclude schizophrenia.

WORKED EXAMPLE

A patient has, over a two-year illness, roughly fourteen months in which a major depressive or manic episode is present and, within that, a clear three-week stretch of persecutory delusions while euthymic. The standalone psychotic fortnight (well over two weeks) rules out a pure mood-with-psychosis label; the mood burden occupying the majority of the illness rules out schizophrenia. The answer is schizoaffective disorder. Shrink the mood component to a couple of brief episodes and the same psychosis becomes schizophrenia with intercurrent mood symptoms.

18.4 Delusional disorder: non-bizarre delusions, otherwise intact

Delusional disorder is the picture built from one or more *non-bizarre* delusions (persecutory, jealous, erotomanic, grandiose, somatic) that could conceivably be true, with functioning outside the direct impact of the delusion largely *preserved* and behaviour not obviously odd (American Psychiatric Association 2022; Marneros 2020). The discriminator from schizophrenia is the *absence of the other core symptoms*: there are no prominent hallucinations, no formal thought disorder, no negative symptoms and no grossly disorganised behaviour; if any of these is prominent, the diagnosis moves toward schizophrenia. In short, schizophrenia is a broad, multi-domain psychosis with functional decline; delusional disorder is a narrow, encapsulated delusional system on an otherwise working person.

18.5 Schizophreniform disorder: the schizophrenia picture, one to six months

Schizophreniform disorder is, symptomatically, schizophrenia: it meets the same active-phase (Criterion A) symptom set. It is separated by *duration alone*, an episode lasting at least one month but less than six months, and, unlike schizophrenia, it does **not** require a marked functional decline (American Psychiatric Association 2022). If the illness is still ongoing when the diagnosis is made, it is labelled "provisional"; should it fail to remit and cross six months, the diagnosis converts to schizophrenia. It is therefore best read as schizophrenia caught before the six-month duration line, or as a good-prognosis episode that resolves before it.

TRAP **Calling a four-month schizophrenia-like psychosis "schizophrenia" under DSM-5-TR.** Below six months total it is schizophreniform disorder (provisional if ongoing); it becomes schizophrenia only once continuous disturbance reaches six months.

18.6 Brief psychotic disorder: under one month, often post-stressor, full recovery

Brief psychotic disorder is the shortest of the primary psychoses: at least one day but *less than one month*, with *eventual full return* to the premorbid level of function (American Psychiatric Association 2022). It frequently, though not necessarily, follows a marked psychosocial *stressor* (the "with marked stressor(s)" specifier; the peripartum-onset specifier captures the postpartum form). The two discriminators from schizophrenia are the sub-one-month duration and the complete recovery to baseline; schizophrenia neither resolves within a month nor reliably returns the patient to premorbid function. Note the tidy duration ladder across the primary non-affective psychoses: under one month is brief psychotic, one to six months is schizophreniform, six months or more is schizophrenia.

<1 month	1 to 6 months	≥6 months
BRIEF PSYCHOTIC DISORDER	SCHIZOPHRENIFORM DISORDER	SCHIZOPHRENIA (DSM-5-TR)

18.7 Organic and substance-induced psychosis: the mandatory first-episode workup

Before any of the primary psychoses can be diagnosed, a psychosis that is *secondary*, driven by a medical illness or a substance, must be excluded. A psychosis attributable to a general medical condition is an organic psychosis (a secondary psychosis); one driven by intoxication, withdrawal or a prescribed agent is a substance-induced psychosis. This is why every first-episode psychosis (a **first episode psychosis**, fep) carries a mandatory organic-and-substance workup: the purpose of the first-episode psychosis assessment is to catch the treatable secondary cause before committing to a lifelong primary label.

Organic causes to exclude. The high-yield secondary causes are autoimmune and infective *encephalitis* (the classic being anti-NMDA receptor encephalitis, NMDARE, driven by antibodies to the NMDA-receptor GluN1 subunit, presenting with new-onset psychosis plus seizures, movement disorder and autonomic instability; Kaplan & Sadock 2024), *temporal-lobe pathology* (temporal-lobe epilepsy, tumour), and *delirium* (an acute, fluctuating confusional state with clouded consciousness, the single most important bedside separator from a primary psychosis, in which the sensorium is clear). Red flags that mandate a hunt for an organic cause include acute or subacute onset, clouding or fluctuation of consciousness, seizures, focal neurology, abnormal

movements, and prominent visual (rather than auditory) hallucinations. **Substances to exclude.** Cannabis, stimulants (amphetamine, cocaine, methamphetamine), hallucinogens, and withdrawal states must be cleared by history and a urine drug screen; a substance-induced psychosis by definition resolves once the agent and a reasonable washout have passed, whereas schizophrenia does not. For the neurochemical pathways and the imaging principles (CT, MRI) that underlie this workup, cross-reference the Neurochemistry, Neuroendocrinology, Neuroimaging and Basic Psychopharmacology notes.

TRAP **Missing an organic or substance cause in a first episode of psychosis.** Diagnosing schizophrenia at a first-episode psychosis without a completed organic and substance-induced psychosis workup is the classic and dangerous exam error; anti-NMDA encephalitis and stimulant psychosis both mimic it and both are treatable.

18.8 The differential at a glance

The table below sets each mimic against the one discriminator that separates it from schizophrenia and the key feature that anchors it, running the affective rivals, the duration-defined rivals, the encapsulated-delusion rival and the two secondary psychoses in the same order as the decision tree (Fig 8.12).

MIMIC	THE ONE DISCRIMINATOR FROM SCHIZOPHRENIA	KEY FEATURE
Mood disorder with psychotic features	**Psychosis present ONLY within a mood episode, remits with the mood**	Often mood-congruent (nihilistic in depression, grandiose in mania)
Schizoaffective disorder	**≥2 weeks of psychosis WITHOUT a mood episode, AND mood present for the MAJORITY of the illness**	The overlap zone: too much standalone psychosis for a mood disorder, too much mood for schizophrenia
Delusional disorder	**Non-bizarre delusion(s) with function otherwise preserved and NO other prominent core symptoms**	Encapsulated delusional system; no prominent hallucinations, thought disorder or negative symptoms
Schizophreniform disorder	**Duration 1 to 6 months; NO functional-decline requirement**	Symptomatically schizophrenia caught before the 6-month line ("provisional" if ongoing)
Brief psychotic disorder	**Duration <1 month with FULL return to baseline; often post-stressor**	Shortest primary psychosis; complete recovery is definitional
Organic / secondary psychosis	**A medical cause (encephalitis, temporal-lobe pathology, delirium) is demonstrable**	Clouded/fluctuating consciousness, seizures, focal signs, visual hallucinations; anti-NMDA encephalitis is the classic
Substance-induced psychosis	**Onset and offset track a substance; resolves after the agent and washout**	Cannabis, stimulants, hallucinogens, withdrawal; cleared by history and urine drug screen

Interleaved differential of schizophrenia against its mimics: each row gives the single discriminator and the anchoring feature, in the order of the decision tree, secondary causes first, then mood, then the duration ladder, with delusional disorder to the side.

GOOD TO REMEMBER

- **Mood disorder with psychotic features:** a major depressive or manic episode carrying delusions or hallucinations; central claim is that psychosis is confined to the mood episode and is often mood-congruent; the discriminator is that it is present only during the mood episode and remits when the mood resolves.
- **Schizoaffective disorder:** a psychosis with a heavy mood burden; core criteria are at least two weeks of psychosis without a mood episode PLUS mood episodes present for the majority of the total illness; the discriminator is the two-week standalone-psychosis rule (excludes mood disorder) with the majority-of-illness mood rule (excludes schizophrenia).
- **Delusional disorder:** non-bizarre delusion(s) on an otherwise intact person; central claim is preserved function outside the delusion with no other prominent core symptoms; the discriminator is the absence of prominent hallucinations, thought disorder, negative symptoms or disorganisation.
- **Schizophreniform disorder:** the full schizophrenia symptom picture; core criterion is a duration of one to six months with NO required functional decline; the discriminator is duration, it converts to schizophrenia at six months.
- **Brief psychotic disorder:** an acute psychosis, often after a stressor; core criteria are duration under one month with full return to premorbid function; the discriminator is the sub-one-month duration plus complete recovery to baseline.
- **Organic (secondary) and substance-induced psychosis:** psychoses driven by a medical illness (autoimmune or infective encephalitis such as anti-NMDA receptor encephalitis, temporal-lobe pathology, delirium) or by a substance; central claim is that they are secondary, not primary; the discriminator is a demonstrable medical or substance cause, which the mandatory first-episode psychosis workup is designed to catch before schizophrenia is diagnosed.

HOLD THIS

Rule out organic and substance-induced psychosis first, then apply the mood exclusion (confined-to-episode is a mood disorder, two-weeks-standalone plus majority-mood is schizoaffective), then read the clock: under one month is brief psychotic, one to six months is schizophreniform, six months or more with dysfunction is schizophrenia, and a non-bizarre delusion on an intact person is delusional disorder.

Course, prognosis and outcome

19 · The phases, natural course and duration of untreated psychosis

Schizophrenia is not a single event but a trajectory. Long before the first frank hallucination there are subtle differences in cognition and social function, then a symptomatic decline, then the first acute episode, and for many patients a chronic course of recurrent episodes on a background of persisting deficit. Being able to name the **phases**, describe the **natural course** and the pattern of **relapse**, and quote the classical outcome data is a staple of both long cases and vivas. The single most examinable modern fact in this topic is that a longer **duration of untreated psychosis** predicts a worse outcome, which is the whole rationale for early intervention.

Exam framing. Expect to be asked to lay out the phases from premorbid to residual, to state the **rule of thirds** and attribute it honestly as an approximation, to name the three WHO cross-cultural **outcome study** generations (International Pilot Study of Schizophrenia, Determinants of Outcome, International Study of Schizophrenia), and to define the duration of untreated psychosis and state its prognostic significance. The classic examiner trap here is to reproduce the Kraepelinian picture of a uniformly deteriorating illness; the modern data show heterogeneous, frequently non-deteriorating outcomes.

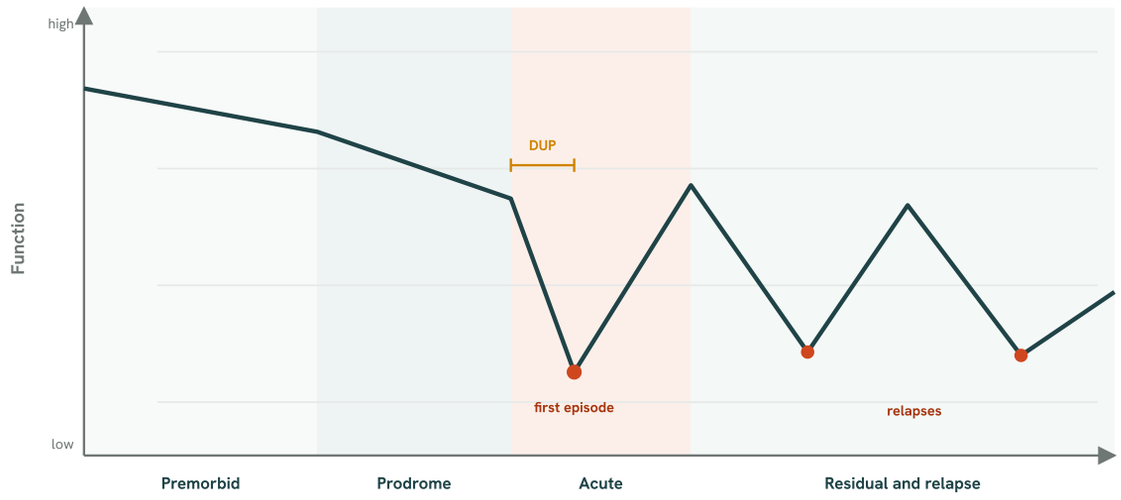


Fig 8.13 The phases and natural course of schizophrenia, plotted as function against time. A near-normal premorbid level declines through the prodrome, drops at the first episode after a duration of untreated psychosis, and then follows a relapsing course with incomplete recovery to a residual baseline. The course is heterogeneous rather than uniformly deteriorating, and a longer duration of untreated psychosis predicts a worse outcome.

19.1 The premorbid phase: subtle differences long before illness

What it is. The premorbid phase is the long period, often reaching back to childhood, in which individuals who will later develop schizophrenia differ subtly from their peers, before any prodromal symptom appears. These **premorbid** differences are typically mild and non-specific: slightly delayed developmental milestones, poorer motor coordination, lower average childhood IQ and academic attainment, more social withdrawal and fewer friendships, and a tendency to solitary or "schizoid" traits (Kaplan & Sadock 2024). They are detectable at a population level in birth-cohort and follow-back studies but are far too non-specific to identify an individual case prospectively. Conceptually this phase is where the neurodevelopmental account of the illness is anchored; for the developmental mechanisms themselves, cross-reference the neurodevelopment material within these notes.

The key point for exams is that these premorbid features are *trait-like* and present well before psychosis, distinguishing them from the prodrome, which is a symptomatic *change* from the person's own baseline.

19.2 The prodromal phase: symptomatic decline before frank psychosis

What it is. The prodromal phase is the period of symptomatic disturbance preceding frank psychosis, evolving over months to years, in which non-specific changes appear first (depressed mood, anxiety, sleep disturbance, irritability, social withdrawal, falling academic or occupational performance) and attenuated subthreshold psychotic features follow (ideas of reference, odd beliefs, perceptual distortions, suspiciousness), held with relatively preserved insight (Yung & McGorry 1996). Classically the **prodromal phase** is a retrospective concept, certain only once psychosis has declared, which is why prospective research reframes it as an at-risk mental state. The detailed operational at-risk criteria and transition data are developed in the prodrome and first-episode topic within these notes; here it sits simply as the second phase of the natural history.

19.3 The acute phase: the first episode and active psychosis

What it is. The acute phase is the period of florid, active psychosis in which positive symptoms (delusions, hallucinations, disorganisation) dominate the picture and typically bring the patient to psychiatric attention. The first such episode is the **acute** first-episode presentation, usually in late adolescence or early adult life, and it is the point at which diagnosis is provisionally made and treatment begun. For the descriptive definitions of what a delusion, a hallucination or formal thought disorder actually *is* as a phenomenon, cross-reference the Psychometry, Assessment and Descriptive Psychopathology notes; here the acute phase is defined by the prominence and activity of those positive symptoms rather than by their form.

Onset may be acute (developing over days to weeks, often with a better prognosis) or insidious (evolving over months to years out of a long prodrome, carrying a worse prognosis). Following the acute episode most patients enter partial or full remission, but a substantial proportion do not return fully to their premorbid level.

19.4 The residual phase: chronic negative and defect states

What it is. The residual phase is the chronic phase that follows one or more acute episodes, in which florid positive symptoms have subsided but attenuated symptoms and, above all, persistent negative symptoms and cognitive impairment remain. The **residual phase** is the substrate of long-term disability: blunted affect, poverty of speech, avolition, social withdrawal and functional decline, often with relatively few active positive symptoms. In this phase deterioration in social role tends to be established rather than progressing; much of the loss of social function occurs during the first two years after diagnosis rather than accruing steadily over decades (Shorter Oxford Textbook of Psychiatry 2018). For the enduring primary negative-symptom construct (the deficit syndrome) as an entity, cross-reference the negative-symptoms topic within these notes.

19.5 The natural course: episodic relapse on a variable background

Pattern. The natural course of schizophrenia in most patients is one of recurrent acute episodes separated by inter-episode periods of variable recovery, superimposed on the phase structure above. Some patients have a single episode with full recovery; some have recurrent episodes with full inter-episode recovery; many have recurrent episodes with incomplete recovery and a

stepwise accumulation of residual deficit; a minority run a continuous, unremitting course. The classic clinical observation is that each **relapse** tends to be followed by slower and less complete remission, and that inter-episode functioning may ratchet downward, though this is far from universal.

ICD-10 course specifiers. The natural course was formally captured in ICD-10 by a set of longitudinal specifiers applied when the illness had been observed for at least a year: continuous; episodic with progressive deficit; episodic with stable deficit; episodic remittent; incomplete remission; and complete remission. Where exams still use ICD-10, these course specifiers remain fair game. ICD-11 and DSM-5-TR have moved away from this scheme toward course qualifiers keyed to episode number and current state (first episode, multiple episodes, continuous), each specified as currently in acute episode, in partial remission or in full remission; both current systems also dropped the classical subtypes in favour of a dimensional symptom-domain approach.

TRAP **Not a uniformly deteriorating Kraepelinian course.** Dementia praecox implied inevitable decline; the natural course is in fact heterogeneous, and a large fraction of patients stabilise or recover rather than deteriorate relentlessly.

19.6 Relapse and its drivers

Relapse. A relapse is the recurrence or marked worsening of active psychotic symptoms after a period of remission or stability. The strongest and most modifiable driver of **relapse** is discontinuation of antipsychotic medication: relapse risk is high when maintenance treatment is stopped after an episode. High expressed emotion in the family environment (critical, hostile or over-involved attitudes), substance misuse (notably cannabis and stimulants) and psychosocial stress are further recognised precipitants. The management levers that reduce relapse (maintenance pharmacotherapy, family intervention, adherence support) belong to treatment and are developed in the Schizophrenia: management, antipsychotics and adverse effects notes; here relapse matters as the engine of the recurrent natural course.

RULE **Stopping the drug is the commonest cause of relapse.** After a first episode, relapse risk is substantially higher once maintenance antipsychotic medication is discontinued.

19.7 Long-term outcome and the rule of thirds

The heterogeneity. The long-term outcome of schizophrenia is strikingly heterogeneous. Long-term follow-up cohorts (including the classic European studies by Manfred Bleuler and by Ciompi) converged on the message that a substantial proportion of patients achieve social recovery or a favourable outcome, contradicting the fatalistic Kraepelinian view. This clinical shorthand is the rule of thirds: as an approximation, roughly one-third of patients have a good **long-term outcome** (recovery or mild residual symptoms with reasonable function), roughly one-third an intermediate outcome (persisting symptoms but some function), and roughly one-third a poor outcome (chronic, severely disabling illness).

RULE **Rule of thirds, quote it as an approximation.** Roughly a third good outcome, a third intermediate, a third poor; a memory aid for heterogeneity, not a precise statistic, and the exact proportions vary by cohort and outcome definition.

Attribution honesty. The rule of thirds is a teaching heuristic distilled from several outcome cohorts rather than the finding of one definitive study, and the precise proportions depend heavily on how "outcome" is defined and on the era, treatment access and length of follow-up. Quote it as an approximate, illustrative figure and name it as a heuristic; do not present it as a precise, source-anchored statistic.

19.8 The WHO cross-cultural outcome studies: IPSS, DOSMED and ISoS

The most important body of **outcome study** evidence comes from three linked generations of a World Health Organization **who study** programme, which followed large cohorts across many countries with standardised instruments.

STUDY	WHAT IT WAS	CENTRAL FINDING
ipss (International Pilot Study of Schizophrenia)	WHO collaborative study, patients ascertained across nine countries from the late 1960s, using standardised structured interviews (Present State Examination, CATEGO)	**Schizophrenia could be reliably identified across diverse cultures; outcomes were variable and often better than expected**
dosmed (Determinants of Outcome of Severe Mental Disorders)	WHO incidence-based follow-up across ten countries, designed to sidestep the sampling bias of prevalence cohorts by studying first-contact cases	**Confirmed a broadly comparable incidence but a heterogeneous, frequently non-deteriorating course**
isos (International Study of Schizophrenia)	WHO long-term (roughly 15 to 25 year) follow-up of the earlier IPSS and DOSMED cohorts	**A large proportion of patients were recovered or substantially improved at very long follow-up; outcomes were not uniformly deteriorating**

The three generations of the WHO cross-cultural outcome programme. Their unifying message is that long-term outcome is heterogeneous and often non-deteriorating, not the inevitable decline implied by dementia praecox (Jablensky 2000).

The much-cited finding that outcomes were *better in developing than in developed countries* came out of this same programme; that specific finding, its size and the debate over whether it is real or an artefact of ascertainment and follow-up, is worked through in the prognosis and prognostic-factors topic within these notes rather than repeated here. For the purposes of the natural course, the load-bearing conclusion is heterogeneity: the WHO data are the empirical refutation of a single deteriorating trajectory.

19.9 The duration of untreated psychosis

Definition. The duration of untreated psychosis (DUP) is the interval between the onset of frank psychotic symptoms and the start of adequate antipsychotic treatment. It is distinct from the duration of untreated *illness*, which reaches back further to the onset of the prodrome. Across

first-episode cohorts a longer DUP is associated with a poorer symptomatic and functional outcome and with slower, less complete remission (Penttila et al. 2014; Fraguas et al. 2014).

Why it matters. Two explanations are advanced for the association between a longer period of **untreated psychosis** and worse outcome (Shorter Oxford Textbook of Psychiatry 2018). The first is confounding: a prolonged, insidious onset is itself a marker of a more severe, treatment-resistant form of the illness, so a long **dup** may be an *index* of severity rather than a cause of poor outcome. The second is the "neurotoxicity" hypothesis: that untreated active psychosis is itself harmful and renders the illness progressively less responsive to treatment. Whichever mechanism dominates, a long DUP flags a worse prognosis, and shortening it is the explicit target of early-intervention and early-detection services. Note the honest caveat that whether early-intervention teams actually reduce DUP, and whether that translates into better long-term outcome, remains debated.

DUP ↑	~2 yr	~1/3
WORSE OUTCOME, SLOWER REMISSION	MOST SOCIAL DECLINE IS EARLY	GOOD LONG-TERM OUTCOME (RULE OF THIRDS)

RULE **Longer DUP predicts worse outcome.** A longer duration of untreated psychosis is associated with poorer symptomatic and functional outcome, which is the central argument for early detection and prompt treatment.

TRAP **Do not read DUP as purely causal.** Part of the association may be confounding: an insidious, prolonged onset is itself a marker of severe, treatment-resistant illness, so a long DUP may index severity rather than cause the poor outcome.

WORKED EXAMPLE

A 19-year-old with a year of falling grades, withdrawal and odd magical beliefs (prodromal phase) develops florid persecutory delusions and voices over three weeks (acute first episode) but is only brought to services eight months later. That eight-month interval from frank psychosis to adequate treatment is the duration of untreated psychosis. Following treatment the positive symptoms remit but blunted affect and avolition persist (residual phase), and after he stops medication he relapses within the year. This single vignette carries the whole natural course: premorbid to prodromal to acute to residual, with relapse on drug discontinuation and a prognostically important long DUP.

HOLD THIS

The natural course runs premorbid to prodromal to acute to residual with relapsing episodes; long-term outcome is heterogeneous (rule of thirds, and the WHO IPSS, DOSMED and ISoS studies show frequently non-deteriorating outcomes), and a longer duration of untreated psychosis predicts a worse outcome.

MNEMONIC

PPARR

Premorbid, **P**rodromal, **A**cute, **R**esidual, **R**elapse: the four phases plus the relapsing pattern that defines the natural course.

GOOD TO REMEMBER

- **Premorbid phase:** trait-like subtle differences (mild motor, cognitive/IQ and social differences) present from childhood, well before any symptom; discriminator is that it is a stable baseline trait, not a change, and is too non-specific to identify an individual case.
- **Prodromal phase:** symptomatic change from the person's own baseline, non-specific decline then attenuated psychotic features over months to years; discriminator is that it is classically a retrospective concept, reframed prospectively as the at-risk mental state.
- **Acute phase:** florid active psychosis dominated by positive symptoms, containing the first episode; discriminator is that acute onset carries a better prognosis than an insidious one.
- **Residual phase:** chronic phase with persisting negative symptoms and cognitive impairment after positive symptoms subside; discriminator is that most social decline is established within the first two years, not accrued steadily over decades.
- **Natural course and relapse:** recurrent acute episodes with variable inter-episode recovery; discriminator is that the commonest and most modifiable driver of relapse is antipsychotic discontinuation.
- **Rule of thirds:** roughly a third good, a third intermediate, a third poor long-term outcome; discriminator is that it is an approximate teaching heuristic, not a precise single-study statistic.
- **WHO outcome studies (IPSS, DOSMED, ISoS):** IPSS showed schizophrenia is identifiable across cultures, DOSMED was the incidence-based ten-country follow-up, ISoS the very long-term follow-up; discriminator/central claim is that outcomes are heterogeneous and frequently non-deteriorating, refuting a uniform Kraepelinian decline (Jablensky 2000).
- **Duration of untreated psychosis (DUP):** interval from onset of frank psychosis to adequate treatment; discriminator is that a longer DUP predicts worse outcome (partly causal "neurotoxicity", partly a marker of insidious severe illness) and is the target of early intervention.

PEARL

The examiner's favourite pivot is from Kraepelin to the WHO data: dementia praecox framed schizophrenia as inevitably deteriorating, but IPSS, DOSMED and ISoS, together with the long-term European cohorts, show a heterogeneous course in which a large minority recover. Lead with heterogeneity, then hang the rule of thirds and the prognostic weight of duration of untreated psychosis off it.

20 · Prognostic factors, cross-cultural outcome and recovery

The course of schizophrenia is heterogeneous and, in the individual case, still largely unpredictable, so what an examiner tests here is not a single verdict but three separable things: which features at first presentation shift the odds toward a better or worse outcome, why the WHO cross-cultural programme found the counterintuitive result that outcome was on average better in the developing world, and what modern operational definitions of remission and recovery actually require. Each of these is a discrete answer with its own evidence, and the

commonest error is to blur them, above all to treat a patient who is symptom-free as though they have recovered.

How to hold it. Learn the good-versus-poor **prognostic factor** lists as paired opposites, keep the three WHO studies (IPSS, DOSMeD, ISoS) as one story with a critique attached, and treat symptomatic **remission** and functional **recovery** as two different thresholds. The raw descriptive definitions of the psychotic phenomena themselves belong to the Psychometry, Assessment and Descriptive Psychopathology notes; antipsychotic treatment, its effect on outcome and rehabilitation belong to the Schizophrenia: management, antipsychotics and adverse effects notes; this topic states them only as far as prognosis requires.

Feature	Good prognosis	Poor prognosis
Onset	Acute, sudden	Insidious, gradual
Precipitant	Clear stressor	None identified
Symptoms	Positive, affective	Negative, deficit
Premorbid	Good adjustment	Poor, withdrawn
Demographics	Female, married, later onset	Male, single, early onset
Untreated psychosis	Short DUP, treated early	Long DUP
Support	Good social support	Poor support, high EE

Weigh the balance of features; no single factor decides the outcome.

Fig 8.14 Good against poor prognostic factors in schizophrenia. The good-prognosis column reads as an acute, affective, well-supported presentation treated early; the poor-prognosis column as an insidious, negative-symptom illness with a long duration of untreated psychosis. The prognosis is the balance across features, not any one of them.

20.1 Good versus poor prognostic factors as paired opposites

Why learn them paired. The predictors of outcome are best held as a single axis with a favourable and an unfavourable pole, because almost every good prognosis feature has a mirror-image poor prognosis feature, and an examiner who gives you one expects the other. The good pole describes an illness that looks reactive, affective and abrupt on a healthy premorbid substrate; the poor pole describes an illness that looks endogenous, negative-symptom-laden and creeping on an already-compromised substrate (Kaplan & Sadock 2024).

The favourable set. A good prognosis is predicted by an acute onset, an identifiable precipitant, prominent mood or affective symptoms, good premorbid functioning, being married or female, and a short duration of untreated psychosis with early treatment (Puri & Hall). Later age of onset, the presence of confusion or perplexity in the acute phase, a family history of mood disorder,

predominant positive symptoms and good treatment concordance sit on the same favourable pole.

The unfavourable set. A poor prognosis is predicted by an insidious onset, prominent negative symptoms, poor premorbid functioning, early onset, male sex, a long duration of untreated psychosis and no identifiable precipitant (an der Heiden & Hafner 2011). Cognitive impairment at presentation, a family history of schizophrenia, chronic course beyond two years, social isolation and structural change such as ventricular enlargement on imaging cluster on this pole. The parsed reviews stress that the predictive value of any single factor is modest, so these shift the odds rather than fix the outcome (Shorter Oxford / an der Heiden & Hafner 2011).

DIMENSION	GOOD PROGNOSIS	POOR PROGNOSIS
Onset	**Acute or abrupt**	Insidious, creeping
Precipitant	**Identifiable stressor present**	No precipitant
Affective symptoms	**Prominent mood component**	Absent; flat or blunted affect
Symptom profile	Predominantly positive symptoms	**Predominant negative symptoms**
Premorbid functioning	**Good premorbid adjustment**	Poor premorbid functioning
Age of onset	Later onset	**Early onset**
Sex and marital status	Female; married	Male; unmarried
Duration of untreated psychosis	**Short DUP, early treatment**	Long DUP, delayed treatment
Family history	Mood disorder	Schizophrenia

The favourable pole reads as reactive, affective and abrupt on a healthy substrate; the poor pole reads as endogenous, negative and insidious on a compromised one. Drawn as Fig 8.8.

RULE **Acute, affective, short DUP predicts better.** An acute onset with an affective component and a short duration of untreated psychosis is the single most reliable favourable triad; treat it as your first-line answer to "what predicts a better outcome".

20.2 Duration of untreated psychosis as a modifiable predictor

Why DUP is special. Most prognostic factors are fixed at presentation and cannot be changed; the duration of untreated psychosis is the one major predictor that is potentially modifiable, which is why it carries such clinical weight. A longer DUP is associated, across cohorts, with a worse symptomatic and functional outcome, and this association is the epidemiological engine behind the early-intervention and first-episode-service movement (Kaplan & Sadock 2024). The causal direction is debated, since an insidious, negative-symptom illness both lengthens DUP and worsens outcome independently, but the working exam position is that shortening DUP through early detection is a legitimate target because at least part of the effect appears causal.

20.3 The WHO cross-cultural programme: IPSS, DOSMeD and ISoS

The three studies as one story. The claim that outcome is better in the developing world rests on a linked WHO cross-cultural programme of three studies. The International Pilot Study of Schizophrenia (IPSS), begun in 1968-69, interviewed patients with psychotic disorders across nine countries using the Present State Examination, and its first achievement was to show that schizophrenia presents in recognisably similar ways across very diverse cultures (WHO 1973; Kaplan & Sadock 2024). Its follow-up then produced the surprise: two-year course and outcome were better in patients from developing centres such as India, Nigeria and Colombia than in developed centres, particularly for the proportion reaching complete remission (WHO 1973; Shorter Oxford / Harrison et al. 2001).

DOSMeD and ISoS. Because IPSS could be criticised for how cases were ascertained, WHO mounted the Determinants of Outcome of Severe Mental Disorders study (DOSMeD), an incidence-based design across ten countries intended to capture first-contact cases and reduce selection bias, which broadly replicated the better developing-country outcome (Jablensky et al. 1992; Jablensky 2000). The International Study of Schizophrenia (ISoS) then reassembled these cohorts for very long-term follow-up at 15 and 25 years, confirming the geographical stability of the difference while also showing that late recovery in a significant minority was more common than therapeutic pessimism had assumed (Harrison et al. 2001; Hopper & Wanderling 2000).

INDIA

India was a centre in all three WHO studies, and the Indian data anchored the better-developing-country finding: in the IPSS follow-up the Indian centres showed a high proportion reaching complete remission. The complementary Indian ICMR study, SOFACOS (Study of Factors Associated with Course and Outcome of Schizophrenia), followed 386 patients across Vellore, Madras and Lucknow and reported a favourable outcome in about two-thirds, higher than the roughly one-half seen in Ciompi's long European cohort (Verghese et al. 1989). Cite India as the exemplar centre for the cross-cultural outcome claim, not as a separate finding.

20.4 The modern critique of the developing-country finding

Why the finding is now contested. The better outcome in developing countries from the WHO cross-cultural studies is one of the most cited results in social psychiatry, but its interpretation is genuinely controversial, and an examiner rewards the critique as much as the finding. Four methodological concerns recur (Cohen et al. 2008; Kaplan & Sadock 2024; Shorter Oxford / an der Heiden & Hafner 2011).

Case-mix and diagnostic non-equivalence

Developing-country samples may have contained more acute, remitting and organically tinged psychoses that would fare better whatever the setting, so like was not compared with like.

Acute-onset over-representation

An excess of acute-onset cases in the developing centres inflates apparent outcome, because acute onset is itself a good prognostic factor, confounding the country comparison.

Follow-up and attrition

Differential loss to follow-up, higher early mortality in some sites, and the difficulty of tracing patients across decades can bias which patients remain to be counted as recovered.

Outcome-definition heterogeneity

Outcome was measured with varying instruments and thresholds across sites and eras, and social outcome, which was often worse than symptomatic outcome, was not always separated from symptom outcome.

Where the debate rests. The subsequent WHO analyses argued that a real difference in the severity and type of illness at first presentation contributed, so the effect is not purely artefactual; but the strong "better outcome in the developing world" headline should be delivered with these caveats, not as a settled truth (Harrison et al. 2001; Cohen et al. 2008). The safe examination line is that the finding is robust in the WHO data yet its explanation, whether social, familial (lower expressed emotion, greater community reintegration) or methodological, remains unresolved.

COMMON TRAP

Reciting "outcome is better in developing countries (WHO)" as a bare fact without the critique. The strong claim rests on IPSS, DOSMeD and ISoS but is undercut by case-mix, an over-representation of acute-onset cases, follow-up and attrition problems, and heterogeneous outcome definitions; the marks are in naming those concerns.

20.5 Remission: the Andreasen operational criteria

Why an operational definition was needed. Before 2005 "remission" in schizophrenia was used loosely, which made trials and cohorts incomparable. The Remission in Schizophrenia Working Group, led by Nancy Andreasen, produced a standard, consensus remission criteria definition to fix this (Andreasen et al. 2005). The definition has two limbs: a severity threshold and a time threshold.

The two limbs. The *severity* limb requires that a defined set of core schizophrenia symptoms across the three domains, positive, negative and disorganised, be rated no higher than mild, operationalised as a score of mild or less on the relevant PANSS or SAPS/SANS items. The *duration* limb requires that this low-severity state be sustained for a minimum period of at least **six months** (Andreasen et al. 2005). Meeting a low symptom score at a single visit is therefore not remission; the six-month persistence is what distinguishes remission from a transient response, and this durational rule is the single most examinable point in the definition.

MNEMONIC

MILD for SIX

Remission (Andreasen 2005) is core symptoms rated MILD or less across positive, negative and disorganised domains, sustained for at least SIX months. Both limbs are needed; the six-month persistence is the discriminator from mere symptomatic response.

20.6 Remission versus functional outcome versus recovery

Three ascending thresholds. These three terms name three different and increasingly demanding states, and conflating them is the classic outcome error. Symptomatic remission (Andreasen) is a low symptom burden sustained for six months. Functional outcome is a separate axis entirely, describing role performance in work, study, independent living and relationships, and it can be poor even when symptoms are in remission, because negative symptoms and cognitive impairment, rather than psychosis, are the chief drivers of disability. Recovery is the most demanding operationalised construct, typically requiring improvement in *both* symptoms and social or functional role, sustained for a longer window, usually at least two years (Shorter Oxford / Jaaskelainen et al. 2013; Harrison et al. 2001).

What the recovery numbers say. A widely cited meta-analysis defining recovery as combined symptomatic and functional improvement sustained for at least two years found that only about **14%** of patients met the criterion, and this figure had not clearly improved over decades (Jaaskelainen et al. 2013). The long-term ISoS and Harrison cohorts found roughly one-sixth in full recovery, with late recovery in a meaningful minority, and studies such as AESOP repeatedly showed that social outcomes were worse than symptomatic ones (Harrison et al. 2001; Morgan et al. 2014). The recovery-movement point, developed further in the management notes, is that recovery in its fullest sense is more than symptom control: it includes agency, meaning and a life the person values, not merely a low PANSS score.

TRAP **Equating symptomatic remission with functional recovery.** A patient in Andreasen remission can remain occupationally and socially disabled; remission is a symptom threshold, recovery requires sustained functional improvement too, and negative symptoms and cognition, not psychosis, drive the residual disability.

HOLD THIS

Good prognosis is acute onset, a precipitant, prominent mood symptoms, good premorbid functioning, married or female and short DUP; the WHO cross-cultural studies (IPSS, DOSMeD, ISoS) found better outcome in developing countries but the finding is undercut by case-mix and acute-onset over-representation; and Andreasen remission is core symptoms mild or less for at least six months, which is not the same as functional recovery.

GOOD TO REMEMBER

- **Good prognostic factors:** features shifting the odds toward better outcome; acute onset, identifiable precipitant, prominent mood symptoms, good premorbid functioning, married or female, short duration of untreated psychosis; discriminator is that they describe a reactive, affective, abrupt illness and predict only probabilistically.
- **Poor prognostic factors:** features shifting the odds toward worse outcome; insidious onset, prominent negative symptoms, poor premorbid functioning, early onset, male sex, long duration of untreated psychosis, no precipitant; discriminator is that negative symptoms and long DUP are the heaviest-weighted of the set.
- **Duration of untreated psychosis (DUP):** time from psychosis onset to first effective treatment; longer DUP predicts worse outcome; discriminator is that it is the one *modifiable* major predictor, hence the target of early-intervention services.
- **IPSS (WHO 1973):** nine-country cross-cultural study using the PSE; showed schizophrenia presents similarly across cultures and, on follow-up, better outcome in developing centres; discriminator is that it was the origin of the cross-cultural outcome claim.
- **DOSMeD (Jablensky et al. 1992):** ten-country incidence-based WHO study of first-contact cases; replicated the better developing-country outcome with reduced selection bias; discriminator is its incidence-based, first-contact design answering the case-ascertainment critique of IPSS.
- **ISoS (Harrison et al. 2001):** 15-to-25-year follow-up reassembling the IPSS/DOSMeD cohorts; confirmed geographical stability of outcome and documented late recovery; discriminator is that it is the very-long-term arm showing recovery can occur late.
- **Andreasen remission criteria (2005):** Remission in Schizophrenia Working Group definition; core symptoms across positive, negative and disorganised domains rated mild or less, sustained at least six months; discriminator is the six-month duration limb, absent from mere symptomatic response.
- **Recovery:** combined symptomatic and functional improvement sustained (typically at least two years); met by roughly 14% in meta-analysis (Jaaskelainen et al. 2013); discriminator is that it requires functional outcome, not symptom control alone, and is more than a low symptom score.

PEARL

Three answers carry every prognosis viva: the favourable triad is acute onset plus affective symptoms plus short DUP; the cross-cultural headline is "better in developing countries (IPSS, DOSMeD, ISoS), but case-mix and acute-onset over-representation cloud it"; and the remission-versus-recovery line is "Andreasen remission is mild symptoms for six months, recovery adds sustained functional improvement".

Figure. The good-versus-poor prognostic-factor grid, favourable and unfavourable poles set against each other across onset, precipitant, affect, symptom profile, premorbid functioning, sex and DUP, is drawn as Fig 8.8.

21 · Suicide, the mortality gap and physical comorbidity

Schizophrenia is not only a disorder of psychosis; it is a disorder of **shortened life**. Two facts anchor the outcome story that examiners return to again and again: patients are at high suicide risk, and, separately, they die many years earlier than the general population from ordinary physical disease. The trap the exam is built to catch is conflating the two. Suicide is the dramatic, early, and preventable killer, but it accounts for a minority of the total lost years. The bulk of the

mortality gap is cardiometabolic, and it is under-recognised and under-treated (Kaplan & Sadock 2024, De Hert 2011).

Why this matters clinically. Framing schizophrenia as a physical-health condition as much as a psychiatric one reorganises what you do at every review: you screen the heart and the metabolism, not just the mental state. The excess deaths are largely from causes that are measurable, modifiable, and shared with primary care, which is exactly why metabolic screening and physical-health monitoring in serious mental illness are now core competencies rather than an afterthought.

21.1 The suicide figure to hold

Lifetime risk. Older texts quote a suicide rate of 10 percent; contemporary meta-analyses put the lifetime suicide risk at roughly **~5%** (Palmer 2005, Popovic 2014; Kaplan & Sadock 2024, Semple & Smyth). The 10 percent figure is a classic exam relic and should be quoted as historical, not current. Non-fatal behaviour is far commoner: suicide attempts and suicidal ideation are frequent, with attempt rates in some series approaching 50 percent (Kaplan & Sadock 2024).

~5%	~15–20 yr	2–4×
LIFETIME SUICIDE RISK	LIFE-EXPECTANCY GAP IN SMI	ALL-CAUSE SMR VS GENERAL POPULATION

RULE **Quote ~5 percent, not 10 percent.** The lifetime suicide risk in schizophrenia is about five percent on modern meta-analysis; the historical 10 percent figure is not supported by contemporary data.

21.2 When and in whom suicide risk is highest

Temporal pattern. Risk is front-loaded. It is greatest early in the illness, including the prodrome and first years, in patients with frequent relapses, and around the time of admission and in the period immediately after discharge (Kaplan & Sadock 2024). The post-discharge window is the single most testable high-risk period: the patient is out of the containing environment, insight may be returning, and follow-up may be loose.

Risk factors. Young age, male sex, and high premorbid function with preserved or emerging insight into the decline (a fear of mental deterioration) all raise risk, as do depression, hopelessness, agitation, prior suicide attempts, substance misuse, and prominent paranoid delusions (Cassidy 2018, Popovic 2014; Kaplan & Sadock 2024). Note the paradox that examiners like: *good* premorbid function and returning insight are risk-raising here, because they let the patient grasp what has been lost. Persistent primary negative symptoms, by contrast, are associated with a lower suicide risk.

WORKED EXAMPLE

A 22-year-old man, previously a high-achieving engineering student, is discharged after a first admission for schizophrenia. His positive symptoms have resolved on medication and he now speaks lucidly about how far behind his peers he has fallen. On paper he looks well. In fact he sits in the highest-risk band: young, male, high premorbid function, emerging insight into decline, and freshly post-discharge. Insight resolving is not the same as risk resolving.

TRAP **Assuming returning insight means falling risk.** Preserved or emerging insight with high premorbid function is a suicide-*risk* factor in schizophrenia, not a reassurance; the early post-discharge period is peak risk.

21.3 The mortality gap: the headline number

Premature death. People with schizophrenia and other serious mental illness (SMI) die prematurely. The commonly cited figure is a reduction in life expectancy of about **15 to 20 years** in serious mental illness (Firth 2019 Lancet Psychiatry Commission). Schizophrenia-specific registry estimates are a little narrower, on the order of 10 to 15 years, with men losing more years than women (Kaplan & Sadock 2024). One influential textbook quotes men dying approximately 20 years and women approximately 15 years prematurely (Semple & Smyth, citing Saha 2007). The direction of travel is the exam point: the gap has, if anything, widened even as general-population mortality has fallen (Saha 2007).

Standardised mortality ratio. Population cohorts consistently find all-cause mortality two to four times that of the general population, that is a standardised mortality ratio of roughly two to four (Olfson 2015, Osby; Kaplan & Sadock 2024). This is a **relative** risk, observed over expected deaths, not an absolute one.

PEARL

The mortality gap is *widening*, not closing. As the general population lives longer, medical gains have largely bypassed people with schizophrenia, so the standardised mortality ratio has drifted upward over recent decades (Saha 2007). It is a marker of a health system failing a population, not of the illness alone.

21.4 Suicide versus cardiometabolic causes: what really drives the gap

The core distinction. Suicide accounts for a good part of the excess mortality early in the course, but across the whole lifespan it is a minority of the lost years. In the Global Burden of Disease framing, chronic physical disease is the primary cause of premature death in schizophrenia, with cardiovascular disease alone accounting for more than a third of premature deaths, while suicide, homicide and accidents together account for under fifteen percent of the excess (Kaplan & Sadock 2024, citing GBD). Registry work agrees: in one 25-year cohort, around eighty percent of patients died of medical disease (Brown; Kaplan & Sadock 2024).

A caveat to hold honestly. Some texts, counting the proportion of specifically *early* excess deaths, put unnatural causes (suicide and accidents) as high as around sixty percent (Semple &

Smyth). The reconciliation is that suicide dominates the *early* years and the *relative* risk in the young, whereas cardiometabolic disease dominates the *total* years of life lost across the lifespan. For a whole-population, whole-lifespan statement, cardiometabolic causes win.

RULE **Cardiometabolic, not suicide.** Most of the mortality gap in serious mental illness is cardiometabolic (chiefly cardiovascular disease), not suicide; suicide dominates the early and relative risk, physical disease dominates the total years lost.

TRAP **Blaming the whole excess mortality on suicide.** Attributing the premature death of people with schizophrenia only to suicide misses the two-thirds-plus that is cardiometabolic and preventable, and it is the classic wrong answer.

21.5 Physical comorbidity: the pattern of illness

Comorbidity is the rule. Physical comorbidity in schizophrenia is the norm, not the exception, and as many as two-thirds of patients carry more than one physical disease, that is multimorbidity (Kaplan & Sadock 2024). The **physical comorbidity** cluster that matters for the mortality gap is cardiometabolic and respiratory.

Metabolic syndrome

Clustered central obesity, dyslipidaemia, hypertension and hyperglycaemia; prevalent even in unmedicated first-episode psychosis (about 10 percent) and rising steeply with treatment and chronicity (Mitchell 2013).

Cardiovascular disease

The leading single cause of death in schizophrenia; pooled relative risk on the order of 1.5, higher for stroke and heart failure, with markedly worse outcomes after acute coronary events (Correll, Fan; Kaplan & Sadock 2024).

Type 2 diabetes

Prevalence roughly two to four times the general population (pooled around 10 to 13 percent), part of it predating antipsychotics, most of it amplified by them; low glucose and lipid screening rates persist (Stubbs, Vancampfort; Kaplan & Sadock 2024).

Smoking

Rates far above the general population, driving the elevated COPD, pneumonia and lung-cancer mortality; a major, modifiable contributor to the excess (Kaplan & Sadock 2024).

DOMAIN	SIGNAL IN SCHIZOPHRENIA	WHY IT MATTERS
Cardiovascular disease	**Leading cause of death; RR ~1.5, worse post-ACS outcomes**	Largest slice of the mortality gap
Type 2 diabetes	**~2–4× prevalence; low screening rates**	Screen glucose/HbA1c; often missed
Metabolic syndrome	~10% at first episode, unmedicated; rises with treatment	Present before drugs, worsened by them
Smoking / respiratory	**High smoking prevalence; raised COPD, pneumonia, lung cancer**	Modifiable; drives respiratory excess
Infections	Raised HIV, hepatitis B/C, TB, severe COVID-19	Contributory, often neglected

The physical-comorbidity map behind the mortality gap: cardiometabolic and respiratory disease carry the excess deaths, and screening is where the gains sit.

21.6 The antipsychotic contribution, in proportion

Two truths at once. Antipsychotics, especially some second-generation agents, contribute materially to the cardiometabolic burden through weight gain and metabolic change, and this is a real driver of **physical comorbidity**. Yet moderate antipsychotic exposure is associated with the *lowest* mortality in schizophrenia, and even higher doses carry lower mortality than no treatment at all (Torniainen 2015; Semple & Smyth). The metabolic liability of individual agents, the monitoring schedules, and how to mitigate them belong to the Schizophrenia: management, antipsychotics and adverse effects notes and are cross-referenced there rather than repeated here.

COMMON TRAP

Concluding that because antipsychotics cause metabolic harm they should be minimised or stopped to protect physical health. The mortality data point the other way: untreated schizophrenia carries the highest mortality, and moderate treatment the lowest. The answer is to treat *and* screen, not to withhold treatment.

21.7 Physical-health and metabolic screening in serious mental illness

The clinical response. Because the excess deaths are cardiometabolic and modifiable, structured physical-health monitoring is now standard care in **serious mental illness**. Metabolic screening means tracking weight and waist circumference, blood pressure, fasting glucose or HbA1c, and a lipid profile, at baseline and at defined intervals after starting or changing an antipsychotic, alongside smoking-cessation support and attention to diet and activity (De Hert 2011, Kaplan & Sadock 2024). The recurring failure the exam probes is that these patients are screened *less*, not more, than the general population despite being at higher risk, so the abnormalities go undetected and untreated (Solmi; Kaplan & Sadock 2024).

INDIA

Very high background smoking and smokeless-tobacco use, rising type 2 diabetes prevalence, and limited integration between psychiatric and general medical services make the physical-health gap especially stark in Indian practice. Baseline weight, blood pressure, fasting glucose and a lipid profile before and during antipsychotic treatment are low-cost, high-yield, and often the only physical-health contact these patients get.

MNEMONIC

SAD PERSONS meets the METABOLIC review

For suicide, remember risk loads onto the young, male, insightful, recently-discharged patient with depression and prior attempts. For the body, run the metabolic review every time: weight/waist, blood pressure, glucose or HbA1c, lipids, and smoking. One patient, two screens: the mind and the metabolism.

HOLD THIS

Roughly five percent lifetime suicide risk (highest early and post-discharge), a 15 to 20 year mortality gap in serious mental illness, and most of that gap cardiometabolic rather than suicide.

GOOD TO REMEMBER

- **Suicide risk in schizophrenia:** lifetime risk about five percent (not the old 10 percent); highest early in illness and just after discharge; discriminating risk factors are young age, male sex, high premorbid function with insight into decline, depression, and prior attempts.
- **Mortality gap:** premature death of roughly 15 to 20 years in serious mental illness (schizophrenia-specific registry figures ~10 to 15 years, more in men); standardised mortality ratio two to four times the general population; discriminator is that it is *widening*, not closing.
- **Physical comorbidity:** cardiovascular disease, type 2 diabetes, metabolic syndrome and heavy smoking; the number to know is that cardiometabolic disease, chiefly cardiovascular, causes the majority of premature deaths, more than a third from cardiovascular disease alone, while suicide/accidents are under fifteen percent of the excess.
- **Antipsychotic contribution:** a real driver of metabolic burden, yet moderate treatment carries lower mortality than none; details of agent-specific risk and monitoring are in the Schizophrenia: management, antipsychotics and adverse effects notes.
- **Metabolic screening in SMI:** weight/waist, blood pressure, fasting glucose or HbA1c, lipids at baseline and intervals, plus smoking cessation; the failure to know is that these patients are screened less than the general population despite higher risk.

Apply and consolidate

22 · Apply: four worked clinical vignettes

Everything in the preceding topics converges on four repeatable clinical moves, and the fastest way to fix them is to watch each one run once on a patient. This topic is that rehearsal: four short worked clinical vignettes, each a brief scenario, then the reasoning, then the read. They are deliberately the four that examiners return to, the workup of a first-episode psychosis, the

schizophrenia-versus-mood-with-psychosis differential, the primary-versus-secondary negative-symptom split, and a prognosis weighing, because between them they exercise the criteria, the differential, the phenomenology and the course in the exact order a viva demands.

How to use it. Read each vignette as a decision procedure, not a story: identify the discriminator the scenario turns on, state it, and only then commit to the label. The raw descriptive definitions of what a **delusion**, a **hallucination** or formal thought disorder actually is belong to the Psychometry, Assessment and Descriptive Psychopathology notes; the full criteria are set out in the criteria and discriminate topics above and are only applied here. Treatment is never decided in these vignettes; the drugs belong to the Schizophrenia: management, antipsychotics and adverse effects notes.

22.1 Vignette one: the first-episode workup

The move. A first frank psychosis is not a diagnosis until the treatable secondary causes are excluded; the first worked example runs that organic and substance workup before any primary label is allowed to settle. A first-episode psychosis (fep) is a syndromal label precisely because the eventual diagnosis is not yet fixed, so the whole exercise is to catch a reversible cause before committing (Kaplan & Sadock 2024).

WORKED EXAMPLE

Case: A 21-year-old man is brought by his family after roughly four months of change. It began with social withdrawal, dropping grades and odd, over-read meaning in ordinary events (attenuated, subthreshold ideas of reference); over the last six weeks it hardened into a fixed persecutory delusion that a neighbour is poisoning him and a running-commentary auditory hallucination. Consciousness is clear, there is no fluctuation, no seizure, no fever and no focal neurology; a urine drug screen is negative and there is no history of cannabis or stimulant use. **The reasoning:** because this is a first episode, the mandatory workup comes first, rule out an organic psychosis (a clear, non-fluctuating sensorium with no seizures, focal signs, abnormal movements or prominent visual hallucinations makes anti-NMDA-receptor encephalitis and temporal-lobe pathology unlikely, though basic screening bloods and imaging are still done) and rule out a substance-induced psychosis (negative screen, no use history, so no offset-on-washout to expect). Only now is a primary non-affective psychosis on the table, and the picture must be run through both current systems. **The read:** under ICD-11 he already qualifies, two core symptoms (persistent delusion plus persistent hallucination), both from the first four groups, present well beyond the one-month threshold. Under DSM-5-TR he meets Criterion A (two of five, including core positives) with a clear functional decline, but the total continuous disturbance is about four months, under the six-month line, so the correct DSM-5-TR label is schizophreniform disorder (provisional, since ongoing), converting to schizophrenia only once continuous disturbance reaches six months.

RULE **Exclude organic and substance causes before naming a primary psychosis.** Every first episode gets an organic-and-substance workup; only then do you apply the criteria and read the clock.

TRAP **Calling this "schizophrenia" under DSM-5-TR at four months.** The same picture is ICD-11 schizophrenia (one month) but DSM-5-TR schizophreniform disorder until six months; the two systems disagree here by design.

22.2 Vignette two: schizophrenia versus mood with psychosis

The move. The second worked example turns entirely on one discriminator, temporal confinement of the psychosis to mood episodes. A psychosis present *only* during a mood episode is a mood disorder; a psychosis that also stands alone, on a heavy mood background, is schizoaffective; a psychosis that persists across mood states with mood present only briefly is schizophrenia (American Psychiatric Association 2022).

WORKED EXAMPLE

Case: Two patients, same presenting complaint of "hearing voices", opposite answers. *Patient A* has had two discrete depressive episodes; in each, at the depth of the low mood, she developed nihilistic and guilt-laden delusions and a derogatory voice, and each time the psychosis cleared completely as the mood lifted, never appearing while she was euthymic. *Patient B*, over a two-year illness, has had a major mood episode present for roughly fourteen of the twenty-four months, but within that span there was a clear three-week stretch of persecutory delusions while fully euthymic. **The reasoning:** for Patient A the psychosis is *confined to the mood episode* and is mood-congruent, and it remits when the mood remits, so it never outlives the affective illness. For Patient B two rules must both be checked: is there at least a two-week period of psychosis in the *absence* of a mood episode (yes, the three euthymic weeks, which excludes a pure mood-with-psychosis label), and is a mood episode present for the *majority* of the total active and residual illness (yes, fourteen of twenty-four months, which excludes schizophrenia). **The read:** Patient A is a major depressive disorder with psychotic features, the discriminator being that psychosis is present only during the mood episode. Patient B is schizoaffective disorder, the discriminator being standalone psychosis of at least two weeks plus mood for the majority of the illness. Shrink Patient B's mood component to a couple of brief episodes and the same psychosis becomes schizophrenia with intercurrent mood symptoms.

RELATIONSHIP OF PSYCHOSIS TO MOOD	DIAGNOSIS	THE DISCRIMINATOR
Present ONLY during a mood episode; remits with the mood	Mood disorder with psychotic features	**Temporal confinement to the mood episode**
≥2 weeks standalone psychosis, AND mood present for the majority of the illness	Schizoaffective disorder	**Two-week standalone rule PLUS majority-mood rule**
Persists across mood states; mood present only for a minority	Schizophrenia	**Psychosis outlives and outweighs the mood**

The mood-versus-schizophrenia decision, one axis: how much of the psychosis stands outside a mood episode, and how much of the illness the mood occupies.

TRAP **Diagnosing schizophrenia inside an untreated mood episode.** Mood-congruent psychosis confined to depressive or manic episodes is a mood or schizoaffective disorder until the mood is treated and re-assessed.

22.3 Vignette three: primary versus secondary negative symptoms

The move. The third worked example never asks "are there negative symptoms"; it asks "what is producing them". A secondary negative symptom is produced by a removable driver, untreated positive symptoms, depression, extrapyramidal side effects or understimulation, and reverses when that driver is treated; a primary negative symptom is intrinsic and is only the residue after every secondary cause is stripped out (Tasman 2024; Kaplan & Sadock 2024).

WORKED EXAMPLE

Case: A 30-year-old man with schizophrenia is flat, near-mute and does almost nothing, hour after hour. Three details decide the read. First, he is on a high dose of a high-potency antipsychotic and has masked facies, a resting tremor and cogwheel rigidity. Second, his mood, sleep and appetite are unremarkable and he denies pervasive low mood or guilt. Third, when the dose is reduced and the parkinsonism settles, his facial expressivity and spontaneous activity partly return, but a core of blunted affect, poverty of speech and avolition remains, and has been present continuously for over a year, including through periods when his delusions were quiescent and he was clinically stable. **The reasoning:** the initial flatness was substantially *secondary*, a drug-induced parkinsonism (the neuroleptic-induced deficit syndrome) mimicking the disease's own negative symptoms; that part reversed with dose reduction, which is the definitional test of a secondary symptom. Depression was excluded as a driver. What survives the reversal is *primary*: it persists between episodes, outside depression and off the offending dose. This enduring primary picture, at least two negative symptoms sustained through the preceding year during clinical stability, meets the deficit syndrome as defined by Carpenter and operationalised by the Schedule for the Deficit Syndrome. **The read:** primary, enduring negative symptoms of the deficit syndrome, not drug-induced parkinsonism, once the reversible layer is removed. Its functional weight is the whole point, because negative symptoms, not psychosis, predict long-term social disability, and the deficit subgroup carries the poorer functional prognosis.

~15%	25 to 30%	≥2
DEFICIT SYNDROME, FIRST-EPISODE	DEFICIT SYNDROME, CHRONIC	NEGATIVE SYMPTOMS IN PAST YEAR (SDS)

RULE **Strip out the reversible causes before calling negative symptoms primary.** Treat positive symptoms, depression, extrapyramidal effects and understimulation first; only the enduring residue between episodes is the deficit syndrome.

TRAP **Labelling drug-induced parkinsonism "primary negative symptoms."** Masked facies and bradykinesia on a high antipsychotic dose are a reversible mimic; question the dose before you commit a patient to a deficit label.

22.4 Vignette four: the prognosis weighing

The move. The fourth worked example lays a patient's features on the two-poled prognostic axis and weighs the favourable against the unfavourable to state a likely course. Almost every good prognosis feature has a mirror-image poor prognosis feature, and the task is not to find one but to weigh the balance, remembering that any single factor only shifts the odds (Kaplan & Sadock 2024).

WORKED EXAMPLE

Case: Two contrasting first presentations. *Patient X*, a 32-year-old married woman, develops an abrupt psychosis over two weeks following a clear bereavement, with prominent affective colouring and perplexity, on a background of good premorbid work and social function; she is brought to care within days, so the duration of untreated psychosis is short. *Patient Y*, a 17-year-old unmarried man, has an insidious two-year slide of deepening social withdrawal, blunting and avolition with no identifiable precipitant, a schizoid premorbid personality, a family history of schizophrenia, and reaches care only after a long duration of untreated psychosis. **The reasoning:** Patient X sits almost entirely on the favourable pole, acute onset, an identifiable precipitant, prominent mood symptoms, good premorbid functioning, married and female, and a short DUP, the reactive, affective, abrupt-onset pattern that predicts better. Patient Y sits on the unfavourable pole, insidious onset, prominent negative symptoms, poor premorbid functioning, early onset, male, no precipitant, a family history of schizophrenia and a long DUP, and negative symptoms plus a long DUP are the heaviest-weighted of the poor set. **The read:** Patient X's balance points to a better-than-average course with a good chance of substantial remission; Patient Y's balance points to a poorer course with higher risk of chronicity and functional disability. The one modifiable lever in either case is the DUP, which is why early detection is the actionable message rather than a fixed verdict.

FEATURE	PATIENT X (FAVOURABLE)	PATIENT Y (UNFAVOURABLE)
Onset	**Acute (2 weeks)**	Insidious (2 years)
Precipitant	**Clear bereavement**	None
Affective symptoms	**Prominent**	Absent; blunted
Premorbid function	**Good**	Poor (schizoid)
Age and sex	32; female; married	**17; male; unmarried**
Duration of untreated psychosis	**Short**	Long
Family history	None stated	**Schizophrenia**

The same seven prognostic dimensions weighed for two presentations; X reads reactive-affective-abrupt (better course), Y reads endogenous-negative-insidious (poorer course), with DUP the one modifiable lever.

RULE **Weigh both poles, do not count one factor.** Prognosis is the balance of favourable against unfavourable features; the acute-affective-short-DUP triad is the strongest favourable signal and negative-symptoms-plus-long-DUP the strongest unfavourable one.

PEARL

The four vignettes share a single grammar: find the discriminator, name it, then read. Workup discriminator is a demonstrable organic or substance cause; mood discriminator is temporal confinement of psychosis to mood episodes; negative-symptom discriminator is reversibility on treating the driver; prognosis discriminator is the balance of the two poles with DUP as the one modifiable lever.

HOLD THIS

Every psychosis case runs the same four moves in order: exclude organic and substance causes first, then apply the mood exclusion (psychosis confined to mood episodes is a mood disorder, not schizophrenia), then read the duration clock, and finally weigh the prognostic poles with the duration of untreated psychosis as the one modifiable lever.

GOOD TO REMEMBER

- **First-episode workup (vignette one):** a first frank psychosis needing organic and substance exclusion before a primary label; core move is rule out encephalitis, temporal-lobe pathology, delirium and substance causes, then apply criteria; the discriminator is that the same picture is ICD-11 schizophrenia at one month but DSM-5-TR schizophreniform disorder until six months.
- **Mood-with-psychosis versus schizophrenia (vignette two):** the affective differential; core move is to ask whether psychosis is confined to mood episodes; the discriminator is temporal confinement (mood disorder if psychosis only ever appears within a mood episode, schizoaffective if there is at least two weeks of standalone psychosis plus mood for the majority of the illness).
- **Primary versus secondary negative symptoms (vignette three):** the negative-symptom split; core move is to strip out positive symptoms, depression, extrapyramidal effects and understimulation; the discriminator is reversibility, and the enduring residue between episodes meeting at least two negative symptoms for the preceding year is the deficit syndrome (Carpenter), roughly 15 percent first-episode and 25 to 30 percent chronic, carrying the greatest functional weight.
- **Prognosis weighing (vignette four):** the course estimate; core move is to lay features on the favourable-versus-unfavourable axis and weigh the balance; the discriminator is the balance itself (acute onset, precipitant, affective symptoms, good premorbid function, married or female, short DUP for a better course; the opposite pole for a worse one), with DUP the single modifiable lever.

23 · Consolidate: mnemonic, retrieval and synthesis

Everything in this chapter has been laid out in bands: the causes, the phenomenon, the criteria and nosological change, and the course. 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 chapter, to recall each band cold under viva pressure, and to redraw the structure of the disorder from a blank page. Consolidation is the step that turns a read note into a retrievable one, and it is where marks are won or lost in the examination.

How to use this page. Three tools, in order. First, the master **mnemonic** that chains the four bands so a single cue unpacks the whole chapter, 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 fact hangs. Do not treat this as a summary to skim; treat it as a set of exercises to perform.

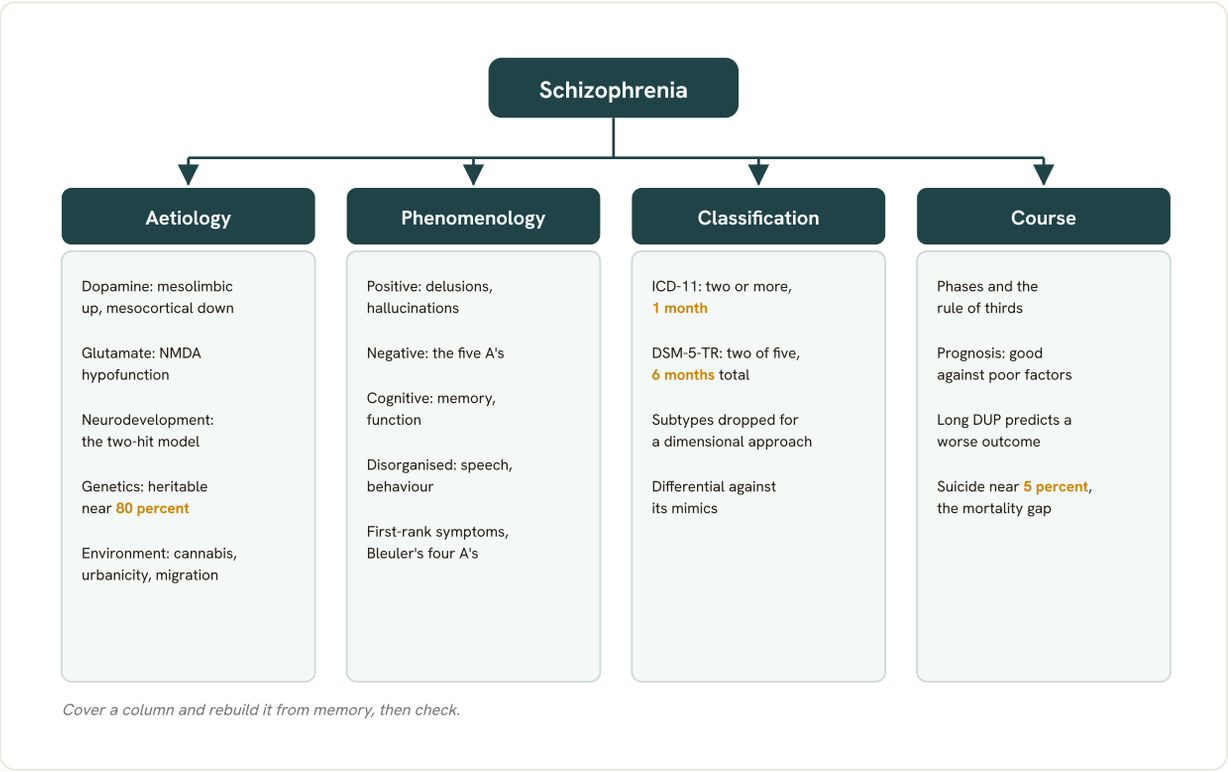


Fig 8.15 The whole chapter as one map, four branches from a single node: aetiology, phenomenology, classification and course. Redraw it from memory, then cover each column and rebuild its contents. The chain runs from cause to phenomenon to criteria to outcome, and holding the four branches together is what turns a list of facts into an understanding of the illness.

23.1 The master mnemonic: the whole chapter on one seed

The seed unpacked. The chapter runs in four bands, and one master mnemonic chains them so that a single cue delivers the entire note: *cause*, then *phenomenon*, then *criteria*, then *course*. This is the payoff of the seed set at orientation: *CAUSE, PHENOMENON, CRITERIA, COURSE*, in reading order. Fix the four Cs and each later topic slots onto its band; the criteria map is the hinge in the middle, the schema the cause bands build toward and the course bands read forward from. The box below unpacks every letter of the chain, chaining the causes, the phenomenon with its domains and first-rank symptoms, the criteria with the nosological change, and the course with its prognosis and outcome.

MNEMONIC

"CAUSE, PHENOMENON, CRITERIA, COURSE": the four bands. CAUSE = "D-G-N-G" (Dopamine, Glutamate, Neurodevelopment, Genes). PHENOMENON = "P-N-C-D-A" (the five domains) + FRS (first-rank symptoms). CRITERIA = ICD-11 forward, DSM-5-TR mapped, subtypes dropped. COURSE = "PPARR" + rule of thirds + suicide/mortality.

Unpack it letter by letter. **CAUSE**, held on **D-G-N-G**, is the aetiology climb: **D**opamine (mesolimbic hyperdopaminergia drives positive symptoms, mesocortical hypodopaminergia the negative and cognitive, reframed as aberrant salience; Howes & Kapur 2009, Kapur 2003), **G**lutamate (NMDA-receptor hypofunction on parvalbumin interneurons, argued from ketamine and PCP), **N**eurodevelopment (the neurodevelopmental and two-hit models: a primed brain plus an adolescent second hit), and **G**enes (heritability **~80%**, MZ concordance **~40-50%** versus DZ **~10-15%**, polygenic plus rare high-penetrance CNVs; Sullivan et al. 2003). No single lesion, a convergence. **PHENOMENON** is the five-domain picture on **P-N-C-D-A**, a **P**ositive symptom (delusion, hallucination), a **N**egative symptom (the deficit, the 5 As), the **C**ognitive impairment, the **D**isorganisation (formal thought disorder, disorganised behaviour) and the **A**ffective disturbance, with Schneider's first-rank symptoms (FRS) suggestive but not pathognomonic laid over the positive and disorganisation domains. **CRITERIA** is the map: ICD-11 (6A20) run forward, DSM-5-TR cross-mapped on the six-month total-duration contrast, ICD-10 flagged legacy, and the nosological change, both systems dropping the subtypes for a dimensional symptom-domain approach. **COURSE** is the natural history on **PPARR** (Premorbid, Prodromal, Acute, Residual, Relapse), the good-versus-poor prognostic poles, the rule of thirds and the WHO cross-cultural outcome data, and the outcome band: suicide **~5%** lifetime and a mortality gap of **~15 to 20 years**. One seed, four bands, the whole chapter.

RULE **One cue, four bands.** If you can say "CAUSE, PHENOMENON, CRITERIA, COURSE" and unpack each into its sub-mnemonic, you can rebuild the entire 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 (D-G-N-G, P-N-C-D-A, ICD-11-forward, PPARR) until each letter opens its own paragraph, or the chain buys you nothing in the viva.

23.2 Retrieval practice across the four 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 all four bands so that a single sitting exercises the whole chapter.

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 four generational forms of the dopamine hypothesis and say which pathway drives positive versus negative symptoms.
2. Explain, in one line each, the glutamate hypothesis and why the ketamine model beats a pure dopamine account.
3. Define the two-hit model: name the first hit and the second hit.
4. Give the heritability of schizophrenia and the monozygotic versus dizygotic twin concordance figures.
5. List the five symptom domains and the five negative-symptom As.
6. Distinguish Bleuler's fundamental symptoms (the four As) from Schneider's first-rank symptoms, and state whether first-rank symptoms are pathognomonic.
7. State the ICD-11 symptom-and-duration criteria for schizophrenia and name at least one core qualifying symptom.
8. Give the single decisive difference between the ICD-11 and DSM-5-TR duration requirements.
9. Name the change ICD-11 made to the status of first-rank symptoms relative to ICD-10.
10. Explain why both DSM-5 and ICD-11 dropped the classical subtypes, and what replaced them.
11. Name the four phases of the natural course in order, plus the relapsing pattern.
12. List the favourable-triad good prognostic factors and the single most modifiable predictor of outcome.
13. Name the three WHO cross-cultural outcome studies and their unifying message.
14. Give the lifetime suicide risk figure and state whether suicide or cardiometabolic disease drives the larger share of the mortality gap.
15. Define the duration of untreated psychosis and state its prognostic significance.

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.

23.3 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, schizophrenia, with four branches, aetiology, phenomenology, classification and course. Off *aetiology* hang dopamine, glutamate, neurodevelopment and genes; off *phenomenology* hang the five domains and the first-rank symptoms; off *classification* hang the ICD-11-forward, DSM-5-TR-mapped, ICD-10-legacy criteria and the dropped subtypes; off *course* hang the phases, prognostic factors, WHO outcome data, suicide and the mortality gap. Rebuild this map from memory, redraw from memory each week until the four branches and their twigs come without prompting, and you own the chapter; the mnemonic in 23.1 is the verbal form of this same map, and each recall prompt in 23.2 tests one twig of it.

HOLD THIS

The whole chapter is one seed, "CAUSE, PHENOMENON, CRITERIA, COURSE", unpacking into four branches, aetiology, phenomenology, classification and course; recall it by active retrieval and redraw the four-branch synthesis map from memory until every twig comes unprompted.

GOOD TO REMEMBER

- **Master mnemonic (CAUSE, PHENOMENON, CRITERIA, COURSE):** the four bands of the chapter in reading order; central claim is that one seed cue unpacks the entire note; discriminator is that each band carries its own sub-mnemonic (D-G-N-G, P-N-C-D-A, ICD-11-forward, PPARR) that must be drilled, not just the top-level acronym.
- **Active recall and retrieval practice:** testing yourself from memory, with answers covered, before re-reading; central claim is that effortful retrieval produces more durable memory than passive review; discriminator is that the benefit depends on attempting each prompt before checking, so answer-free prompts are the correct format.
- **Synthesis map:** a central schizophrenia node with four branches, aetiology, phenomenology, classification and course, each with its twigs; central claim is that redrawing it from memory proves the structure is held, not just the facts; 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, the central schizophrenia node with its four branches, aetiology (dopamine, glutamate, neurodevelopment, genes), phenomenology (five domains, first-rank symptoms), classification (ICD-11 forward, DSM-5-TR mapped, subtypes dropped) and course (phases, prognosis, WHO outcome, suicide and mortality), to be redrawn from memory, is drawn as Fig 8.9.

Previously asked

Schizophrenia is one of the most heavily examined topics of the clinical paper, and it is tested **whole**: as full long essays on aetiopathogenesis and on the different types, and as a steady stream of short notes on the neurobiology, the phenomenology, the prodrome and the outcome. The essays often carry a management tail, and that part is developed in the Schizophrenia: management, antipsychotics and adverse effects notes; the other psychotic disorders and catatonia, which sit in the differential here, are their own chapter. The genuine questions below are grouped by the four bands of these notes.

HOW THIS TERRITORY IS ACTUALLY TESTED

Q **Aetiology and neurobiology.** The commonest long essay asks you to discuss the etiopathogenesis of schizophrenia (with a drug-management tail that belongs to the management notes); the neurobiology also comes as "describe the neuroanatomical studies in schizophrenia" and "MRI in schizophrenia," and the perennial "recent advances in schizophrenia" is asked again and again. long essay and short note, recurring

Q **Clinical features and phenomenology.** Short notes single out "cognition in schizophrenia," the "prodrome of schizophrenia," and the "need, clinical implications and problems of the psychiatric rating scales of schizophrenia." short note

Q **Classification and nosological change.** The classic long essay to "discuss the etiology, clinical features and management of the different types of schizophrenia in detail" now turns on the reason both systems abolished those types. long essay

Q **Course, prognosis and outcome.** The outcome is tested directly as "predictors of schizophrenia," "prognosis in schizophrenia," "disability assessment in schizophrenia," and even "marriage in schizophrenia." short note

Prepare this material to be argued, not just recited: the criteria map, the differential decision tree and the four worked vignettes in these notes are built to the way the topic is examined. Antipsychotic pharmacotherapy, adverse effects and psychosocial rehabilitation are developed in the Schizophrenia: management, antipsychotics and adverse effects notes; schizoaffective disorder, delusional disorder and catatonia as entities are developed in the Other psychotic disorders, delusional syndromes and catatonia notes; these notes own the aetiology, the phenomenology, the classification and the course.

Quick review

The whole subject in one table	
ORIENTATION AND THE CRITERIA MAP	Schizophrenia is a chronic, multifactorial psychotic disorder of the young adult, defined by a syndrome not a test. The diagnosis needs two or more core symptoms, at least one from the positive or disorganisation cluster, for the required duration: ICD-11 asks one month, DSM-5-TR a six-month total with functional decline, after a mood, substance and organic cause are excluded.
EPIDEMIOLOGY	Lifetime risk near one percent; incidence roughly fifteen per hundred thousand per year with real geographic variation. Onset is earlier in men (early-to-mid twenties) than women (late twenties, with a second peri-menopausal peak). Life expectancy is reduced by about fifteen to twenty years, most of it cardiometabolic.
GENETICS	Heritability is about eighty percent, the strongest risk being an affected first-degree relative. Monozygotic concordance is roughly forty to fifty percent against ten to fifteen percent for dizygotic twins; adoption studies separate genes from rearing. The architecture is polygenic (over a hundred GWAS loci, the C4 signal) with rare high-penetrance copy number variants, above all the 22q11.2 deletion.
DOPAMINE HYPOTHESIS	From excess dopamine to a regional model: mesolimbic hyperdopaminergia drives the positive symptoms, mesocortical hypofunction the negative and cognitive ones. Kapur's aberrant salience reframes psychosis as dysregulated dopamine assigning undue salience to neutral stimuli, with delusions and hallucinations the attempt to explain it.
GLUTAMATE AND OTHER SYSTEMS	NMDA receptor hypofunction, argued from the ketamine and PCP model that reproduces positive, negative and cognitive symptoms, is the strongest challenge to a pure dopamine account. Parvalbumin GABA interneuron deficits, the 5-HT2A serotonin model, cholinergic contributions and neuroinflammation (microglia, the kynurenine pathway) complete the picture.
NEURODEVELOPMENT AND ENVIRONMENT	An early static lesion expressed at adolescent maturation: the two-hit model pairs a genetic and prenatal first hit (obstetric complications, maternal infection, winter or spring birth) with an adolescent second hit (excess synaptic pruning, cannabis, psychosocial stress). Cannabis is a dose- and age-dependent component cause; social drift explains the low-socioeconomic association.
NEUROIMAGING AND NEUROPATHOLOGY	Lateral ventricular enlargement is the most replicated structural finding, with grey-matter and hippocampal reduction and functional hypofrontality. Neuropathology shows reduced neuropil, excess synaptic pruning and, crucially, an absence of gliosis, which argues for a

The whole subject in one table	
	neurodevelopmental rather than a neurodegenerative process.
THE SYMPTOM DOMAINS	Five semi-independent domains, positive, negative, cognitive, disorganised and affective, describe a profile rather than a subtype. Crow's type I (positive, reversible) versus type II (negative, structural) and Liddle's three syndromes (reality distortion, disorganisation, psychomotor poverty) are the dimensional models.
POSITIVE SYMPTOMS	Delusions (persecutory, referential, grandiose, control and passivity, bizarre) and hallucinations (third-person and running-commentary auditory voices most characteristic), with formal thought disorder inferred from disorganised speech. No positive symptom is specific; prominent visual hallucinations should prompt an organic search.
NEGATIVE SYMPTOMS	The five A's: affective flattening, alogia, avolition, anhedonia and asociality. Separate primary (intrinsic, enduring) from secondary (from positive symptoms, depression, extrapyramidal effects or understimulation, and reversible). The deficit syndrome is enduring primary negative symptoms; assess with the SANS and the PANSS negative subscale.
DISORGANISATION	Disorganised speech is the clinical face of formal thought disorder (derailment, tangentiality, word salad, neologism), with disorganised behaviour and inappropriate affect. The catatonic phenomena are flagged here but developed as an entity in the Other psychotic disorders, delusional syndromes and catatonia notes.
FIRST-RANK AND FUNDAMENTAL SYMPTOMS	Schneider's first-rank symptoms (thought insertion, withdrawal and broadcast, passivity, third-person and commentary voices, delusional perception) are not pathognomonic and have lost their special status in DSM-5 and ICD-11. Bleuler's four A's (loosened associations, blunted affect, ambivalence, autism) are fundamental, against the accessory hallucinations and delusions.
COGNITION	Impaired processing speed, working memory, attention, verbal learning, executive function and social cognition are a core feature, present before onset and the strongest predictor of function. D2 antipsychotics do not restore cognition, so cognition is a treatment target through cognitive remediation and newer agents such as the muscarinic xanomeline-trospium (detail in the management notes). Insight is multidimensional and predicts adherence.
PRODROME AND FIRST EPISODE	The prodrome and the at-risk mental state (ultra-high-risk and clinical high risk) precede frank psychosis, with transition about twenty-two percent at one year and thirty-six percent by three years. Antipsychotics are not routinely recommended in the at-risk state to prevent transition; use cognitive behavioural therapy, monitoring and treatment of

The whole subject in one table	
	comorbidity. Endophenotypes (smooth-pursuit, P50 gating, working memory) mark risk.
DIAGNOSTIC CRITERIA	ICD-11: two or more core symptoms, at least one a core positive or disorganisation symptom, for one month, with domain qualifiers and course specifiers. DSM-5-TR: two of five, a six-month total with one month active, plus functional decline and exclusions. Legacy ICD-10 required one month, weighted first-rank symptoms and kept the subtypes.
CLASSIFICATION AND NOSOLOGICAL CHANGE	Kraepelin's dementia praecox became Bleuler's schizophrenias. Both ICD-11 and DSM-5 dropped the historical subtypes (paranoid, hebephrenic, catatonic, simple, residual, undifferentiated) for poor reliability, temporal instability and low predictive validity, replacing them with a dimensional symptom-domain approach.
THE SPECTRUM	The neighbours of schizophrenia, schizotypal, schizophreniform, brief psychotic, schizoaffective and delusional disorder, sit on a psychosis continuum. Psychotic-like experiences occur in the general population; the extended phenotype supports a dimensional over a purely categorical view.
DISCRIMINATE: THE DIFFERENTIAL	Rule out an organic or substance cause first, then a mood-confined psychosis (a mood disorder), then schizoaffective disorder (two weeks of psychosis without mood, mood most of the illness), then delusional disorder (non-bizarre, function preserved). Sort the remainder by duration: under one month brief psychotic, one to six months schizophreniform, six months with decline schizophrenia.
COURSE	Premorbid, prodromal, acute and residual phases with a relapsing course. The rule of thirds (roughly a third good, a third intermediate, a third poor) and the WHO cross-cultural studies (IPSS, DOSMeD, ISoS) show heterogeneous, often non-deteriorating outcomes. A longer duration of untreated psychosis predicts a worse outcome.
PROGNOSIS	Good prognosis with acute onset, a precipitant, affective symptoms, good premorbid function, female sex, marriage, a short duration of untreated psychosis; poor prognosis with insidious onset, negative symptoms, poor premorbid function, early onset, male sex and a long duration. The WHO better-outcome-in-developing-countries finding is read with its modern critique. Remission uses the Andreasen criteria; symptomatic remission is not functional recovery.
OUTCOME AND MORTALITY	Lifetime suicide risk about five percent, highest early and after discharge. The mortality gap of fifteen to twenty years is mostly cardiometabolic, driven by metabolic syndrome, cardiovascular disease, diabetes and smoking, so physical-health and metabolic screening are essential in serious mental illness.

The whole subject in one table	
APPLY AND CONSOLIDATE	Four worked vignettes: a first-episode workup, a schizophrenia versus mood-with-psychosis differential, a negative-symptom-predominant picture, and a prognosis assessment. Then the master mnemonic (cause to phenomenon to criteria to course), answer-free retrieval prompts, and the four-branch synthesis map to redraw from memory.

References

The material is grounded in the standard psychiatry texts (the source hierarchy below), which anchor the settled facts on aetiology, phenomenology, classification and course; the descriptive-phenomenology definitions follow the specialist symptom texts. The historical framing of the disorder rests on the foundational sources, and every landmark, contested or numeric claim carries a PubMed-verified journal citation. Each PMID here was checked against PubMed this build, matched on title, first author and year; any citation whose identifier did not resolve to the cited paper was corrected or dropped rather than guessed. A small number of inline references (for example Jablensky's Dialogues in Clinical Neuroscience review and a few society-guideline and monograph items) are not carried in the journal list because they have no stable PubMed record; the claims they support are also covered by the verified citations retained here.

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PART II

II

Schizophrenia: Management, Antipsychotics and Adverse Effects

Treating schizophrenia: the antipsychotics, how they are chosen and combined, and the adverse effects to watch for.

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.

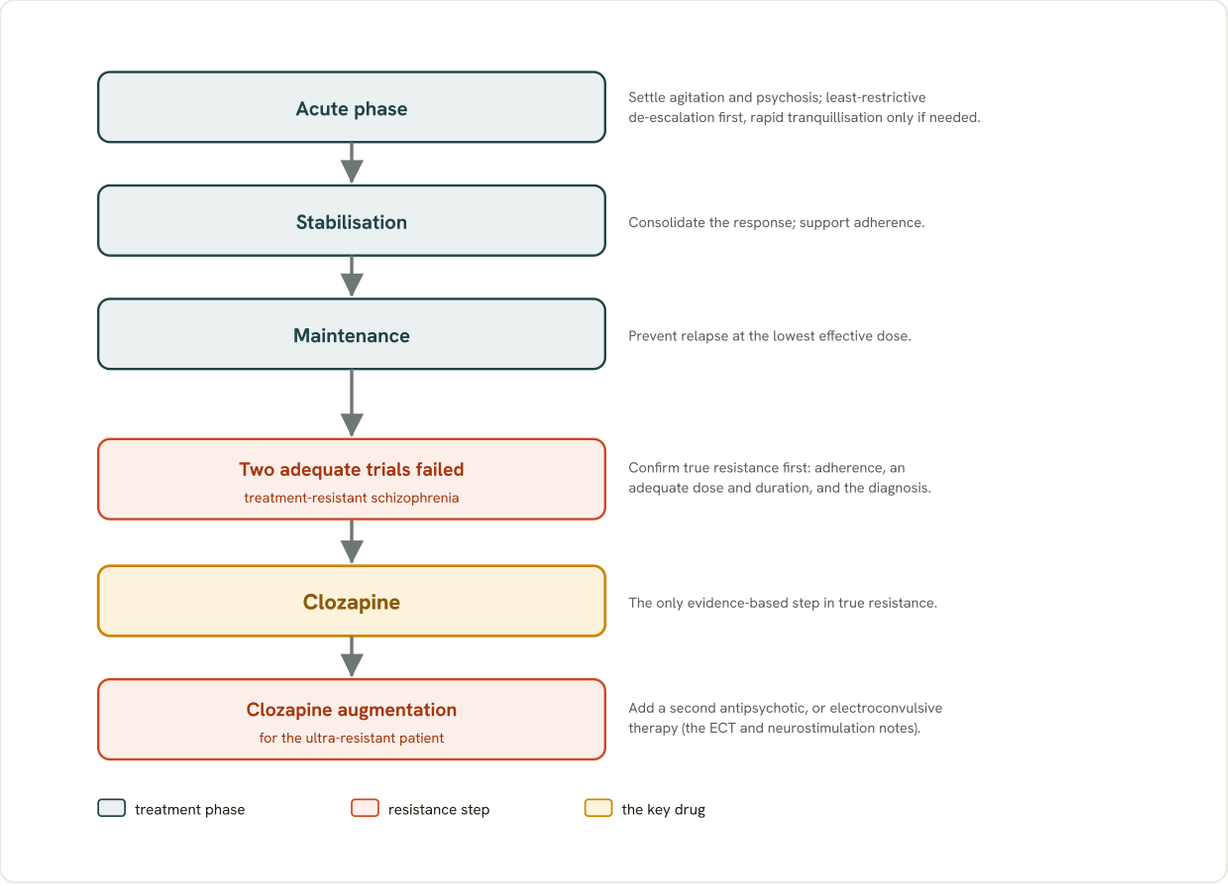

Fig 9.1 The antipsychotic treatment algorithm. Care runs down the phase ladder, acute to stabilisation to maintenance at the lowest effective dose. When two adequate trials have genuinely failed, the illness is treatment-resistant and the evidence-based next step is clozapine, not a third same-class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

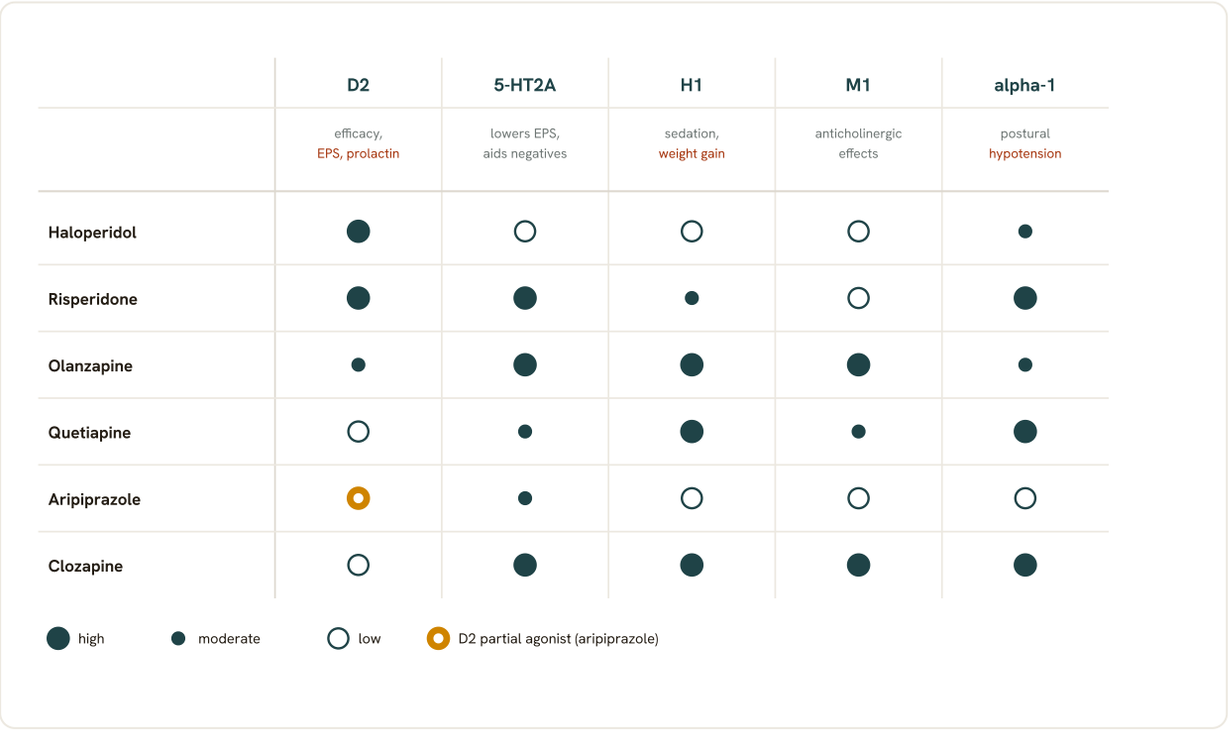

Fig 9.2 The receptor-affinity grid. A drug's receptor profile predicts its adverse-effect signature: D2 blockade buys efficacy but costs extrapyramidal effects and prolactin; 5-HT2A antagonism lowers the extrapyramidal burden; H1 drives sedation and weight gain; M1 the anticholinergic effects; and alpha-1 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.

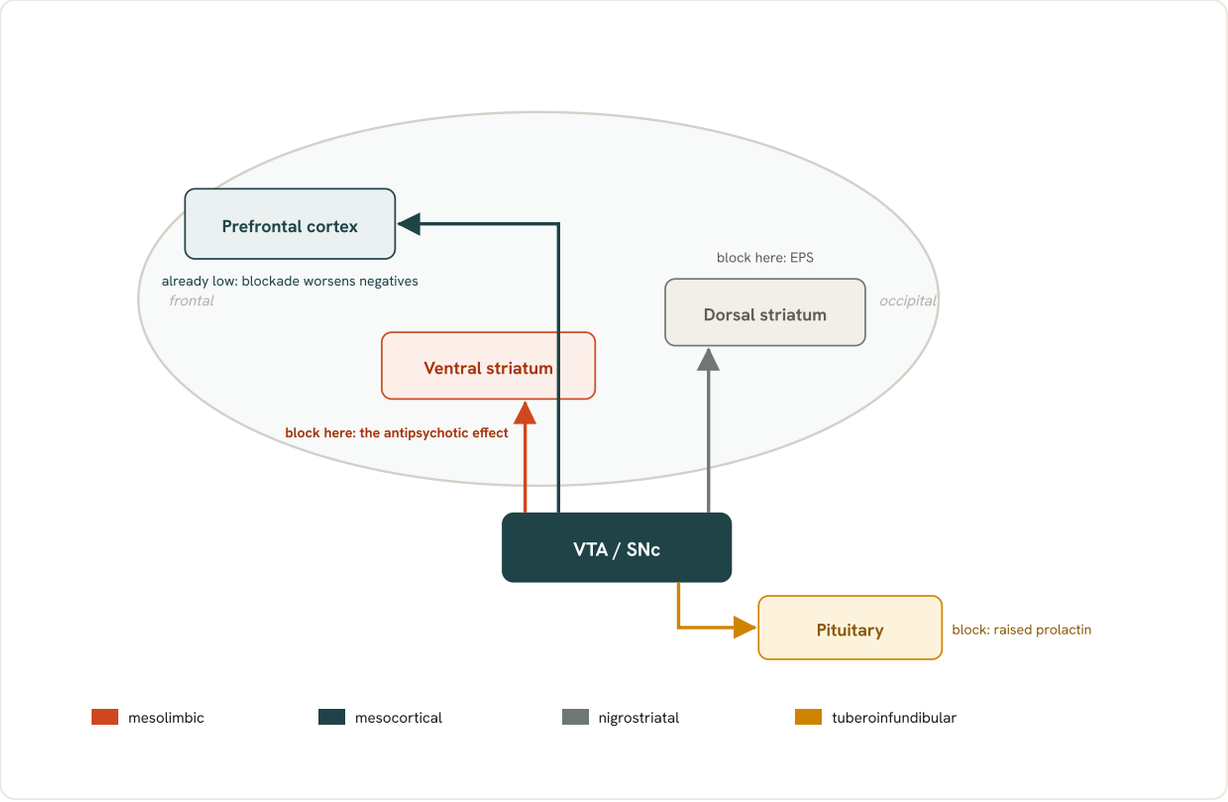

Fig 9.3 What D2 blockade does in each dopamine pathway. Blocking the overactive mesolimbic tract to the ventral striatum produces the antipsychotic effect. The same blockade in the nigrostriatal tract causes extrapyramidal effects, in the tuberoinfundibular tract raises prolactin, and in the already-underactive 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.

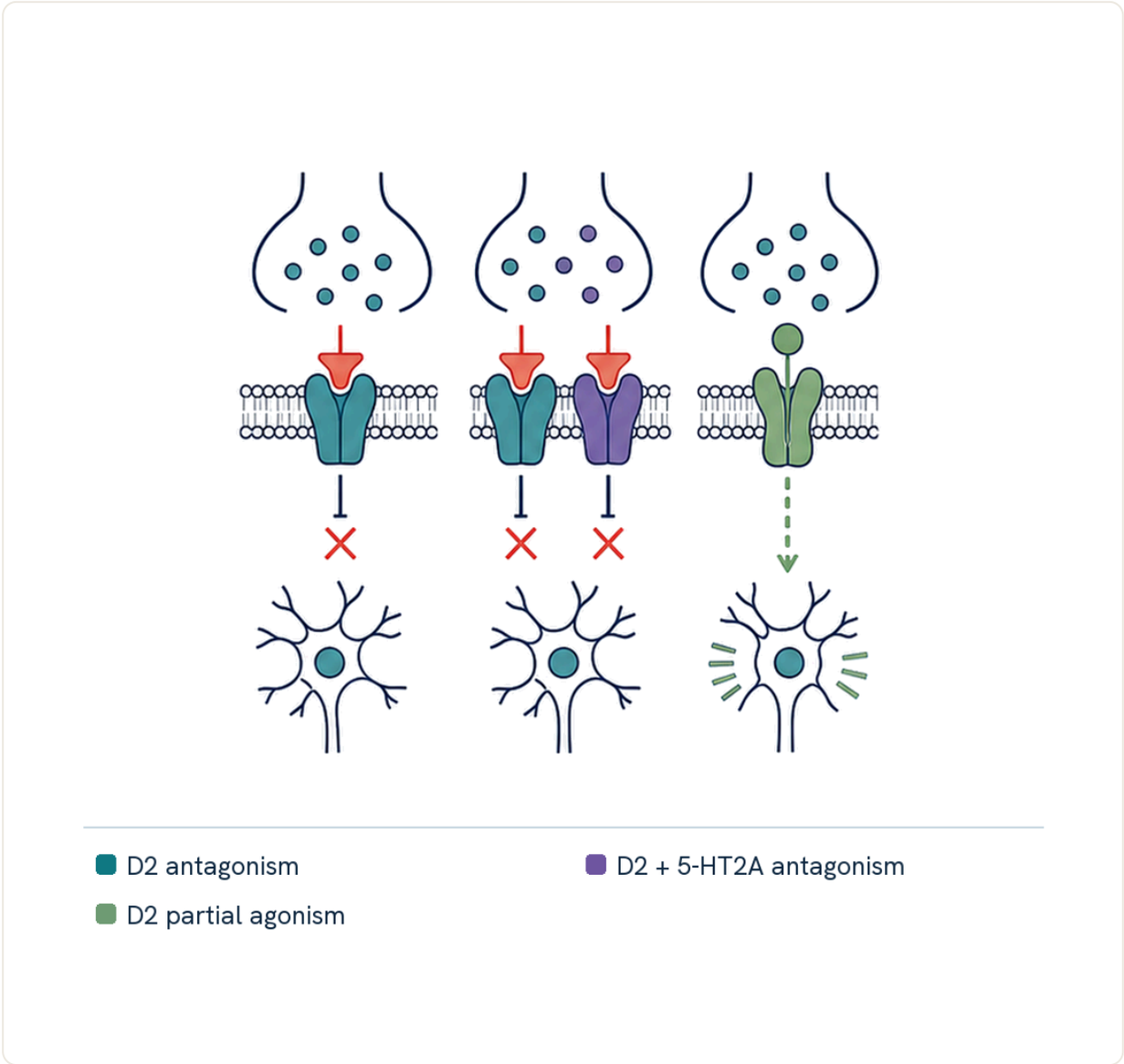

Fig 9.4 Three antipsychotic receptor strategies: dopamine D2 antagonism, combined D2 and 5-HT2A antagonism, and D2 partial agonism that stabilises signalling across different dopamine states.

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
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).

Fig 9.5 The first-episode pathway: prompt assessment and shared choice lead to cautious antipsychotic initiation, family engagement, coordinated early-intervention care and longitudinal relapse prevention.

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).

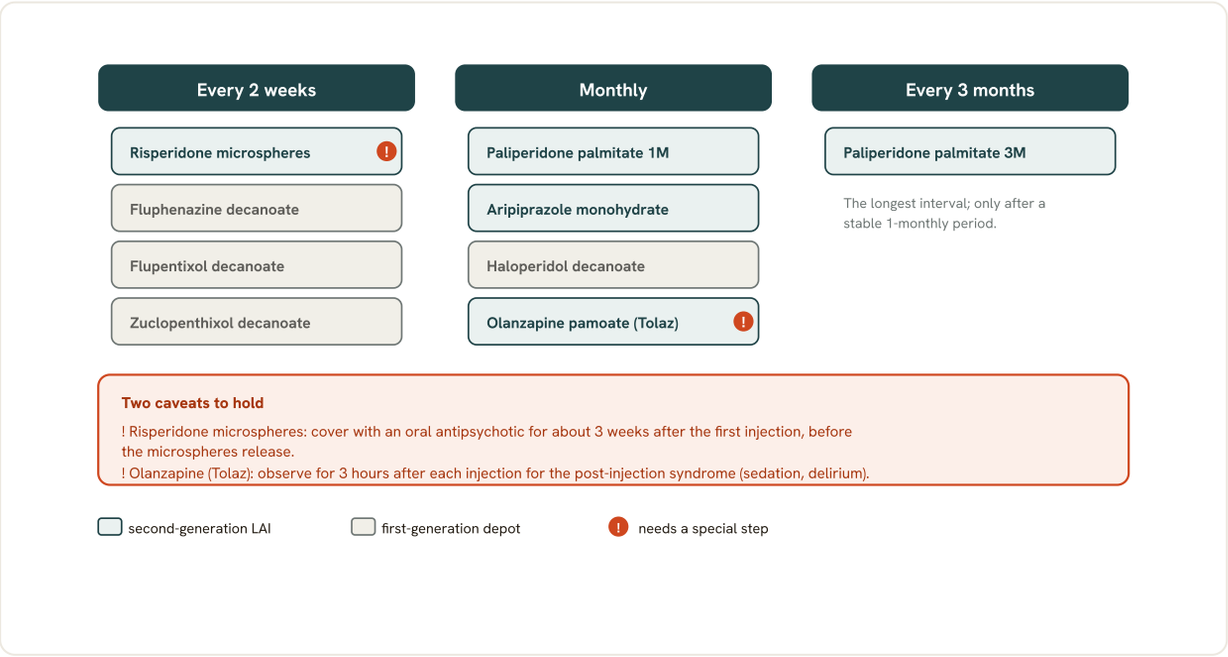

Fig 9.6 Depot and long-acting injectable antipsychotics, grouped by dosing interval. An assured-adherence tool that cuts relapse, worth considering early rather than only after failure. Two caveats matter: risperidone microspheres need oral cover for about three weeks after the first dose, and the olanzapine 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.

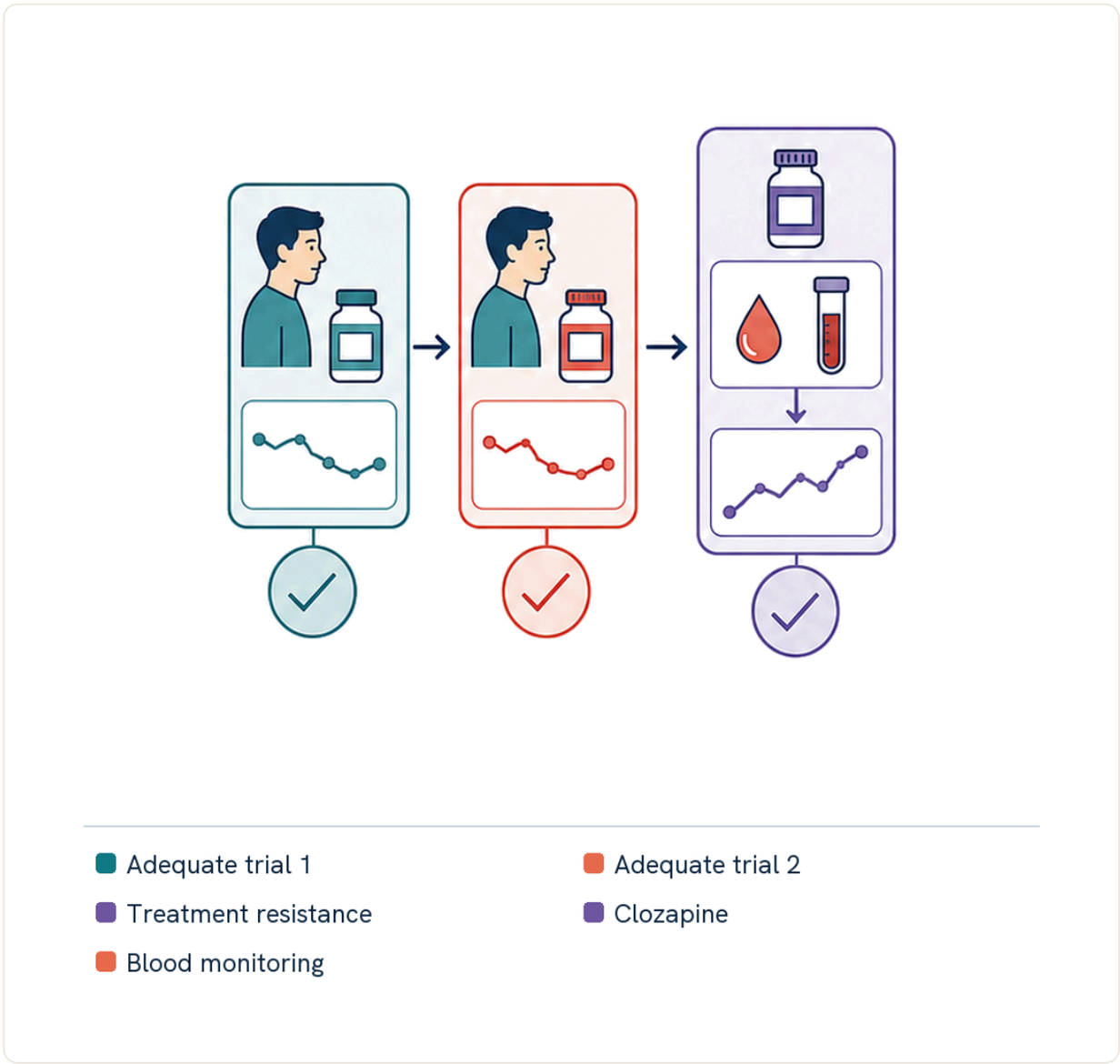

Fig 9.7 Treatment-resistant schizophrenia is established after two adequate antipsychotic trials have failed; the subsequent clozapine pathway requires structured haematological and clinical monitoring.

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.

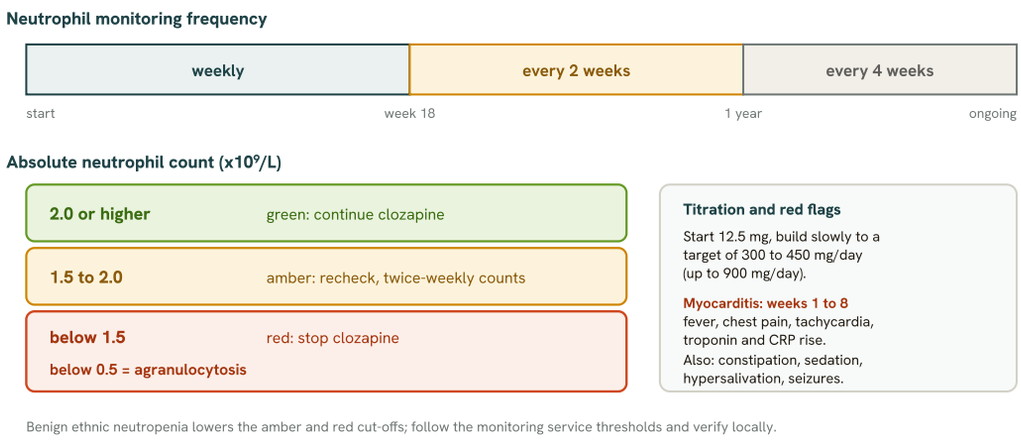

Fig 9.8 Clozapine titration and neutrophil monitoring. Counts run weekly for the first 18 weeks, then every 2 weeks to a year, then every 4 weeks. The traffic-light rule on the absolute neutrophil count decides continuation: green at 2.0 or above, amber at 1.5 to 2.0, red below 1.5 (stop), with agranulocytosis 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.

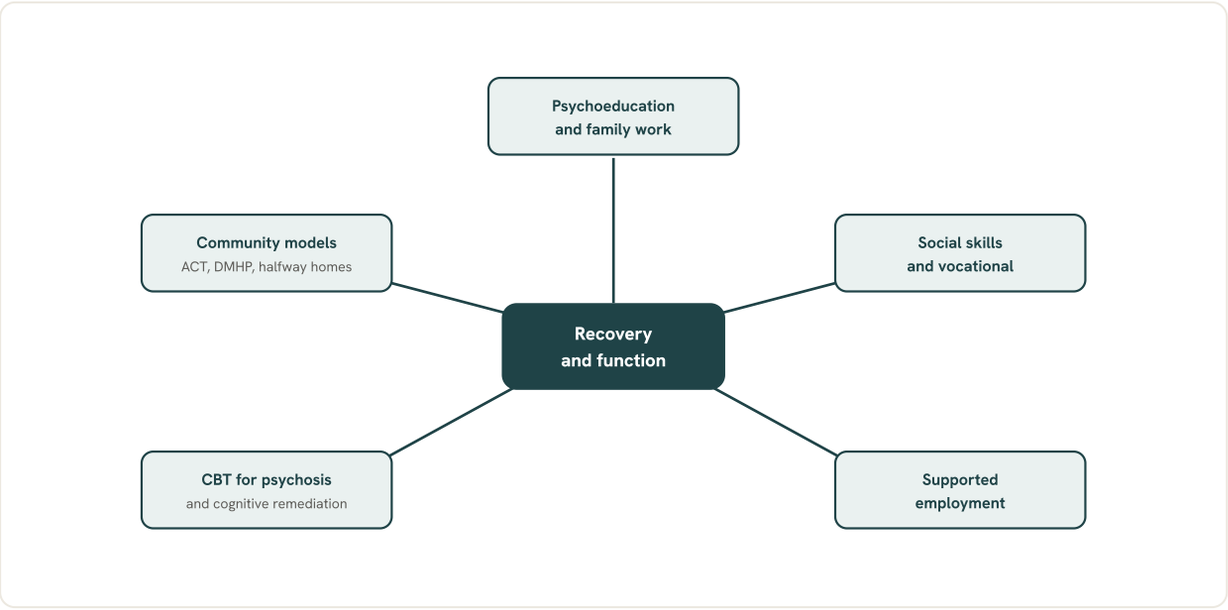

Fig 9.9 The components of psychosocial rehabilitation. Medication controls symptoms, but function and recovery come from the psychosocial half: psychoeducation and family work in high-expressed-emotion households, social skills training and supported employment, the psychological therapies, and the community 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% OF US PATIENTS EMPLOYED	**50 to 75%** WANT COMPETITIVE WORK	**~40** RCTS FAVOUR IPS	**2 to 3x** 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.

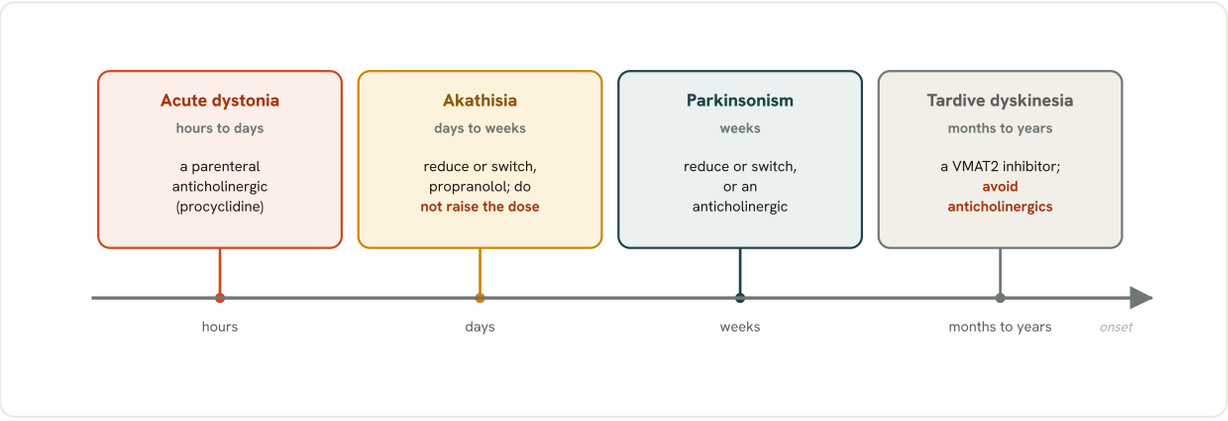

Fig 9.10 The extrapyramidal timeline, ordered by onset. Acute dystonia strikes in hours, akathisia in days, parkinsonism in weeks, and tardive dyskinesia after months to years. The management differs: an anticholinergic helps dystonia and parkinsonism but worsens tardive dyskinesia, akathisia is treated 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.

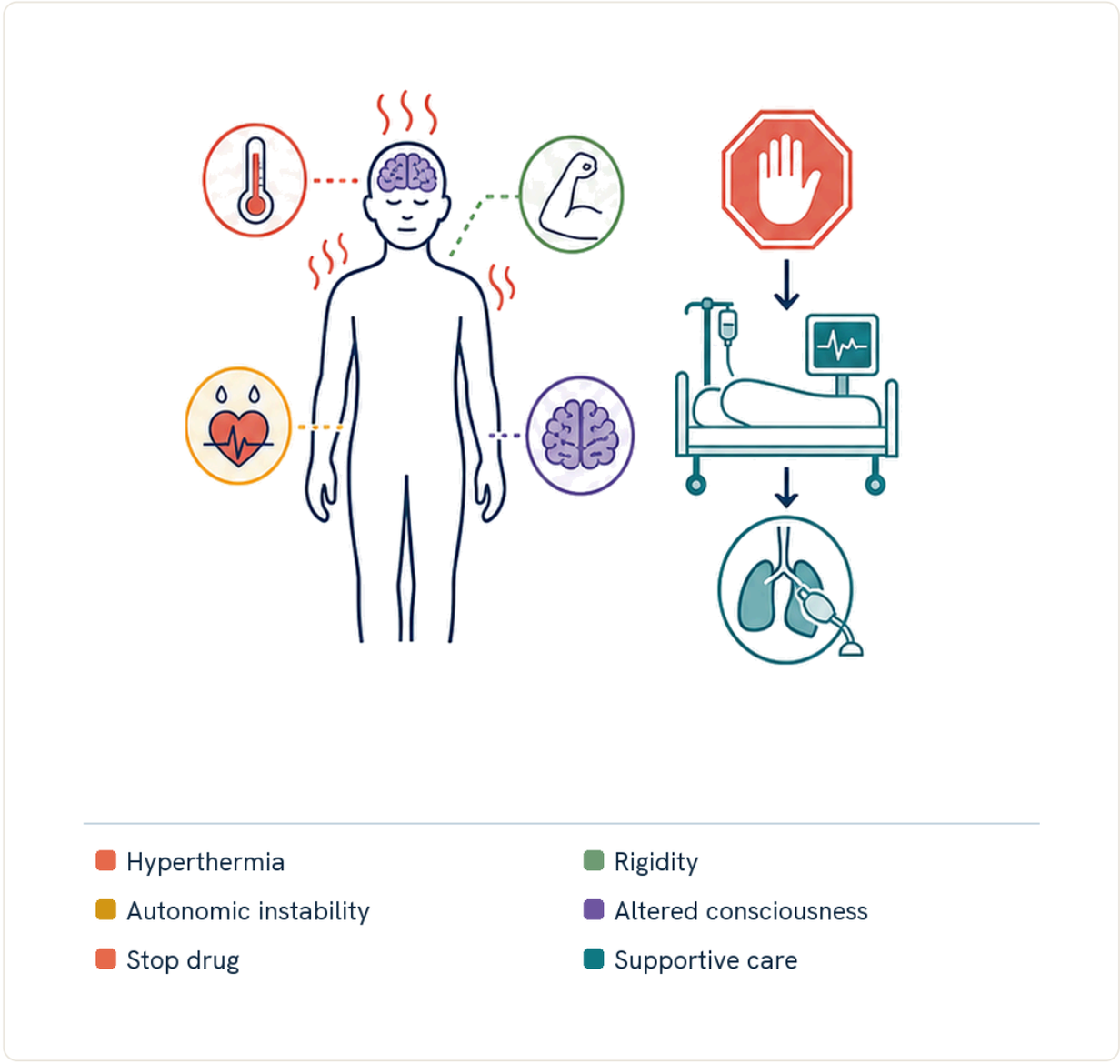

Fig 9.11 The clinical pattern of neuroleptic malignant syndrome: hyperthermia, severe rigidity, autonomic instability and altered consciousness demand immediate withdrawal of the offending drug and urgent supportive management.

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.

	Baseline	6 weeks	12 weeks	Annually
Weight and BMI	●	●	●	●
Waist circumference	●	–	–	●
Fasting glucose or HbA1c	●	–	●	●
Lipid profile	●	–	●	●
Blood pressure	●	–	●	●

● measure at this visit – not required this visit Schedule per the standard guidance; verify locally.

Fig 9.12 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
WEIGHT/BMI/WAIST, FASTING GLUCOSE+HBA1C, LIPIDS, BP BEFORE DOSE

6 wk
EARLY RE-CHECK (WEIGHT WEEKLY TO 6 WK, NICE)

12 wk
GLUCOSE/HBA1C, LIPIDS, BP, WEIGHT (NICE)

Annually
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
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 9.13 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**

ENTITY	TRIGGER	RIGIDITY VS CLONUS	REFLEXES	PUPILS	BOWEL SOUNDS	THE ONE DISCRIMINATOR
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**
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.

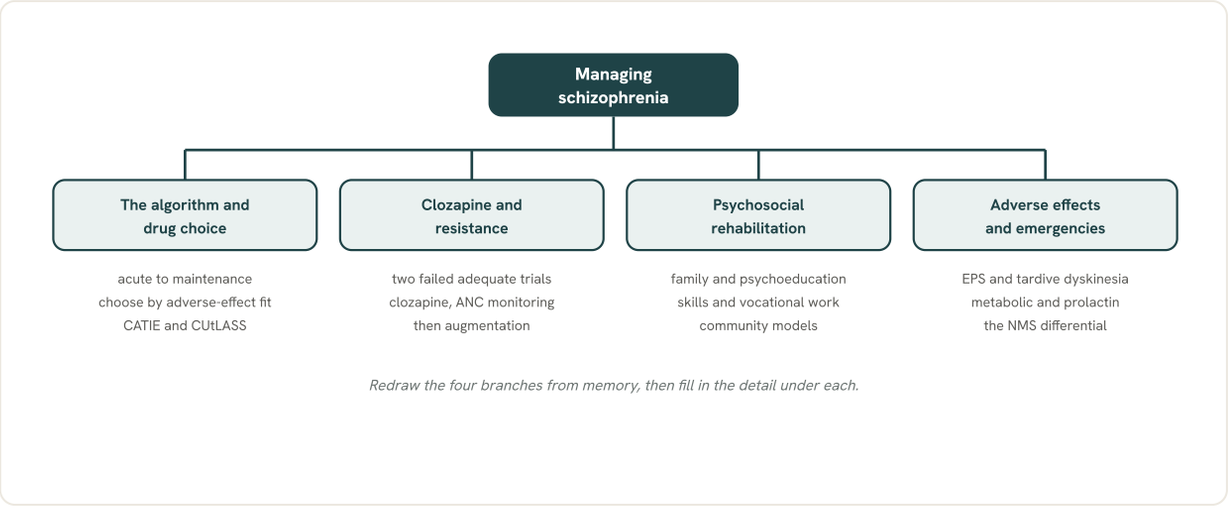

Fig 9.14 The whole-chapter synthesis map. Managing schizophrenia has four branches: the treatment algorithm and drug choice, clozapine and treatment resistance, psychosocial rehabilitation, and the adverse effects and their emergencies. Cover the detail, redraw the four branches from memory, then reconstruct 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 9.14):** 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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PART III

III

Other Psychotic Disorders, Delusional Syndromes and Catatonia

The psychoses beyond schizophrenia: the delusional and brief syndromes, shared and organic psychosis, and catatonia.

PAPER II

Other psychotic disorders, delusional syndromes and catatonia

Four sections · one complete notes document

This material closes the schizophrenia-spectrum block, gathering into one document the psychotic disorders that are not schizophrenia, the delusional syndromes, and catatonia. The first band is **other primary psychotic disorders**: the schizophrenia-spectrum decision tree that separates them by duration and mood-loading, then schizoaffective disorder, delusional disorder, the life-cycle of a delusion from its formation to its dissolution, the acute and transient psychotic disorders, brief psychotic disorder, the induced and shared delusional disorders, postpartum psychosis and the late-onset psychoses, the attenuated psychosis syndrome, and the interleaved differential that tells them apart. The second band is **delusional misidentification and named delusional syndromes**: Capgras, Fregoli, intermetamorphosis and the subjective doubles, and the named monothematic syndromes of De Clerambault, Othello, Cotard and Ekbom, each keyed on its core delusional content. The third band is **catatonia**: the classical and modern signs and the examination, the psychiatric, neurological and medical causes and the transdiagnostic placement, the lorazepam challenge and benzodiazepine management, malignant catatonia and its differential from neuroleptic malignant syndrome, and the place of electroconvulsive therapy. The examinable skill is discrimination: to place a psychotic presentation on the spectrum by its duration, mood-loading and delusion-type, to name a syndrome by its core content, and to recognise catatonia and its malignant form and act.

HOW TO USE THESE NOTES

Read the three bands as one exercise in telling psychotic presentations apart. The **other primary psychotic disorders** band opens with the spectrum decision tree, then teaches each disorder against schizophrenia and against each other, and closes on the interleaved differential; each named entity ends with a **Good to remember** box giving what it is, the core criteria or the one discriminating feature, and the one number or eponym to hold. The **delusional misidentification and named syndromes** band draws the eponymous syndromes as grids keyed on the core delusional content, distinguishing which are the content of a delusion from which are named disorders. The **catatonia** band runs from the signs and their examination, through the causes and the transdiagnostic placement, to the lorazepam challenge and the malignant-catatonia emergency. Figures declare one axis and code it in colour: **petrol** marks structure and the neutral case, **coral** marks the trap or the danger, and **marigold** highlights the number or eponym to hold. Several boundaries are worth stating up front: the phenomenology, aetiology, criteria and course of schizophrenia itself are taught in the Schizophrenia: aetiology, phenomenology, classification and course notes and are not repeated here; the antipsychotic drugs and neuroleptic malignant syndrome as an entity belong to the Schizophrenia: management, antipsychotics and adverse effects notes, needed here only inside the malignant-catatonia differential; the technique of electroconvulsive therapy lives in the ECT and neurostimulation notes; the mood-episode criteria for schizoaffective disorder live in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; and the raw descriptive definitions of the individual delusions and misidentification phenomena live in the Psychometry, Assessment and Descriptive Psychopathology notes, applied here rather than re-derived. This is doctor-facing revision, so the full technical vocabulary is used, and every criterion, eponym and number is verified against a source.

Other primary psychotic disorders

1 · Orientation: the schizophrenia-spectrum decision tree

Why this matters. Schizophrenia does not stand alone. It sits at the centre of a **schizophrenia-spectrum** family of related psychotic disorders that share the same positive symptoms but are told apart by three things the examiner returns to again and again: how long the illness has lasted, whether a full mood episode is riding on top of it, and what kind of delusion is present. Get those three axes straight and the whole block resolves into a clean **decision tree**. This orienting topic builds that tree, seeds the master mnemonic that chains the chapter, and hands the reader a map to the delusional syndromes and to catatonia that follow. The illness schizophrenia itself is not re-taught here: its phenomenology, aetiology, criteria and course are owned by the Schizophrenia: aetiology, phenomenology, classification and course notes and are cross-referenced, not re-derived.

The governing idea: everything in this family is a positive-symptom psychosis, so you never separate them by "is there psychosis" but by the three discriminators. The **criteria map** below is worth memorising as a single object, because in the exam a stem rarely asks "define

schizophreniform"; it hands you a duration and a mood picture and asks you to place the patient. Nosology here is given ICD-11 primary (the current CDDR grouping, "schizophrenia and other primary psychotic disorders") with the DSM-5-TR labels cross-mapped, because the two systems draw the duration lines differently and the difference is itself examinable.

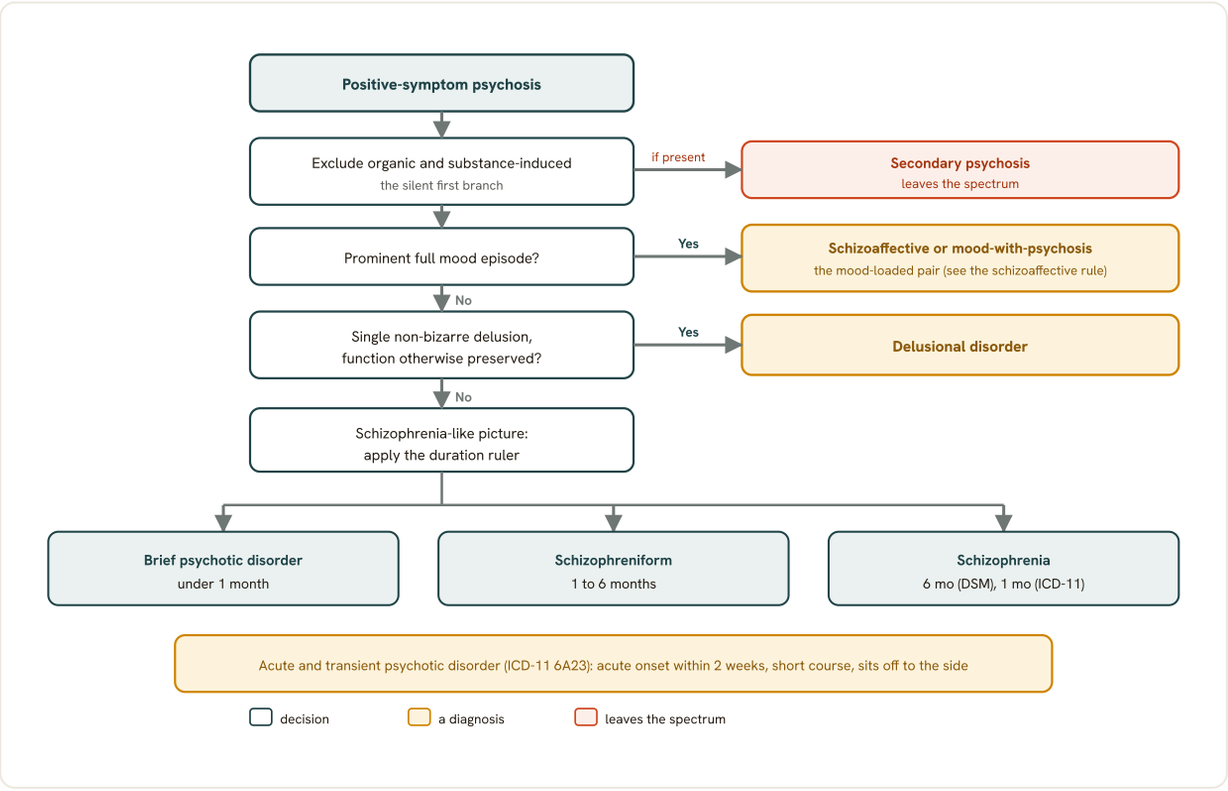

Fig 10.1 The schizophrenia-spectrum decision tree. Exclude the organic and substance-induced first (the silent branch), then walk three axes in order: mood-loading (a prominent mood episode pulls out schizoaffective disorder and mood-with-psychotic-features), delusion-type (a single non-bizarre delusion with preserved function is delusional disorder), and finally, for the remaining schizophrenia-like pictures, the duration ruler (under one month, one to six months, six months or more), with the acute and transient psychotic disorder sitting off to the side.

1.1 The spectrum as one object: what belongs, what does not

The schizophrenia-spectrum and other primary psychotic disorders, in the ICD-11 grouping, comprises schizophrenia, **schizoaffective disorder**, schizotypal disorder, the acute and transient psychotic disorders, and delusional disorder (ICD-11 CDDR). The DSM-5-TR chapter, "Schizophrenia Spectrum and Other Psychotic Disorders", covers the same ground plus brief psychotic disorder and schizophreniform disorder as separate short-duration entities, and organises itself explicitly along a gradient: sub-threshold conditions first, then single-domain conditions (delusional disorder, catatonia), then the time-limited psychoses, then schizophrenia (Kaplan & Sadock 2024). Two members earn their place here for reasons worth naming: **catatonia**, which the chapter carries because it is a psychomotor syndrome that cuts across the whole grouping, and **postpartum (puerperal) psychosis**, owned here as a psychotic presentation while the wider obstetric frame belongs to the Perinatal/women's mental health and emergency psychiatry notes.

What does not belong: a psychosis that is a direct physiological consequence of a substance, medication or medical condition is a secondary psychosis and is excluded before any spectrum

label is applied. That exclusion is the silent first branch of the whole tree, and forgetting it is the classic beginner error.

RULE **Exclude the organic and the substance-induced first, then place on the spectrum.** A secondary psychosis is not a point on this decision tree; it is what you rule out before you enter it.

1.2 Axis one, duration: the timeline that separates the short psychoses from schizophrenia

The first and most heavily tested axis is **duration**. Holding the same positive-symptom picture constant, DSM-5-TR splits the family purely by how long it has run. Brief psychotic disorder lasts at least one day and remits within one month, with full return to premorbid function; below one month is its signature (Kaplan & Sadock 2024). Schizophreniform disorder occupies the middle band, at least one month but less than six, and, crucially, does not require a decline in functioning. Schizophrenia is diagnosed once the illness has run six months or more (including at least one month of active-phase symptoms). Alongside these sit the acute and transient psychotic disorders (ATPD, ICD-11 6A23), defined not by a fixed ceiling but by an acute onset, psychotic symptoms emerging without a prodrome and reaching the full picture within two weeks, and a characteristically short, fluctuating course.

A trap the examiner sets deliberately: the two systems do not agree on where schizophrenia begins. ICD-11 requires symptoms for one month or more, so many cases that DSM-5-TR would call schizophreniform (one to six months) are already schizophrenia in ICD-11 (Kaplan & Sadock 2024). Read the stem for which system it is using.

under 1 mo	1 to 6 mo	6 mo or more	within 2 wk
BRIEF PSYCHOTIC DISORDER	SCHIZOPHRENIFORM (DSM-5-TR)	SCHIZOPHRENIA (DSM-5-TR)	ATPD ACUTE ONSET (ICD-11)

TRAP **Do not swap the duration thresholds between systems.** DSM-5-TR schizophrenia needs six months; ICD-11 needs one month, so DSM schizophreniform maps largely onto ICD-11 schizophrenia.

1.3 Axis two, mood-loading: does a full mood episode ride on the psychosis

The second axis, **mood-loading**, asks whether a prominent, full mood episode (depressive or manic) is part of the picture, and if so, how it sits in time against the psychosis. Two members of the family carry a prominent mood episode by definition: schizoaffective disorder and mood disorder with psychotic features. Two members carry none: delusional disorder and schizophrenia (where any mood symptoms are, by rule, a minority of the total course). The whole discrimination turns on a single temporal criterion. In DSM-5-TR schizoaffective disorder, a major mood episode is present for the majority of the total duration of the illness (Criterion C), and there must have been at least two weeks of delusions or hallucinations in the absence of a major mood episode at some point in the lifetime course (Criterion B) (Kaplan & Sadock 2024). If instead the delusions occur exclusively during mood episodes, the diagnosis is mood disorder with psychotic features. The mood-episode criteria themselves are cross-referenced to the Mood

disorders: classification, depressive and bipolar syndromes, neurobiology notes and not re-derived here.

TRAP **Never diagnose schizoaffective without the at-least-two-weeks-of-psychosis-without-prominent-mood rule.** Psychosis only ever during mood episodes is mood disorder with psychotic features, not schizoaffective disorder.

1.4 Axis three, delusion-type and bizarreness: where delusional disorder splits off

The third axis reads the **content and bizarreness** of the delusion and the state of the rest of the person. Delusional disorder is the anchor case: at least one month of one or more delusions, classically **non-bizarre** (though DSM-5-TR now allows a "with bizarre content" specifier), with no other active-phase symptom of schizophrenia and, strikingly, apart from the direct impact of the delusion itself, function and behaviour are not obviously bizarre and psychosocial functioning is largely preserved (Kaplan & Sadock 2024). This is the discriminator to hold: a well-systematised, encapsulated, often plausible-sounding delusion in an otherwise intact person points to delusional disorder, whereas the same content embedded in disorganisation, hallucinations and negative symptoms points to schizophrenia. Marneros frames it as a disorder in which the delusion is well-systematised and long-lasting while other mental and personality domains stay comparatively intact (New Oxford Textbook of Psychiatry). The raw descriptive definitions of the delusion types and of the misidentification phenomena are cross-referenced to the Psychometry, Assessment and Descriptive Psychopathology notes.

RULE **Delusional disorder is a single non-bizarre delusion in an otherwise preserved person.** No prominent hallucinations, no disorganisation, no negative symptoms, and no functional collapse beyond what the delusion itself drives.

1.5 The decision tree assembled: reading a stem in order

The three axes chain into an ordered walk, and reading them in this order is the fastest route through any placement stem. First, exclude the organic and substance-induced (the silent branch). Second, ask the mood question: is a full mood episode prominent, and what is its temporal relation to the psychosis, which pulls out mood-with-psychotic-features and schizoaffective disorder. Third, if not mood-loaded, ask the content question: is this a single non-bizarre delusion in an otherwise intact person, which pulls out delusional disorder. Fourth, for the remaining schizophrenia-like pictures, apply the duration ruler: under one month (brief psychotic), one to six months (schizophreniform), six months or more (schizophrenia), with the ATPD sitting off to the side as an acute-onset, short-course entity. The illness schizophrenia is the tree's endpoint and is fully taught in the Schizophrenia: aetiology, phenomenology, classification and course notes; here it is only the destination the other branches are defined against. This ordered tree is the concept figure for the block.

WORKED EXAMPLE

A 24-year-old man, well until three weeks ago, is brought with florid persecutory delusions and auditory hallucinations of abrupt onset; no drugs on screen, no mood episode, no prior episodes. Walk the tree: organic and substance-induced excluded; no prominent mood episode (not schizoaffective, not mood-with-psychosis); the picture is not a single encapsulated delusion in an intact person (not delusional disorder); on duration it is under one month with acute onset. The answer is brief psychotic disorder (DSM-5-TR), and given the acute, prodrome-free onset within two weeks, an acute and transient psychotic disorder (ICD-11). Only if it runs past one month, then past six, does it climb to schizophreniform and then schizophrenia.

1.6 The criteria map in one table

The single table below is the object to memorise: each row is a spectrum member, and the columns are the three discriminating axes. The highlighted cell in each row is the one feature that clinches that diagnosis against its neighbours.

DISORDER (DSM-5-TR / ICD-11)	DURATION AXIS	MOOD-LOADING AXIS	DELUSION / DISCRIMINATOR
Brief psychotic disorder (F23)	**at least 1 day, under 1 month, full recovery**	none required	any positive symptom; often stress-triggered
Schizophreniform disorder (F20.81)	**1 to 6 months**	none required	schizophrenia picture, no functional-decline requirement
Schizophrenia (F20.9 / 6A20)	6 months or more (DSM); 1 month or more (ICD-11)	mood a minority of total course	**full active-phase picture; taught elsewhere**
Schizoaffective disorder (F25 / 6A21)	concurrent, over the illness course	**mood episode for majority of course, plus at least 2 weeks psychosis without prominent mood**	psychosis and mood interwoven
Mood disorder with psychotic features	within mood episodes	**psychosis only during mood episodes**	mood-congruent or incongruent delusions
Delusional disorder (F22 / 6A24)	1 month or more of delusion	none prominent	**single non-bizarre delusion, function otherwise preserved**
Acute and transient psychotic disorder (6A23)	**acute onset, full picture within 2 weeks, short course**	variable	often polymorphic, rapidly shifting

The schizophrenia-spectrum criteria map: read each row across the three axes; the highlighted cell is the clinching discriminator.

MNEMONIC

"SPECTRUM by Duration, Mood, Delusion; then the DELUSIONAL syndromes; then CATATONIA moves."

The master chain for the whole chapter. First place the psychosis on the SPECTRUM using the three axes, Duration, Mood-loading, Delusion-type. Then work the named DELUSIONAL syndromes (the jealous, erotomanic, somatic and persecutory types, and the misidentification set). Then finish on CATATONIA, the transdiagnostic psychomotor syndrome that "moves" across the whole grouping. Duration, Mood, Delusion is the three-axis core the examiner rewards.

1.7 India and the systems footnote

The acute and transient psychoses are of particular Indian relevance: acute-onset, brief, full-recovery non-affective psychoses are seen commonly in Indian practice and carry, on the whole, a favourable outcome, which is why ATPD and its ICD-10 antecedents are heavily represented in Indian teaching and examination (Kaplan & Sadock 2024, on the cycloid-psychosis and ATPD overlap). Delusional disorder, by contrast, typically presents in middle to later adult life and is comparatively uncommon in first-contact samples. This material is largely generic and disorder-defining rather than drug-focused; where any pharmacology is needed it is given as a pointer, and the antipsychotic detail is cross-referenced to the Schizophrenia: management, antipsychotics and adverse effects notes.

INDIA

The acute and transient psychotic disorders are a familiar and clinically important presentation in Indian settings: an abrupt, florid, often polymorphic psychosis in a previously well adult, frequently remitting fully within a short course. Treat the episode, then watch longitudinally, because a minority declare themselves later as schizophrenia or a mood disorder on relapse.

HOLD THIS

Every disorder in this family is a positive-symptom psychosis; you separate them by three axes only, duration, mood-loading and delusion-type, after first excluding the organic and substance-induced.

PEARL

Schizophreniform disorder is often **provisional**: if you make it before six months have elapsed and the illness has not yet remitted, you are labelling a work in progress. About one-third of patients recover within the six-month window and keep the schizophreniform label; the majority of the rest convert to schizophrenia or schizoaffective disorder (Kaplan & Sadock 2024).

GOOD TO REMEMBER

- **Schizophrenia spectrum:** the ICD-11 grouping of primary psychotic disorders (schizophrenia, schizoaffective, schizotypal, ATPD, delusional disorder); told apart by duration, mood-loading and delusion-type after organic/substance causes are excluded.
- **Brief psychotic disorder (F23):** at least one day and under **one month** with full recovery; the shortest member; any positive symptom, often stress-related.
- **Schizophreniform disorder (F20.81):** the same picture lasting **one to six months** with no functional-decline requirement; provisional if diagnosed early; introduced by Langfeldt in 1939.
- **Schizophrenia:** DSM-5-TR **six months or more**, ICD-11 **one month or more**; the endpoint of the duration axis, taught in the Schizophrenia: aetiology, phenomenology, classification and course notes.
- **Schizoaffective disorder (F25 / 6A21):** a mood episode present for the majority of the illness plus **at least two weeks** of psychosis without prominent mood (DSM-5-TR Criteria B and C); the two-week rule is the whole discrimination.
- **Delusional disorder (F22 / 6A24):** at least **one month** of a single non-bizarre delusion with function otherwise preserved and no other active-phase symptom; the one-domain psychosis.
- **Acute and transient psychotic disorder (6A23):** acute onset reaching the full psychotic picture **within two weeks**, short fluctuating course, often polymorphic; favourable outcome, clinically common in India.

2 · Schizoaffective disorder

Why this matters. **Schizoaffective disorder** is the schizophrenia-spectrum diagnosis the examiner uses to test whether you can hold two ideas at once: that a patient can have psychosis meeting the full schizophrenia bar together with a full mood episode, and that this is still not enough to call it schizoaffective unless a precise temporal rule is satisfied. The whole topic turns on one gate and one balance: a period of psychosis without a prominent mood episode, and mood symptoms occupying the majority of the illness. Get those two right and the diagnosis is secure; blur them and you have simply relabelled a mood disorder with psychotic features.

The governing sentence: schizoaffective disorder requires that, over the lifetime of the illness, delusions or hallucinations were present for a period of at least **two weeks** in the *absence* of a prominent mood episode, while mood symptoms meeting full criteria were present for the majority of the total duration of the illness (Kaplan & Sadock 2024, DSM-5-TR 2022). 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 raw mood-episode criteria (major depressive, manic, mixed) are cross-referenced to the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; and the drug detail is cross-referenced to the Schizophrenia: management, antipsychotics and adverse effects notes.

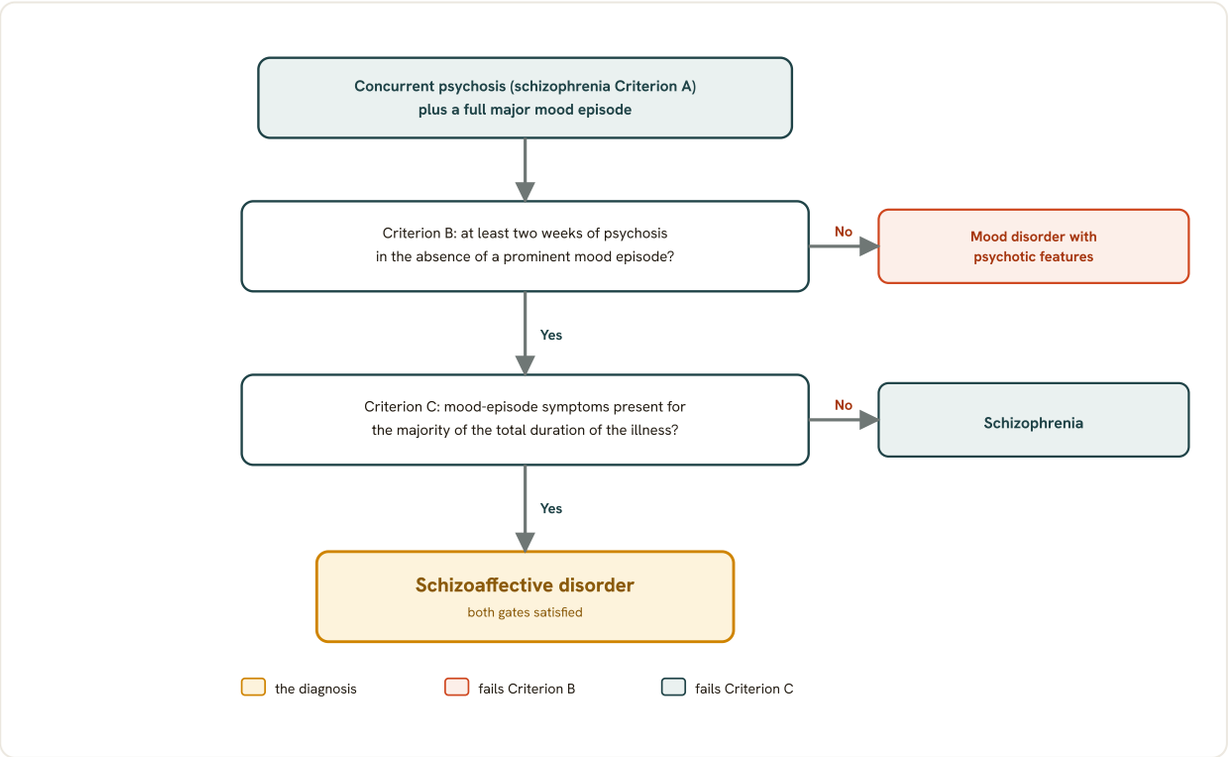

Fig 10.2 The schizoaffective decision rule (DSM-5-TR). Criterion B, at least two weeks of psychosis in the absence of a prominent mood episode, separates it from a mood disorder with psychotic features; Criterion C, mood-episode symptoms for the majority of the total illness, separates it from schizophrenia. Both gates must be satisfied. ICD-11 substitutes onset timing (simultaneous or within a few days, each lasting at least one month) and roughly equal prominence within a single episode.

2.1 The origin: Kasanin and a diagnosis born between two houses

The term schizoaffective psychosis was coined by Jacob Kasanin in a 1933 paper, describing a subgroup of nine young patients with good premorbid functioning, sudden onset of both schizophrenic and mood symptoms, and good outcome (Kasanin 1933, Kaplan & Sadock 2024). Kraepelin had already noticed that his own rich case material included many patients with features of both dementia praecox and manic-depressive illness, and Bleuler held that the co-occurrence of mood and schizophrenic symptoms in the same episode did not change the diagnosis of schizophrenia. Kasanin's category has survived every classification since, but a modern reading of his original case histories finds that all nine could today be diagnosed as a mood disorder with psychotic features, which is a fair emblem of the diagnosis it seeded: real enough to keep, unstable enough to argue about.

2.2 The DSM-5-TR criteria: the two-week gate and the majority rule

DSM-5-TR frames the diagnosis around an uninterrupted period of illness and four criteria (DSM-5-TR 2022). **Criterion A** requires an uninterrupted period during which there is a major mood episode (major depressive or manic) that is a **concurrent mood** episode running alongside psychosis meeting Criterion A of schizophrenia; because anhedonia is common in schizophrenia, a qualifying major depressive episode must include depressed mood itself (Criterion A1), not merely loss of interest. **Criterion B** is the defining rule: delusions or hallucinations for two or more weeks in the *absence* of a major mood episode during the lifetime duration of the illness. **Criterion C** requires that mood-episode symptoms are present for the majority of the total

duration of the active and residual portions of the illness. **Criterion D** excludes substances and another medical condition.

The two criteria that do the diagnostic work point in opposite directions. Criterion B separates schizoaffective disorder from a mood disorder with psychotic features: it demands a stretch of *pure* psychosis, at least two weeks, with no prominent mood episode running. Criterion C separates it from schizophrenia: it demands that mood symptoms dominate the majority of the illness, not a brief slice of it. A presentation can fail either way, and the diagnosis lives only in the narrow band where both hold.

RULE **Two weeks of psychosis without a prominent mood episode, plus mood for the majority of the illness.** Criterion B (the two-week pure-psychosis window) rules out a mood disorder with psychotic features; Criterion C (mood for the majority of the total duration) rules out schizophrenia. Both must hold.

TRAP **Calling any co-occurring psychosis and mood "schizoaffective".** Concurrent psychotic and mood symptoms alone do not make the diagnosis: without the two-week period of psychosis in the absence of a prominent mood episode, this is a mood disorder with psychotic features, where psychosis is confined to the mood episode.

2.3 A worked temporal example

DSM-5-TR gives a canonical pattern worth memorising. An individual has prominent auditory hallucinations and persecutory delusions for two months before a major depressive episode begins; psychosis and the full depressive episode then run together for four months; the depression lifts but the psychosis persists a further one month before it too clears (DSM-5-TR 2022). Total illness about seven months: psychosis alone in the first two months and the last one month (three months of pure psychosis, well over the two-week gate), with depression present for four of the seven, a majority. Both Criterion B and Criterion C are satisfied, so this qualifies as schizoaffective disorder.

WORKED EXAMPLE

Contrast the DSM-5-TR counter-case: a patient with a four-year history of active and residual schizophrenia develops depressive and manic episodes that, taken together, occupy less than one year of those four years. Criterion C fails, mood does not reach the majority of the illness, so the diagnosis is schizophrenia, not schizoaffective disorder, even though full mood episodes did occur.

2.4 Bipolar type and depressive type

DSM-5-TR requires a subtype specifier. The bipolar type (F25.0) applies if a manic episode is part of the presentation, whether or not depressive episodes also occur; the depressive type (F25.1) applies if only major depressive episodes are part of the presentation (DSM-5-TR 2022). The split is not cosmetic: bipolar type tends to present in younger adults, depressive type in older adults, and the bipolar/unipolar division maps onto the split running through the mood disorders themselves, whose full episode criteria are set out in the Mood disorders: classification,

depressive and bipolar syndromes, neurobiology notes. A **with catatonia** specifier is available and coded separately.

2.5 DSM-5 versus ICD-11: two framings of the same problem

The two systems agree on the spirit but differ in the letter, and the examiner likes the contrast. DSM-5-TR builds the diagnosis on the lifetime-course architecture above: a **concurrent mood** episode alongside schizophrenia-criterion psychosis, plus the two-week rule (Criterion B) and the majority rule (Criterion C). ICD-11 collapses the frame onto the current episode: its essential feature is that all the diagnostic requirements for schizophrenia are met concurrently with mood symptoms meeting the requirements of a moderate or severe depressive episode, a manic episode or a mixed episode, with the two symptom sets roughly equally prominent within the same episode (ICD-11 CDDR). The ICD-11 boundary text is exact: the onsets of the psychotic and mood symptoms are either simultaneous or occur within a few days of one another, and both must last at least one month; if the psychotic symptoms without mood symptoms end up much longer than the concurrent phase, the episode is better called schizophrenia. ICD-11 diagnoses episode by episode, so a previous schizoaffective episode does not preclude a later diagnosis of schizophrenia, and vice versa.

FEATURE	DSM-5-TR	ICD-11 CDDR
Unit of diagnosis	Lifetime, uninterrupted period of illness	**Current or most recent episode**
Core requirement	Mood episode concurrent with schizophrenia Criterion A	Schizophrenia requirements met concurrently with a full mood episode, roughly equally prominent
Pure-psychosis rule	**Delusions or hallucinations for at least two weeks in the absence of a prominent mood episode (Criterion B)**	No two-week rule; uses onset timing (simultaneous or within a few days) and duration
Mood-burden rule	**Mood symptoms for the majority of the total duration (Criterion C)**	Psychotic and mood symptoms concurrent and each lasting at least one month
Subtypes	Bipolar type (F25.0), depressive type (F25.1)	Course specifiers (first/multiple episode); type read from the mood episode

The two-week gate and the majority rule are DSM-5-TR devices; ICD-11 substitutes onset-timing and equal-prominence within a single episode.

2.6 The validity controversy: a diagnosis that will not sit still

Schizoaffective disorder is the classic example of a category of debated reliability and validity that sits between the mood and the psychotic disorders, and whose membership shifts with the criteria used (Kaplan & Sadock 2024). The instability is documented, not rhetorical. In a series of roughly 700 first-admission patients with psychotic features, 6% received a diagnosis of schizoaffective disorder at discharge, but only half of these (about 3% of the total) met DSM-III-R research criteria on review; two years later, only one-third of those originally diagnosed were still

called schizoaffective, one-third had become schizophrenia, and one-third an affective disorder (Kaplan & Sadock 2024). Family, twin and adoption studies find raised risks of both schizophrenia and affective disorder in relatives, marking it as a heterogeneous condition, and recent phenomenological work has failed to support the validity of the very two-week cutoff on which the DSM diagnosis rests. In practice the diagnosis is made more often than a strict application of the criteria would justify.

COMMON TRAP

Do not treat the schizoaffective label as a stable, once-and-for-all diagnosis. Because the relative proportion of mood to psychotic symptoms changes over time, DSM-5-TR itself expects the diagnosis to migrate: a severe four-month depressive episode in the first six months of a chronic psychosis may qualify as schizoaffective, then be revised to schizophrenia if psychosis persists for years without a further mood episode. The diagnosis is provisional by design.

at least 2 weeks PSYCHOSIS WITHOUT A PROMINENT MOOD EPISODE (CRITERION B)	**about one-third as common** AS SCHIZOPHRENIA	**0.3%** LIFETIME PREVALENCE, FINNISH SAMPLE (DSM-5-TR)

2.7 Course, prognosis and where it sits on the spectrum

Prognostically the disorder behaves as its name suggests, intermediate: outcome is better than schizophrenia but worse than a pure mood disorder (Kaplan & Sadock 2024, DSM-5-TR 2022). Negative symptoms and cognitive deficits occur but tend to be less severe and less persistent than in schizophrenia, and insight, though often impaired (anosognosia is common), may be less globally lost. Prevalence is about one-third that of schizophrenia, with a lifetime figure of **0.3%** in a Finnish sample and a female preponderance under DSM-IV criteria; the DSM-5 Criterion C (mood for the majority of the illness) is more stringent than the DSM-IV requirement of a merely substantial portion, so measured rates are expected to fall. This intermediate position, better than schizophrenia and worse than mood disorder, is exactly what makes its place on the schizophrenia spectrum contested.

2.8 Management pointers

This is a diagnosis topic, not a treatment topic, so the management is given as pointers only. The principle is combination: an **antipsychotic** to treat the psychotic dimension plus **mood-targeted treatment** for the affective dimension (a mood stabiliser or lithium for bipolar type, an antidepressant added with the usual caution for depressive type), the two chosen to match the subtype (Kaplan & Sadock 2024). Several second-generation antipsychotics carry mood benefit that suits this population, and the full drug detail, mechanisms, dosing and adverse effects, is cross-referenced to the Schizophrenia: management, antipsychotics and adverse effects notes; the mood-episode criteria that determine which affective arm to treat are set out in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes. Paliperidone is the one antipsychotic with a specific schizoaffective licence, but treat brand and licensing detail as belonging to the management notes.

INDIA

In Indian practice the diagnosis is used but, as elsewhere, applied loosely, and the same instability applies: an initial schizoaffective label frequently resolves to schizophrenia or to a mood disorder with psychotic features on longitudinal follow-up. Management follows the same combination logic (antipsychotic plus mood-targeted agent); brand-level detail belongs to the Schizophrenia: management, antipsychotics and adverse effects notes.

MNEMONIC

2 WEEKS PURE, MOOD FOR MOST

Two weeks of pure psychosis (no prominent mood episode) is the gate that excludes a mood disorder with psychotic features (Criterion B); mood for most of the illness is the balance that excludes schizophrenia (Criterion C). Hold both halves and the DSM-5-TR diagnosis is complete.

HOLD THIS

Schizoaffective disorder = at least two weeks of psychosis in the absence of a prominent mood episode (Criterion B), with mood symptoms present for the majority of the total duration of the illness (Criterion C); miss the two-week rule and it is only a mood disorder with psychotic features.

GOOD TO REMEMBER

- **Schizoaffective disorder:** a chronic psychosis with a full mood episode concurrent with schizophrenia-criterion psychosis; the discriminating rule is delusions or hallucinations for at least **two weeks** in the absence of a prominent mood episode (DSM-5-TR Criterion B); coined by Kasanin (1933).
- **Criterion B (the two-week gate):** at least two weeks of psychosis without a prominent mood episode over the lifetime of the illness; separates it from a mood disorder with psychotic features; the exam number is **two weeks**.
- **Criterion C (the majority rule):** mood-episode symptoms present for the majority of the total duration of the active and residual illness; separates it from schizophrenia; the phrase to hold is "majority of the total duration".
- **Bipolar type (F25.0) vs depressive type (F25.1):** bipolar type if a manic episode is part of the presentation (younger adults); depressive type if only major depressive episodes (older adults); the distinguishing feature is the presence or absence of a manic episode.
- **ICD-11 framing:** schizophrenia requirements met concurrently with a full mood episode, roughly equally prominent within the same episode, onsets simultaneous or within a few days, each lasting at least 1 month; no two-week rule, the number to hold is 1 month.
- **Validity controversy:** debated reliability and validity, sitting between mood and psychotic disorders, membership shifting with criteria; the demonstrative figure is that at 2-year follow-up only about one-third of those first diagnosed retain the label (Kaplan & Sadock 2024).

3 · Delusional disorder

Delusional disorder is the diagnostic home for the patient who holds one or more fixed false beliefs yet is, in every other respect, unremarkable: the personality is intact, the affect fits the belief, work and relationships hold up outside the delusional zone, and there are none of the hallucinations, thought disorder or negative symptoms that would push the diagnosis toward

schizophrenia. The examiner loves it precisely because it is a disorder defined by what is *absent* as much as by what is present, and because the classic error, calling it schizophrenia the moment a delusion appears, is so easy to make. This is a clinical-disorder topic: the schizophrenia symptoms it is contrasted against are owned by the Schizophrenia: aetiology, phenomenology, classification and course notes, and the raw descriptive definitions of each delusion type (persecutory, grandiose, jealous, erotomanic, somatic) are cross-referenced to the Psychometry, Assessment and Descriptive Psychopathology notes rather than re-derived here.

Fig 10.3 Delusional disorder commonly preserves much everyday functioning outside a circumscribed fixed belief. Major themes include persecutory, jealous, grandiose, erotomanic and somatic presentations.

How to use this page. Fix the core first (a **non-bizarre** delusion for at least a month, function otherwise preserved, no prominent hallucinations or other schizophrenia symptoms), then the **subtypes** by delusional theme, then Kendler's **dimensions of delusional** severity as a rating frame that cuts across the subtypes, and finally the epidemiology and the management pointers. The duration threshold is the single fact most often swapped in a viva: DSM-5-TR asks for one month, ICD-11 for three.

3.1 The core: a non-bizarre delusion with preserved function

What defines it. Delusional disorder is the presence of one or more persistent delusions, classically **non-bizarre** (plausible in principle, drawn from ordinary life: being followed, deceived by a spouse, loved from afar, infested), in the *absence* of the other features that would make the diagnosis schizophrenia (Kaplan & Sadock 2024, ICD-11 CDDR). There are no prominent or persistent hallucinations, no formal thought disorder, no passivity or first-rank phenomena, and no negative symptoms; apart from the actions and attitudes flowing directly from the delusional system, affect, speech and behaviour are typically unaffected. Personality is relatively preserved, and social and occupational functioning show much less deterioration than in schizophrenia (ICD-11 CDDR). The one nuance introduced by DSM-5 is that the *non-bizarre requirement was removed* from the core criterion and replaced by a "with bizarre content" specifier, so a bizarre delusion no longer excludes the diagnosis in DSM; the non-bizarre character remains the prototype and is retained in the ICD tradition (Kaplan & Sadock 2024).

RULE **A non-bizarre delusion with otherwise preserved functioning.** The whole diagnosis is one or more circumscribed delusions with the personality, affect and function outside the delusional zone essentially intact, and none of the hallucinations, thought disorder or negative symptoms of schizophrenia.

TRAP **Calling it delusional disorder when function is broadly impaired or other psychotic features dominate.** If there is global deterioration, persistent hallucinations, formal thought disorder or negative symptoms, the diagnosis is schizophrenia (or a mood-with-psychosis disorder), not delusional disorder.

3.2 Duration and the diagnostic boundaries

The duration threshold, the fact most often swapped. The delusion must persist for a minimum period: DSM-5-TR requires the delusion(s) for **at least 1 month**, whereas ICD-11 (6A24) requires it **typically for at least 3 months** and often much longer (DSM-5-TR 2022, ICD-11 CDDR). Both systems permit hallucinations only if they are non-prominent, non-persistent and thematically tied to the delusion, the classic example being tactile hallucinations in delusional infestation. The differential is drawn against three neighbours and one exclusion, and holding the discriminator for each is the exam-yield here.

CONTRAST	SHARED FEATURE	DISCRIMINATOR (WHAT MAKES IT DELUSIONAL DISORDER)
Schizophrenia	Persistent delusions	**No prominent hallucinations, thought disorder, passivity or negative symptoms; personality and function preserved; later onset**
Mood disorder with psychotic features	Persecutory, grandiose or somatic delusions	**Delusions occur at times *without* any mood episode; a full manic/depressive syndrome is absent or brief relative to the delusion (mood criteria in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes)**
Paranoid personality disorder	Suspiciousness, guardedness, litigiousness	**A frank, held delusion is present, not merely a pervasive distrustful trait; may be diagnosed alongside the personality disorder**
Illness anxiety / OCD / body dysmorphic disorder	Somatic or contamination preoccupations	**Belief is held with delusional conviction and insight is absent; if only an overvalued idea, code the primary disorder with the "absent insight / delusional beliefs" specifier**
Organic / substance cause	Delusions (often persecutory)	**Excluded first: delirium, dementia, basal-ganglia and limbic disease, amphetamine/cocaine; if present, code psychotic disorder due to another condition**

The differential is drawn by absence: delusional disorder is what remains once schizophrenia, a mood syndrome, a personality trait, an overvalued idea and an organic cause are each excluded (Kaplan & Sadock 2024, ICD-11 CDDR).

3.3 The subtypes by delusional theme

Named by content, not by severity. Both DSM-5-TR and ICD-11 classify delusional disorder into **subtypes** according to the predominant delusional theme (DSM-5-TR 2022). The raw descriptive definition of each delusion is owned by the Psychometry, Assessment and Descriptive Psychopathology notes; here the subtype is defined operationally by its central theme.

Persecutory type

The central theme is being conspired against, cheated, spied on, followed, poisoned, maligned or obstructed; the commonest subtype.

Grandiose type

The central theme is a great unrecognised talent, insight or discovery, or a special identity or relationship.

Jealous type

The central theme is that a spouse or partner is unfaithful (delusional jealousy, the Othello theme); the one subtype more common in men.

Erotomanic type

The central theme is that another person, usually of higher status, is in love with the patient (De Clerambault syndrome, psychose passionelle).

Somatic type

The central theme is bodily: infestation, malfunction, deformity or odour (older term monosymptomatic hypochondriacal psychosis); presents to dermatology, surgery or dentistry, rarely to psychiatry.

Mixed type

No single theme predominates; more than one of the above coexists. (An unspecified type covers themes that fit none of the above.)

MNEMONIC

PG-JES-M

The subtypes in one string: **P**ersecutory, **G**randiose, **J**ealous, **E**rotomanic, **S**omatic, **M**ixed. Persecutory is the commonest; jealous is the one that skews male; erotomanic is the one with the eponym (De Clerambault).

3.4 The named eponyms attached to the subtypes

Three eponyms travel with the themes. The examiner expects the eponyms, but also expects you to know they are *presentations*, not diagnoses in their own right: each can arise in delusional disorder, in schizophrenia, in a mood disorder or organically. De Clerambault syndrome is the erotomanic theme (a person of higher status is secretly in love with the patient, who reads rejection as concealed courtship). Othello syndrome is the delusional-jealousy theme (the conviction of a partner's infidelity, with checking behaviour and a real risk of violence). Ekbom syndrome is delusional infestation or delusional parasitosis, the prototypical somatic-type presentation, often with linked tactile hallucinations of things crawling on or under the skin.

TRAP **Calling any morbid jealousy Othello syndrome.** Othello syndrome is *delusional* jealousy; obsessional or overvalued jealousy, or jealousy secondary to alcohol or a mood state, is not, and the same theme can be a symptom of schizophrenia or a mood disorder rather than delusional disorder.

3.5 Kendler's dimensions of delusional severity

A rating frame, not a subtype scheme. Where the subtypes classify a delusion by *content*, Kendler's **dimensions of delusional** experience classify it by *form and severity*: a set of largely independent axes along which any single delusion can be rated, and along which two patients with the "same" persecutory belief may differ enormously (Kendler 1983). The point for the exam is that **delusional severity** is multidimensional, so a delusion is not simply "present or absent" but strong or weak on several separable measures, and these dimensions do not correlate tightly with each other.

Conviction
The degree of certainty with which the belief is held, from partial doubt to absolute incorrigibility.

Extension
How far the delusion reaches into other areas of the person's life and world (a single encapsulated idea versus a pervasive delusional system).

Bizarreness
How implausible or impossible the belief is by ordinary cultural standards.

Disorganisation
How internally consistent and systematised the belief is, versus fragmented and contradictory.

Pressure
The degree of preoccupation, the amount of mental space and time the delusion occupies.

Affective response (a commonly-taught later addition, not in Kendler's original five)
The intensity of emotion attached to the belief.

Deviant (acting-out) behaviour (a commonly-taught later addition, not in Kendler's original five)
The extent to which the person acts on the delusion (stalking, litigation, assault), the dimension of greatest forensic weight.

Because these are independent, they are useful for *rating* and tracking a delusion (and for understanding why an encapsulated, low-pressure, non-acted-on delusion is compatible with preserved function) rather than for assigning a subtype. This dimensional view sits alongside the standard classifications and is worth naming when a question asks how a delusion is characterised beyond its theme (Kendler 1983).

> **PEARL**
> Content and form answer different questions. If asked to *classify* a patient's delusion, give the subtype (persecutory, jealous and so on); if asked to *characterise or rate* the delusion, reach for the dimensional frame: Kendler's original five (conviction, extension, bizarreness, disorganisation, pressure), with affective response and acting-out commonly added. The "acting-out" dimension is the one that drives risk and admission, whatever the theme.

3.6 Epidemiology and course

Uncommon, and later than schizophrenia. Delusional disorder is relatively uncommon: a general-population study from Finland found a lifetime prevalence of DSM-IV delusional disorder of **0.18%**, and in clinical series it accounts for roughly **1% to 4%** of psychiatric admissions (Kaplan & Sadock 2024). The **age of onset** is characteristically later than in schizophrenia, generally in the **mid- to late-30s**, usually insidious, and the delusions once formed tend to be stable and fixed (Kaplan & Sadock 2024, ICD-11 CDDR). The persecutory subtype is the most common; other than the jealous type, which is more common in men, the disorder is roughly equally distributed between the sexes, with males tending to a younger onset. Functioning is generally preserved, with adverse outcomes arising mainly when the person acts on the belief; a minority progress to schizophrenia over time, and a premorbid personality disorder (classically paranoid) is over-represented.

0.18%	mid to late 30s	1 mo / 3 mo
LIFETIME PREVALENCE (FINLAND, DSM-IV)	TYPICAL AGE OF ONSET	MINIMUM DELUSION DURATION (DSM-5-TR / ICD-11)

3.7 Management pointers

Engagement first, then cautious pharmacology. The management of delusional disorder is dominated by one problem: these patients rarely see themselves as ill, so they present late, reluctantly, and often to a non-psychiatrist. The first task is therefore *engagement and the therapeutic alliance*, working with the distress and the functional consequences rather than confronting the belief head-on, since a frontal challenge to a fixed delusion tends to entrench it and end the consultation. Pharmacologically, antipsychotics are used but the *evidence base is limited* and largely uncontrolled: response is generally more modest and less reliable than in schizophrenia, and the drug detail (agent choice, dosing, adverse effects) is cross-referenced to the Schizophrenia: management, antipsychotics and adverse effects notes rather than re-taught. Comorbid *depression* is common (sometimes an understandable response to the delusional predicament) and should be identified and treated, as it worsens course. Risk assessment is integral, particularly in the jealous and erotomanic subtypes where acting-out (violence, stalking) is the main danger.

WORKED EXAMPLE

A 42-year-old, employed and socially intact, presents only because his wife insists, convinced over eight months that a neighbour is conducting an affair with her; he checks her phone and clothing and has confronted the neighbour once. There are no hallucinations, no thought disorder, no negative symptoms, and no mood episode; outside this belief he functions normally. This is delusional disorder, jealous subtype (Othello theme): non-bizarre delusion, over the duration threshold, preserved function, no other schizophrenia features. The clinical priority is risk (delusional jealousy carries a real risk of violence), then engagement, then a cautious antipsychotic trial and screening for comorbid depression, with the belief itself worked around rather than argued against.

INDIA

In Indian practice, delusional disorder classically presents to non-psychiatric specialists first: the somatic type (delusional infestation, Ekbom syndrome, and delusional parasitosis) reaches dermatology and general physicians, and the jealous type surfaces in the context of marital and family conflict, so much of the early clinical experience is of engaging a patient who does not accept a psychiatric frame. Diagnosis follows the ICD-11 (and long-familiar ICD-10) three-month non-bizarre-delusion template that Indian teaching texts use. The system-wide rule that no diagnosis is named to the patient sits comfortably here: management is framed around the distress and its consequences rather than the label, which also aids engagement. Generic antipsychotics dominate and are affordable; verify the local brand before naming one.

HOLD THIS

Delusional disorder is one or more non-bizarre delusions for at least a month (DSM-5-TR; three months in ICD-11), with personality, affect and function preserved outside the delusion and none of the hallucinations, thought disorder or negative symptoms of schizophrenia; classified by theme into persecutory (commonest), grandiose, jealous (male-predominant, Othello), erotomanic (De Clerambault), somatic (Ekbom) and mixed subtypes, onset in the mid- to late-30s.

GOOD TO REMEMBER

- **Delusional disorder (the diagnosis):** one or more persistent non-bizarre delusions with function otherwise preserved and no other schizophrenia symptoms; the discriminator from schizophrenia is preserved personality/function plus absence of prominent hallucinations, thought disorder and negative symptoms; the number to hold is the duration, at least 1 month (DSM-5-TR) or 3 months (ICD-11 6A24).
- **Subtypes (by theme):** persecutory, grandiose, jealous, erotomanic, somatic, mixed; the discriminator is the predominant delusional content; persecutory is the commonest and jealous the one more common in men.
- **De Clerambault syndrome (erotomanic type):** the delusion that a higher-status person secretly loves the patient; the discriminator is the reading of rejection as concealed courtship; the eponym to hold is De Clerambault (psychose passionelle).
- **Othello syndrome (jealous type):** the delusion of a partner's infidelity; the discriminator from ordinary or obsessional jealousy is delusional conviction; the fact to hold is its association with violence risk.
- **Ekbom syndrome (somatic type):** delusional infestation / delusional parasitosis, often with tactile hallucinations; the discriminator is the fixed conviction of infestation despite normal examination; presents to dermatology, not psychiatry.
- **Kendler's dimensions of delusional severity (the rating frame):** the original five are conviction, extension, bizarreness, disorganisation and pressure (Kendler 1983), with affective response and acting-out commonly added in later descriptive-psychopathology teaching; the discriminator from the subtypes is that these rate form and severity, not content.
- **Epidemiology and management (the pointers):** lifetime prevalence about 0.18%, onset mid- to late-30s, function preserved; engagement and alliance first, antipsychotics with limited evidence, treat comorbid depression; drug detail cross-referenced to the Schizophrenia: management, antipsychotics and adverse effects notes.

Figure. A concept figure contrasting delusional disorder with schizophrenia along two axes (breadth of impairment and presence of non-delusional psychotic features), with the delusional disorder region marked as narrow-impairment, delusion-only, is flagged for central drawing.

4 · The life-cycle of a delusion: formation and dissolution

A delusion is not a static false belief that a patient simply "has"; phenomenologists describe it as a process with a beginning, a crystallisation and, in recovery, a dissolution. Two German-tradition observers frame the two ends of that arc. **Klaus Conrad** traced the *formation* of an evolving psychosis as a staged transformation of the whole field of experience, and **Karl Jaspers** named the discrete primary *forms* in which a true (schizophrenic) delusion first appears. At the far end, Eugen Bleuler's clinical observations of how a settled delusion coexists with, or is sealed off from, ordinary reality describe the ways a psychosis is contained or worked through.

Why it matters. This topic supplies the descriptive spine for the delusion viva: it lets you narrate *how* a persecutory system came into being, distinguish a primary delusion (heavily weighted in the diagnosis of schizophrenia) from a secondary one, and explain why a chronically deluded patient can hold a bizarre belief and a mundane life side by side without felt contradiction. The raw definitions of each delusional form are cross-referenced to the Psychometry, Assessment and Descriptive Psychopathology notes rather than re-derived here; the disorder schizophrenia itself (its phenomenology, criteria and course) is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes.

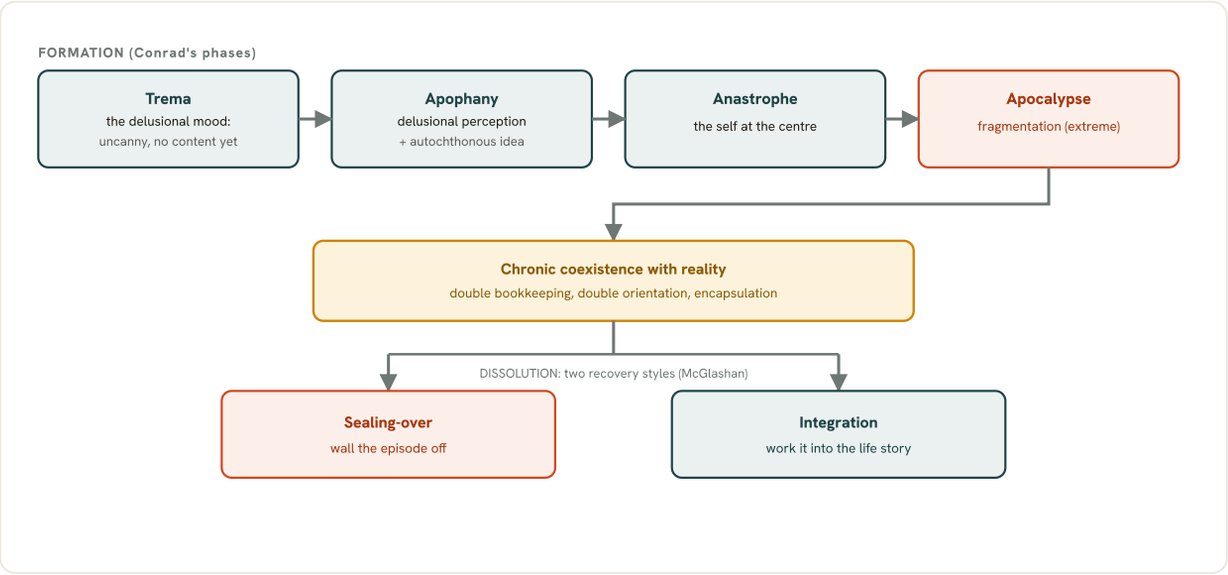

Fig 10.4 The life-cycle of a delusion. Formation runs through Conrad's phases, the trema (delusional mood, an uncanny atmosphere) preceding the apophany (the crystallised delusional perception), then anastrophe and, at the extreme, apocalypse. Once formed, a delusion coexists with reality (Bleuler's double bookkeeping and double orientation, and encapsulation), and at recovery is either sealed over or integrated into the life story.

4.1 Formation: Conrad's phases of an evolving psychosis

Klaus Conrad (1958), studying young soldiers with acute schizophrenia, described the beginning of psychosis as a sequence of gestalt transformations rather than a single event (Conrad 1958; reviewed by Mishara 2010). The sequence is a favourite viva scaffold because it maps the subjective experience onto Jaspers' forms.

Trema

The opening delusional mood (Conrad's word, borrowed from the German for pre-performance stage-fright): a tense, uncanny atmosphere that something momentous is impending, a total change in the perception of the world with no explicit content yet (Mishara 2010).

Apophany

The apophanous phase: the sudden crystallisation of a specific meaning where the patient finds new significance for events. This is the moment of the delusional perception and the autochthonous delusional idea, when "now it all makes sense" (Mishara 2010).

Anastrophe

The world comes to revolve around the self; the patient is placed at the centre of the reorganised field of meaning, heightening the psychosis.

Apocalypse

At the extreme, the disintegration or fragmentation of experience, with dissolution of the coherent world into perplexity and terror.

Conrad's fuller German scheme runs to six phases in all, the four acute phases above followed by *consolidation* (a new psychological world is built on the new meanings) and *residuum* (an eventual defect or autistic end-state); the AIIMS Clinical Methods summary gives a five-stage version (trema, apophany, anastrophe, consolidation, residuum) that folds away the apocalyptic phase (Conrad 1958; AIIMS Clinical Methods 2024, citing Mishara 2010). For the exam the load-bearing point is the ordering of the early phases: the **trema** (delusional mood) is the *prodromal atmosphere* that precedes the **apophany** (the crystallised delusional perception).

RULE **Mood before meaning.** Conrad's trema, the delusional mood, precedes the apophanous delusional perception: the uncanny atmosphere comes first, the specific "now it all makes sense" crystallisation comes second.

4.2 Jaspers' primary delusional forms, applied to this arc

Karl Jaspers separated **primary** delusions (arising *de novo*, ununderstandable, un-derivable from any preceding mental event, and given considerable diagnostic weight in schizophrenia) from **secondary** delusions (psychologically understandable from mood, culture or other symptoms). Four primary forms are recognised; each is a moment on Conrad's formation arc. The crisp descriptive definitions live in the Psychometry, Assessment and Descriptive Psychopathology notes and are only cross-referenced here (Sims 2015; Shorter Oxford 2018).

PRIMARY FORM	ONE-LINE CHARACTER	POINT ON THE ARC
Delusional mood (delusional atmosphere)	**A state of perplexity: something uncanny is going on that involves the patient in unspecified ways, content not yet fixed**	Conrad's *trema* (prodromal)
Delusional perception	**A real, normal percept is invested with a new, self-referential delusional meaning not derivable from mood; Schneider's "two-memberedness"**	Conrad's *apophany*
Sudden delusional idea (autochthonous delusion / delusional intuition)	**A fully formed conviction appearing in an instant "like a bolt from the blue", a single-stage event (no antecedent percept)**	Conrad's *apophany*
Delusional memory (retrospective delusion)	A past memory (real or false) is reinterpreted delusionally, often to explain the illness	Later elaboration

Jaspers' four primary delusional forms mapped onto Conrad's phases. Note the discriminator between delusional perception (two stages: normal perception, then delusional meaning) and the autochthonous sudden idea (one stage: the idea simply arrives), verified against AIIMS Clinical Methods 2024 and Kaplan & Sadock 2024.

WORKED EXAMPLE

A 25-year-old man saw the yellow leaves of the tree outside his house falling and, in that instant, knew this was a signal from God that he was "the chosen one", the sole person able to intercept it. The *percept* (yellowing leaves) is entirely normal; the delusion is the immediate, self-referential meaning attached to it, with no pre-existing delusional system to derive it from. That is a **delusional perception** and its "two-memberedness" (percept, then meaning) is Schneider's diagnostic hallmark (AIIMS Clinical Methods 2024).

4.3 Dissolution: how a delusion is held, contained and given up

Once formed, a delusion may persist, encapsulate, or dissolve. The descriptive vocabulary for the *persistence-alongside-reality* end is Bleulerian; the vocabulary for *recovery* comes from the schizophrenia outcome literature.

Double bookkeeping

Bleuler's observation that the delusion and everyday reality are held in parallel *without felt contradiction*: the patient who insists their food is poisoned will nevertheless eat it, and the espoused belief is not consistently acted upon (Bleuler; Kaplan & Sadock 2024).

Double orientation

The delusion is held with conviction yet has little influence on feelings and actions: a patient may believe himself a member of the royal family while living contentedly in a group home; this separation usually occurs in chronic schizophrenia (Shorter Oxford 2018).

Delusional encapsulation

An *encapsulated delusion* is walled off so that it has limited impact on the person's overall behaviour, the belief coexisting with otherwise intact functioning (AIIMS Clinical Methods 2024).

At recovery, two contrasting *recovery styles* are described (McGlashan, Levy and Carpenter 1975). In sealing-over, the patient walls the psychotic episode off, minimising and encapsulating it as alien and best not examined ("sealing over"). In **integration**, the patient works the experience into the life story, remaining curious about it and weaving it into a continuous sense of self. Integration is generally associated with better insight and engagement; sealing-over with more guarded, defended recovery.

TRAP **Coexistence is not insight.** Do not read double bookkeeping (delusion and reality coexisting, the belief not acted upon) as regained insight: the conviction is intact, only the behavioural consequence is muted.

PEARL

Double bookkeeping, double orientation and encapsulation all describe a delusion that *survives* alongside reality; sealing-over and integration describe two ways the episode is *metabolised* in recovery. Keep the two axes separate in an answer: the first is about how the belief coexists with reality during illness, the second about the stance the patient takes toward the episode afterwards.

4.4 India note and the figure to hold

India. In much Indian public-sector practice the delusional-formation vocabulary is examined from the descriptive-psychopathology tradition (Fish, Sims, and the AIIMS Clinical Methods text), and delusional perception and the autochthonous sudden idea are high-yield viva points precisely because they are the primary forms carrying the greatest diagnostic weight for schizophrenia. Candidates are expected to name the eponyms (Conrad, Jaspers, Schneider, Bleuler) and to distinguish the one-stage sudden idea from the two-stage delusional perception; misattributing these, or swapping the order of trema and apophany, is a classic error.

HOLD THIS

Trema (delusional mood) precedes apophany (delusional perception): mood first, crystallised meaning second, world-around-self (anastrophe) next, fragmentation (apocalypse) at the extreme.

GOOD TO REMEMBER

- **Conrad's phases:** the staged formation of an evolving psychosis; core sequence trema (delusional mood) to apophany (delusional perception) to anastrophe (self at centre) to apocalypse (fragmentation); eponym Conrad 1958.
- **Trema:** the opening delusional mood, a tense uncanny "something is impending" atmosphere with no fixed content; discriminator = prodromal, precedes any specific delusion.
- **Apophany:** the apophanous crystallisation where a specific meaning appears and "now it all makes sense"; discriminator = the moment of the delusional perception and autochthonous idea.
- **Delusional perception:** a normal percept given new self-referential delusional meaning; discriminator = Schneider's "two-memberedness" (two stages), eponym Schneider 1959.
- **Sudden (autochthonous) delusional idea:** a fully formed delusion arriving in one step "like a bolt from the blue"; discriminator = single-stage, no antecedent percept.
- **Delusional memory:** a past memory reinterpreted delusionally (retrospective delusion); discriminator = the falsification lies in the recall, not a current percept.
- **Double bookkeeping:** delusion and reality held in parallel without felt contradiction, belief not consistently acted on; eponym Bleuler.
- **Double orientation:** delusion held with conviction but little effect on feeling or action, typical of chronic schizophrenia; discriminator = conviction intact, behaviour unaffected.
- **Delusional encapsulation:** the belief walled off with limited impact on overall behaviour; discriminator = preserved functioning around a contained delusion.
- **Sealing-over vs integration:** two recovery styles, walling the psychosis off (sealing-over) versus working it into the life story (integration); eponym McGlashan 1975.

5 · Acute and transient psychotic disorders

The **acute and transient psychotic disorders** are the schizophrenia-spectrum group defined by their *tempo* rather than their content: an abrupt onset from a well state into full psychosis, a rapidly shifting clinical picture, and a short, self-limiting course with a characteristically **good outcome**. They are the nosological home of a family of historical syndromes, the French bouffee delirante among them, that European and non-European psychiatrists kept re-describing under different names because the phenomenon is real and recurrent (Kaplan & Sadock 2024). The exam wants three things: the **icd-11** category structure, the abrupt-onset short-course rule with its good prognosis, and the follow-up caveat that a minority re-diagnose over time.

This is a discrimination topic. Master the boundary against schizophrenia (duration and symptom stability) and against mood disorder (whether an affective episode is sustained), and hold the one management pointer: treat the episode, but *follow up*. The raw descriptive definitions of the delusions, hallucinations and perplexity referenced below sit in the Psychometry, Assessment and Descriptive Psychopathology notes; the disorder schizophrenia itself is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes and is not re-taught here.

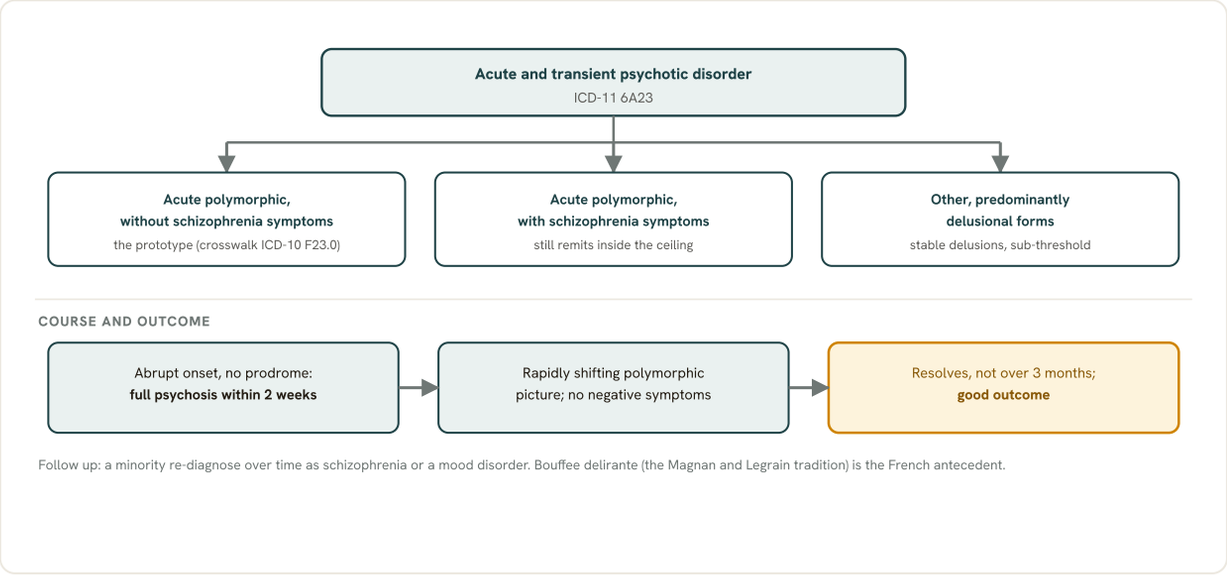

Fig 10.5 The ICD-11 acute and transient psychotic disorders, category and course. The single 6A23 category holds the acute polymorphic form (with or without symptoms of schizophrenia) and the other predominantly-delusional forms. The tempo defines it: abrupt onset to full psychosis within two weeks, a rapidly shifting polymorphic picture with no negative symptoms, and resolution within three months with a characteristically good outcome, though a minority re-diagnose on follow-up.

5.1 The icd-11 category and its essential features

One code, one gestalt. The **icd-11** collapses the older subtypes into a single category, acute and transient psychotic disorder (6A23), whose essential features are: acute onset of psychotic symptoms (delusions, hallucinations, disorganised thinking, or experiences of influence, passivity or control) *without a prodrome*, progressing from a non-psychotic to a clearly psychotic state within **2 weeks**; symptoms that *change rapidly* in nature and intensity, sometimes over the course of hours; *absence of negative symptoms*; and a duration that does not exceed **3 months**, most often lasting from a few days to 1 month (ICD-11 CDDR). Psychomotor disturbance including catatonia may be present. The picture must not be organic, substance-induced, or better explained by schizophrenia or another primary psychotic disorder.

RULE **Tempo defines it.** Acute onset (within 2 weeks) plus a rapidly shifting picture plus a short duration (not over 3 months) with a good outcome is **atpd**, but follow up because some become schizophrenia.

5.2 The acute polymorphic ("kaleidoscopic") picture

Symptoms that will not sit still. The prototype is the acute polymorphic psychotic disorder: an abruptly onset, rapidly shifting, "kaleidoscopic" picture of changing delusions, hallucinations and

affect, with the type and intensity of symptoms fluctuating in relatively rapid succession, and marked emotional turmoil, perplexity or confusion superimposed (ICD-11 CDDR). The polymorphic form comes in two flavours, *with or without symptoms of schizophrenia*: if schizophrenia-type symptoms are present but the whole episode still remits inside the duration ceiling, it remains within this group rather than becoming schizophrenia. The other forms are the *other acute, predominantly-delusional* presentations, in which comparatively stable delusions or hallucinations dominate but do not meet the schizophrenia threshold. In the icd-11, this fluctuating polymorphic quality is the *defining* feature of the single 6A23 category (ICD-11 CDDR).

TRAP **Do not fix schizophrenia on a first brief episode.** A first, brief, polymorphic episode with rapidly shifting content and full remission is **atpd**, not schizophrenia, even if the cross-section technically shows schizophrenia-type symptoms.

5.3 Course, good outcome and the follow-up imperative

Mostly remits, a minority declares itself later. The natural history is a rapid deterioration in social and occupational functioning, then full remission with return to the premorbid level. Favourable outcomes are associated with acute onset, short duration, good premorbid functioning and female gender (ICD-11 CDDR). A proportion of patients, however, re-diagnose over time as schizophrenia, another primary psychotic disorder, or a mood disorder, so the diagnosis is always provisional and follow-up is mandatory. Male gender and younger age of onset carry the greater risk of subsequent schizophrenia. Episodes are often stress-precipitated (an acute stressor is commonly reported but is not required), and the disorder is commoner in women and in developing countries (Kaplan & Sadock 2024).

WORKED EXAMPLE

A 24-year-old woman is brought in three days after a family bereavement: over hours her talk swings between grandiose religious certainty and terrified persecutory fear, voices come and go, and her affect lurches from ecstasy to dread. She is fully alert and oriented. Ten days later she is symptom-free. This is an acute polymorphic presentation of **atpd** (6A23.0, first episode): acute onset under 2 weeks, kaleidoscopic shifting picture, no negative symptoms, full remission. You still book follow-up, because a first episode does not exclude later schizophrenia or a mood disorder.

within 2 weeks	3 months	1 day to under 1 month
ONSET TO FULL PSYCHOSIS (ICD-11)	MAXIMUM DURATION; USUALLY DAYS TO 1 MONTH	DSM-5-TR BRIEF PSYCHOTIC DISORDER

5.4 Bouffee delirante and its nosological place

The French antecedent. Descriptions of acute-onset, remitting psychoses recur across traditions: Meynert's *amentia*, Kleist and Leonhard's cycloid psychosis, the Scandinavian *reactive (psychogenic) psychosis*, and the French bouffee delirant of the late 19th century (Kaplan & Sadock 2024). The nosological place of the bouffee delirante is precisely as the historical antecedent of the acute polymorphic category: an abrupt "delusional flash" out of a clear sky, richly

polymorphic, with rapid full recovery, later distilled (with the cycloid and reactive concepts) into ICD-10's acute and transient category and then ICD-11's 6A23 (Kaplan & Sadock 2024). The classic attribution is to the French degeneration-school tradition of Magnan and his pupil Legrain (Kaplan & Sadock 2024 dates the joint concept to 1895), so name the tradition rather than betting on a single author or year.

PEARL

The recurring theme across all these historical labels is identical: acute onset, polymorphic content, rapid full recovery. That the same syndrome was independently described across cultural and linguistic boundaries is exactly why a unified acute and transient category was worth creating.

5.5 The icd-10 to icd-11 shift, and DSM-5

From subtypes to a single tempo-defined code. ICD-10 split the group into acute polymorphic psychotic disorder (with or without symptoms of schizophrenia) and an acute schizophrenia-like psychotic disorder, each further specified for the presence or absence of an associated acute stressor. The **icd-11** unified all of this into one category, 6A23, in which the rapidly fluctuating polymorphic picture is the essential feature; the official crosswalk maps 6A23 back to ICD-10 F23.0, acute polymorphic psychotic disorder without symptoms of schizophrenia (ICD-11 CDDR). Course is then coded by specifiers only: first episode (6A23.0) or multiple episodes (6A23.1), each further as currently symptomatic, in partial remission, or in full remission.

DSM-5 has no exact equivalent. The DSM-5-TR has no dedicated acute-and-transient section; its nearest match is brief psychotic disorder, defined by a duration of **at least 1 day but less than 1 month** with full return to premorbid functioning (Kaplan & Sadock 2024). Most patients meeting icd-11 **atpd** criteria map onto DSM-5-TR brief psychotic disorder, but a substantial minority fall instead into schizophreniform or other specified schizophrenia-spectrum categories, so the fit is inexact.

INDIA

The acute, benign-course psychoses that this category captures were reported with high frequency in India, Africa and the Caribbean, and the diagnosis is used heavily in Indian practice. Many psychiatrists, especially from developing countries such as India, drove recognition of the acute polymorphic picture as a distinct, good-prognosis entity rather than early schizophrenia.

FEATURE	ACUTE AND TRANSIENT (ICD-11 6A23)	SCHIZOPHRENIA	MOOD DISORDER WITH PSYCHOSIS
Onset	**Abrupt, no prodrome, within 2 weeks**	Often insidious, poor premorbid adjustment	Follows onset of the mood episode
Symptom stability	**Rapidly shifting, polymorphic, over hours to days**	Stable, fixed (same delusion for months)	Mood-congruent, tied to the episode
Negative symptoms	**Absent during the episode**	Often present	Not the defining feature
Duration	Does not exceed 3 months (usually days to 1 month)	At least 1 month florid; typically much longer	Mood episode persists days and usually much longer
Outcome	**Good; full remission to premorbid level**	Variable, often chronic	Episodic, defined by mood recovery

The three-way discrimination: tempo and symptom instability separate **atpd** from schizophrenia; a sustained affective episode separates it from a mood disorder. The mood-episode criteria themselves are in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes.

MNEMONIC

ABRUPT

Acute onset (within 2 weeks), **B**rief (not over 3 months), **R**apidly shifting polymorphic picture, **U**nremarkable premorbid state, **P**rognosis good, **T**rack them (follow up: some become schizophrenia or a mood disorder).

GOOD TO REMEMBER

- **Acute and transient psychotic disorder (icd-11 6A23):** abrupt-onset, short-course psychosis with a good outcome; discriminator is the rapidly shifting polymorphic picture with no negative symptoms; the number to hold is onset within 2 weeks, duration not over 3 months.
- **Acute polymorphic psychotic disorder:** the prototype and the icd-11 crosswalk to ICD-10 F23.0; discriminator is kaleidoscopic changing delusions, hallucinations and affect, with or without symptoms of schizophrenia; the point to hold is that it is the defining form of 6A23.
- **Bouffee delirante:** the French late-19th-century acute polymorphic psychosis, a "delusional flash" with rapid recovery; discriminator is its historical role as the antecedent of the acute polymorphic category; eponym to hold is the Magnan and Legrain tradition (Kaplan & Sadock 2024).
- **Cycloid psychosis:** Kleist and Leonhard's acute-onset, good-prognosis, frequently-recurring psychosis; discriminator is the same acute-remitting theme in a different tradition; hold Leonhard as the name attached to the concept.
- **DSM-5-TR brief psychotic disorder:** the nearest DSM match, with no dedicated acute-and-transient section; discriminator is the duration window; the number to hold is at least 1 day but less than 1 month with full remission.

HOLD THIS

Acute onset within 2 weeks, a rapidly shifting polymorphic picture with no negative symptoms, and full remission within 3 months is acute and transient psychotic disorder (icd-11 6A23), good outcome expected, but follow up because a minority declare as schizophrenia or a mood disorder.

6 · Brief psychotic disorder

The **brief psychotic disorder** of DSM-5-TR is the shortest-lived of the schizophrenia-spectrum entities: a storm of positive psychotic symptoms that erupts suddenly, burns out inside a month, and leaves the person back at their premorbid baseline. It is the diagnosis you reach for when a previously well patient presents floridly delusional or hallucinated after, say, a bereavement or a delivery, and then clears rapidly. For the exam it is a duration problem first and a differential problem second: get the **less than a month** boundary right, name the specifiers, and know that the good prognosis is real but conditional on follow-up.

Why it earns a place. It anchors the short end of the psychosis duration ladder (brief psychotic, then schizophreniform, then schizophrenia), it carries the historical concepts examiners love (brief reactive psychosis, bouffee delirante), and it forces you to weigh a benign transient episode against the first presentation of a lifelong illness. The raw descriptive definitions of the delusions and hallucinations themselves are cross-referenced to the Psychometry, Assessment and Descriptive Psychopathology notes; the disorder schizophrenia itself is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes and is not re-taught here.

6.1 The DSM-5-TR entity: sudden onset, days to weeks, full recovery

Core criterion. Brief psychotic disorder (DSM-5-TR, coded **F23**, page 108) requires the sudden onset of at least one positive psychotic symptom, and one of them must be delusions, hallucinations or disorganised speech (grossly disorganised or catatonic behaviour alone does not qualify). The episode lasts **at least a day but less than a month**, with an eventual full return to the premorbid level of functioning (APA 2022; Kaplan & Sadock 2024). Tasman frames it crisply as a transient psychotic state, not caused by a medical condition or a substance, lasting at least one day and up to the one month upper bound (Tasman 2015).

The bracketing. The one month upper bound is the hinge. Cross the one month line and, if criterion A for schizophrenia is met, the diagnosis becomes schizophreniform disorder (at least one month but less than six months); cross six months and it becomes schizophrenia. The whole point of the entity is that the psychosis is over inside a month and the person is restored.

RULE **Under a month, full recovery.** Brief psychotic disorder resolves within one month with a full return to premorbid functioning; if it runs past a month it is no longer brief psychotic disorder.

HOLD THIS

Brief psychotic disorder = sudden positive psychosis lasting at least a day but less than a month, with full return to premorbid functioning; the post-stressor form is the old brief reactive psychosis.

6.2 The three specifiers: stressor, post-stressor, peripartum

The stressor axis. DSM-5-TR tags the episode *with marked stressor(s)* or *without marked stressor(s)*. The **post-stressor** form, coded when florid psychosis follows an event that would be markedly stressful to almost anyone in that culture, is the modern home of the historical brief

reactive psychosis of DSM-III and DSM-III-R, whose criteria explicitly required a severe precipitant such as a major loss or a combat-type trauma (Kaplan & Sadock 2024). The without-stressor form has no identifiable precipitant.

The peripartum axis. The third specifier is *with peripartum onset*, applied when onset is during pregnancy or within four weeks postpartum. This is the DSM-5-TR route by which a postpartum psychotic episode that clears inside a month is captured; the wider perinatal frame for postpartum psychosis as a psychiatric emergency is developed in the Perinatal/women's mental health and emergency psychiatry notes.

SPECIFIER	WHEN APPLIED	HISTORICAL / LINKED CONCEPT
With marked stressor(s)	**Onset shortly after an event markedly stressful to almost anyone**	Old brief reactive psychosis (DSM-III/III-R); the post-stressor form
Without marked stressor(s)	No identifiable precipitant	Distinguishes reactive from non-reactive episodes
With peripartum onset	**Onset in pregnancy or within four weeks postpartum**	Captures brief postpartum psychotic episodes

The three DSM-5-TR specifiers for brief psychotic disorder; the marked-stressor form is the direct descendant of brief reactive psychosis.

6.3 The ICD-11 near-equivalent: acute and transient psychotic disorder

The counterpart. The ICD-11 acute and transient psychotic disorder (ATPD) is the near-equivalent of brief psychotic disorder: an acute onset of psychotic symptoms that fluctuate rapidly, characteristically with a polymorphic, shifting picture, resolving within a short period. Kaplan & Sadock explicitly link the two, noting that both overlap with the older concept of cycloid psychosis (Kaplan & Sadock 2024). ATPD in turn absorbs the historical European syndromes: the French bouffee delirante and the Scandinavian reactive psychosis tradition (Shorter Oxford 2018).

Where they diverge. The ICD lineage is more elaborate than the single DSM criteria set. ICD-10 split acute and transient psychotic disorders into several types by symptom picture and course, with the maximum duration varying by type: roughly one month for schizophrenia-like symptoms and up to three months for the predominantly delusional form (Tasman 2015). DSM-5, by contrast, uses one criteria set and a single maximum of one month. When mapping in an exam, note that ICD-11 places catatonia transdiagnostically as a separate cross-cutting entity rather than tucking it inside these categories.

TRAP **Do not swap the durations.** Brief psychotic disorder tops out at one month; the predominantly delusional acute and transient psychotic disorder in the ICD lineage may run longer, and schizophreniform runs one to six months. Mismatching these loses the mark.

6.4 Differential from early schizophrenia, and why follow-up is the whole game

The problem of the first episode. The single hardest discrimination is between a true brief psychotic disorder and the opening act of schizophrenia (or a mood disorder with psychotic

features). At presentation they can look identical; only duration and outcome separate them. This is why the diagnosis is provisional in spirit: it is confirmed only in retrospect, once the episode has fully resolved inside a month and the person has been observed to hold their recovery.

Diagnostic instability. The prognosis is genuinely good, but the label is unstable on follow-up: in one clinical series only **23%** of patients given a discharge diagnosis of brief psychotic disorder still held that diagnosis a year later, a proportion having declared a chronic psychotic or mood illness on longer observation (Kaplan & Sadock 2024). The New Oxford Textbook makes the same operational point: individuals who have shown a brief psychotic episode must be monitored to assess the stability of function and the possible emergence of further brief or chronic disorders (New Oxford 2020). Disorder-specific management is short-course antipsychotic cover for the acute episode plus structured follow-up; the antipsychotic drug detail is cross-referenced to the Schizophrenia: management, antipsychotics and adverse effects notes.

TRAP **Not following up.** Treating a resolved brief psychotic episode as closed and discharging without review misses the substantial minority who convert to a chronic psychotic or mood illness; the good prognosis is contingent on surveillance.

under 1 mo	1 to 6 mo	23%
BRIEF PSYCHOTIC DISORDER DURATION	SCHIZOPHRENIFORM DISORDER	RETAINED THE DIAGNOSIS AT 1 YEAR (REST RECLASSIFIED)

WORKED EXAMPLE

A 26-year-old woman, previously well, becomes floridly paranoid and hears accusatory voices ten days after her father's sudden death. She is perplexed, sleepless and frightened; there is no drug use and the physical workup is clean. She is given brief antipsychotic cover and settles completely over three weeks, back to her baseline job and relationships. The provisional formulation is brief psychotic disorder, with marked stressor(s), the post-stressor form. Because a minority declare schizophrenia or a mood illness later, she is not discharged outright but reviewed; if a fresh episode or persistent symptoms emerge, the diagnosis is revised.

INDIA

Acute, short-lived, remitting psychoses after a stressor are a familiar Indian clinical picture and map onto the ICD acute and transient psychotic disorder category used in routine practice; the classic non-affective acute remitting psychosis studied in Indian and other low-and-middle-income-country cohorts sits close to this construct. Treat the episode, then follow up, since a proportion evolve into a chronic illness.

PEARL

Think of brief psychotic disorder as the psychosis that ends before schizophreniform can even begin: same florid positive symptoms, but the clock stops before one month and the person walks out whole. The diagnosis is a promise the follow-up must keep.

GOOD TO REMEMBER

- **Brief psychotic disorder:** sudden onset of one or more positive psychotic symptoms lasting at least a day but less than a month, with full return to premorbid functioning; hold the number: DSM-5-TR F23, one month upper bound.
- **Post-stressor form (with marked stressor(s)):** the psychosis follows an event stressful to almost anyone; the one discriminator is the marked precipitant; the eponymic history is brief reactive psychosis (DSM-III/III-R).
- **With peripartum onset:** onset in pregnancy or within four weeks postpartum; the one number to hold is the four-week postpartum window.
- **Acute and transient psychotic disorder (ICD-11):** the near-equivalent, acute polymorphic rapidly-shifting psychosis; the discriminating feature is the fluctuating polymorphic picture; it subsumes bouffee delirante and cycloid psychosis.
- **Follow-up rule:** good prognosis but diagnostically unstable; the one number is 23% retaining the diagnosis at one year in one series, the rest reclassified to a chronic psychotic or mood illness.

7 · Induced and shared delusional disorder (folie a deux)

A delusion is usually the most private of symptoms, arising and staying inside one mind. The exam-relevant curiosity here is a delusion that **crosses between two people**: a genuinely psychotic, dominant primary transmits a belief to a passive, suggestible secondary who comes to hold it as their own. The entity has collected many names across a century and a half of nosology, and the examiner's favourite hook is precisely that thicket of eponyms and the one management principle that follows from the mechanism.

Why it matters. This is a small, high-yield topic where marks are won on three things: naming the entity correctly across ICD and DSM, attributing the classical folie a deux eponyms without swapping them, and stating the treatment rule (separate the pair) with its diagnostic corollary. The raw descriptive account of delusion as a symptom belongs to the Psychometry, Assessment and Descriptive Psychopathology notes; here the task is the disorder and its discrimination.

7.1 The entity and its many names

One belief, two carriers. The core phenomenon is the transfer of a delusion from a primary, dominant, genuinely psychotic person to a passive, suggestible, usually closely bound and socially isolated secondary who comes to share it (Tasman). Across editions and traditions the same entity is called the **induced delusional** disorder (ICD-10 term), the **shared psychotic** disorder (DSM-IV term), the **shared delusional** disorder, and, in the classical French, the folie a deux (Kaplan & Sadock 2024). Older synonyms include shared paranoid disorder, induced psychosis and double insanity (Kaplan & Sadock 2024).

RULE **Two people, one genuine psychosis.** Only the dominant primary has an authentic, independently generated delusion; the secondary's belief is borrowed and rests on the relationship.

7.2 Nosological placement: ICD-11, DSM-5-TR, ICD-10

Where the codebooks put it. The nosology has drifted, and knowing the current placement is the discriminator. In **ICD-11** the condition no longer has a standalone code: it is folded into

delusional disorder (6A24) as an additional clinical feature, described as "shared or induced delusional disorder", in which one person adopts the delusional belief of another where the two have a strong emotional or situational link (ICD-11 CDDR). In **DSM-5-TR** the discrete category was deleted; the presentation is captured as "delusional symptoms in partner of individual with delusional disorder", coded under other specified schizophrenia spectrum and other psychotic disorder (Kaplan & Sadock 2024). **ICD-10** retained a separate rubric, F24 induced delusional disorder (Shorter Oxford). The wider diagnostic frame for delusional disorder itself is cross-referenced to that topic; the raw phenomenology of the shared delusion is in the Psychometry, Assessment and Descriptive Psychopathology notes.

TRAP **Do not call it a DSM-5 disorder.** DSM-5 and DSM-5-TR deleted the standalone category; ICD-11 also demoted it to a feature of delusional disorder. Only ICD-10 keeps it as a named F24 diagnosis.

7.3 The primary, the secondary and the relationship

An asymmetric pair. The primary (inducer) is typically the older, more intelligent, better educated, dominant partner who carries a genuine psychotic illness, most often schizophrenia or delusional disorder (Tasman). The secondary (induced) is usually more suggestible, more dependent, often less intelligent, more passive or more lacking in self-esteem, and frequently predisposed by personality traits or social circumstance (Tasman). The two are closely associated over a long period, live together, and are relatively or completely isolated from outside social and cultural correction, which removes the reality-testing a wider circle would supply (Tasman). Almost all cases occur within a single family, the commonest dyads being sister-sister, husband-wife and mother-child (Tasman). The content is usually persecutory or hypochondriacal and, being borrowed, tends to stay within the realm of possibility rather than becoming as bizarre as delusions in schizophrenia (Tasman).

7.4 The classical variants

Four named forms, one entity. The historical literature subdivides the syndrome by how the shared belief arose. Hold the two the sources anchor firmly, and recognise the full quartet: **folie imposee**, **folie communiquee**, **folie induite** and **folie simultanee**.

folie imposee

The common, prototypical form: the dominant primary imposes the delusion on a healthy, suggestible secondary, whose belief typically fades on separation (Tasman).

folie communiquee

The delusion is communicated to the secondary after a period of resistance, and the secondary then holds it independently, so that it may persist even after separation (Baillarger's original 1860 description, Tasman).

folie induite

An already-psychotic secondary adds new delusions induced by the dominant partner to their own pre-existing ones.

folie simultanee

Similar delusional systems develop independently and at the same time in two closely associated, often already predisposed people, rather than one being transferred from the other (Tasman).

When the shared system extends beyond a dyad the count is named directly: folie a trois, folie a quatre, folie a cinq, and folie a famille when a whole family is involved; these are rare (Tasman).

MNEMONIC

I C I S: Imposed, Communicated, Induced, Simultaneous

The four classical variants in one string. IMPOSED = healthy secondary, resolves on separation (the exam default); COMMUNICATED = accepted after resistance, may persist; INDUCED = added onto an already psychotic secondary; SIMULTANEOUS = two predisposed people, no true transfer.

7.5 Management: separation, then treat the primary

The pivot is the pair. The single therapeutic and diagnostic manoeuvre is **separation** of the pair. On separating the two, the secondary's delusion frequently resolves, and this resolution both treats the secondary and retrospectively confirms the diagnosis (ICD-11 CDDR; Tasman). The primary does not remit on separation and needs treatment in the usual way for their underlying psychotic illness, the antipsychotic detail of which is cross-referenced to the Schizophrenia: management, antipsychotics and adverse effects notes. Resolution in the secondary on separation is frequent but not invariable, and is least reliable in the communiquee and induite forms where the belief has become independently rooted (Tasman). Supportive work with the secondary during separation, aimed at rebuilding self-esteem and reality contact, supports the recovery.

RULE **Separation is both diagnostic and therapeutic for the secondary.** The delusion that lifts when the pair is parted was never independently generated; the manoeuvre proves and treats the induced case in one move.

TRAP **Do not treat both members as independently and equally psychotic.** Loading the passive secondary with the same long-term antipsychotic plan as the primary misreads a borrowed belief as an autonomous psychosis; separate first, then treat the primary in the usual way.

HOLD THIS

Separate the pair: the secondary's borrowed delusion usually lifts on separation (which both diagnoses and treats them), while the dominant, genuinely psychotic primary is treated in the usual way and does not remit on separation.

INDIA

In Indian family psychiatry the closely bound, co-resident, relatively isolated multigenerational household is exactly the substrate in which induced delusional disorder is described, and the commonest reported dyads, mother-child and husband-wife, map onto that structure. Separation is harder to arrange where the pair share a single home and depend on each other economically, so admission of the secondary, or of the primary, is often the practical route to the therapeutic separation.

PEARL

The bizarreness of the belief is a quiet clue: an induced delusion tends to stay within the realm of the possible (a persecution, an infidelity, a hypochondriacal fear), because a suggestible mind borrows a plausible story more readily than a bizarre one. A frankly bizarre, incoherent delusion in the secondary should push you back toward an independent primary psychosis rather than a shared one.

FEATURE	PRIMARY (INDUCER)	SECONDARY (INDUCED)
Delusion origin	**Authentic, independently generated**	**Borrowed from the primary**
Underlying illness	Genuine psychosis, often schizophrenia or delusional disorder	Usually none; often personality vulnerability
Role in the dyad	Dominant, older, more able	Passive, suggestible, dependent
Effect of separation	Delusion persists; needs treatment	**Delusion frequently resolves**
Management	Treat the underlying psychosis in the usual way	Separate first; support; medicate only if it fails to resolve

The asymmetry of the pair drives the whole management: the discriminator is what happens on separation.

GOOD TO REMEMBER

- **Folie a deux / shared psychotic disorder / induced delusional disorder:** transfer of a delusion from a dominant, genuinely psychotic primary to a passive, suggestible, closely bound and socially isolated secondary. Discriminator: only the primary has an authentic psychosis. Number/eponym to hold: Lasegue and Falret, 1877.
- **folie communiquee:** the delusion is communicated to the secondary after resistance and then held independently, so it may persist after separation. Eponym: Jules Baillarger, 1860.
- **folie imposee:** the common form, a healthy secondary onto whom the belief is imposed; resolves on separation. Hold: this is the exam default variant.
- **folie simultanee:** similar delusions arise independently and simultaneously in two predisposed, closely associated people; no true transfer. Hold: not a genuine induction.
- **folie induite:** an already-psychotic secondary acquires additional delusions induced by the dominant partner. Hold: the secondary is not delusion-free at baseline.
- **Nosology:** ICD-10 F24 induced delusional disorder (standalone); ICD-11 a feature of delusional disorder (no separate code); DSM-5-TR deleted, coded as delusional symptoms in partner of individual with delusional disorder. Hold: only ICD-10 keeps it as a named diagnosis.
- **Management:** separation of the pair is both diagnostic and therapeutic for the secondary; treat the primary's psychosis in the usual way. Hold: the secondary's delusion frequently, though not invariably, resolves on separation.

8 · Postpartum psychosis and the late-onset psychoses

Two psychotic presentations are bound to a life stage rather than to a diagnosis. **Postpartum psychosis** erupts in the days after a delivery and is one of the true psychiatric emergencies of the discipline; the **late-onset** and **very-late-onset** schizophrenia-like psychoses declare themselves in middle and old age, carry the historical burden of paraphrenia, and hide a neurodegenerative or organic cause behind an apparently functional picture. For the exam they are a pair of high-yield edge cases at either end of adult life, each with its own numbers, its own one discriminator, and its own classic trap.

Abrupt postpartum onset
Psychosis
Urgent specialist care
Mood symptoms
Mother–infant safety

Fig 10.6 Postpartum psychosis is an abrupt, severe perinatal mood-psychosis presentation requiring urgent specialist assessment, coordinated family support and protection of both mother and infant.

Why they earn a place. Postpartum psychosis is where a psychotic-disorders answer meets emergency psychiatry: get the two-week onset window, the bipolar link, and the protect-mother-and-baby imperative right. The late-onset psychoses are where a psychosis answer meets old-age psychiatry: get the international-consensus split at 40 and 60, the paraphrenia lineage, and the duty to exclude a dementing or organic process. The raw descriptive definitions of the delusions themselves are cross-referenced to the Psychometry, Assessment and Descriptive Psychopathology notes; the disorder schizophrenia itself is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes and is not re-taught here.

8.1 Postpartum psychosis: the acute, delirium-like, often affective psychosis of the early puerperium

The entity. Postpartum psychosis, historically puerperal psychosis, is a new onset of a severe psychotic episode in the immediate puerperium. In around **90%** of cases the onset is within the first **two weeks** of delivery (New Oxford 2020). The picture is characteristically affective, most often a manic or mixed episode with psychotic features, and it is strongly associated with bipolar

I disorder (APA 2022; Kaplan & Sadock 2024). Kaplan & Sadock treat postpartum psychosis as, in effect, a subtype of bipolar disorder.

The delirium-like quality. What sets it apart from an ordinary manic relapse is its fluctuating, delirium-like texture: confusion, perplexity and a rapidly shifting, kaleidoscopic symptom picture that can escalate within hours (New Oxford 2020). The Companion notes that perplexity is seen par excellence in puerperal psychosis (Companion 2010). This is why the classic bedside advice is to exclude an organic cause and treat the presentation as an emergency, not to assume a benign course. The raw phenomenology of the perplexity and the delusions is cross-referenced to the Psychometry, Assessment and Descriptive Psychopathology notes.

RULE **Postpartum psychosis is a psychiatric emergency: protect mother and baby, and admit.** Because of the risk of suicide and of infanticide, urgent assessment and, in the majority of cases, admission (ideally to a mother-and-baby unit) are the default.

HOLD THIS

Postpartum psychosis is an acute, fluctuating, delirium-like, usually bipolar-spectrum psychosis with onset within the first two weeks in 90% of cases; it is a psychiatric emergency because of suicide and infanticide risk, so admit and safeguard the infant.

8.2 Why it is a psychiatric emergency: suicide and infanticide

The danger. Postpartum psychosis is a **psychiatric emergency** because it carries an increased risk of both suicide and infanticide (New Oxford 2020). Suicide is a leading cause of maternal death in the perinatal period, and infanticide is more commonly associated with postpartum psychosis than with postpartum depression (Kaplan & Sadock 2024). Roughly **half** of episodes are the woman's first contact with psychiatric services and so could not have been predicted, which is exactly why prompt assessment matters (New Oxford 2020). The wider perinatal frame (maternity blues, postnatal depression, the perinatal service model) is developed in the Perinatal/women's mental health and emergency psychiatry notes; postpartum psychosis is owned here as a psychotic disorder.

TRAP **Treating it as postnatal blues.** Reassuring a confused, perplexed, psychotic new mother and sending her home misreads a psychiatric emergency; the suicide and infanticide risk demands urgent assessment and usually admission.

8.3 Risk factors: bipolar disorder, a previous postpartum psychosis, primiparity, sleep loss

The high-risk profile. The dominant risk factor is a personal history of a **bipolar disorder**: a woman with bipolar disorder has about a **1 in 5** chance of postpartum psychosis with each delivery, and a previous episode of postpartum psychosis confers a risk in excess of **1 in 2** for the next (New Oxford 2020). A family history of postpartum psychosis roughly doubles the risk in women who already have bipolar disorder. **Primiparity** is the most robust obstetric risk factor identified, and sleep loss around the delivery is a recognised precipitant (Sharma 2003; New Oxford 2020). The risk of a manic episode in the first four weeks postpartum is dramatically raised (New Oxford 2020).

within 2 wk	1 in 5	over 1 in 2	1 to 2 / 1000
ONSET IN 90% OF POSTPARTUM PSYCHOSIS	RISK PER DELIVERY WITH BIPOLAR DISORDER	RISK AFTER A PREVIOUS POSTPARTUM PSYCHOSIS	INCIDENCE PER DELIVERIES

8.4 Management principles: urgent assessment, admission, and safeguarding the infant

The disorder-specific pointers. Management rests on urgent assessment and, in the majority, admission, ideally to a mother-and-baby unit so that mother and infant are kept together and the baby is safeguarded (New Oxford 2020). Pharmacological treatment is the mainstay: antipsychotics and mood stabilisers, with a stepped approach of a benzodiazepine, then a dopamine antagonist or partial agonist, then lithium, achieving remission in the large majority; lithium outperforms an antipsychotic alone for maintenance (New Oxford 2020). Electroconvulsive therapy is used, and can be strikingly rapid, in severe, treatment-resistant or life-threatening episodes; the ECT technique itself is cross-referenced to the ECT and neurostimulation notes, and the antipsychotic and mood-stabiliser drug detail to the Schizophrenia: management, antipsychotics and adverse effects notes. Safeguarding the infant runs in parallel with treating the mother.

WORKED EXAMPLE

A 28-year-old primiparous woman with a prior diagnosis of bipolar I disorder becomes elated, overactive and sleepless four days after delivery, then over 48 hours becomes perplexed, disoriented and convinced the baby has been swapped. The picture fluctuates hour to hour. She is treated as a psychiatric emergency: urgent assessment, exclusion of an organic cause, admission to a mother-and-baby unit with the infant safeguarded, and antipsychotic plus mood-stabiliser cover, with ECT held in reserve for a severe non-response. This is postpartum psychosis on a bipolar substrate, not the maternity blues.

INDIA

Acute, fluctuating postpartum psychoses are a familiar Indian clinical picture and are commonly managed on general psychiatry wards, since dedicated mother-and-baby units are scarce in Indian practice; keeping the mother and infant together and safeguarding the baby therefore has to be arranged within general adult inpatient care. ECT is available and used in Indian psychiatry for severe or treatment-resistant postpartum psychosis where a rapid response is needed.

GOOD TO REMEMBER

- **Postpartum psychosis (puerperal psychosis):** an acute, fluctuating, delirium-like, usually affective (bipolar-spectrum) psychosis of the early puerperium; the one discriminator is the confused, perplexed, rapidly shifting picture; hold the number, onset within two weeks in 90% of cases.
- **Emergency status:** a psychiatric emergency because of suicide and infanticide risk; the one imperative is admit and safeguard the infant; hold that infanticide is more linked to postpartum psychosis than to postpartum depression.
- **Risk factors:** bipolar disorder, a previous postpartum psychosis, primiparity, sleep loss; the biggest single number is a 1 in 5 risk per delivery with bipolar disorder, rising above 1 in 2 after a prior postpartum psychosis.

8.5 The late-onset psychoses: the international-consensus split at 40 and 60

The nosology. An international consensus (Howard, Rabins, Seeman & Jeste 2000) recommended that schizophrenia with onset between ages **40 and 60** be termed late-onset schizophrenia, and psychosis with onset after age **60** be termed very-late-onset schizophrenia-like psychosis, that is, a very late onset variant (Kaplan & Sadock 2024). The **late-onset schizophrenia-like** label thus spans the middle-aged and elderly cases that older classifications handled poorly. The very-late-onset group is the modern home of the old concept of paraphrenia, Kraepelin's term for a paranoid psychosis of middle and later life that was separated from dementia praecox because it lacked the emotional and volitional deterioration, later revived by Roth as late paraphrenia (Shorter Oxford 2018; Companion 2010). ICD-11 keeps a single schizophrenia category rather than a separate age-defined disorder; note that ICD-11 additionally places catatonia transdiagnostically as a cross-cutting entity, a high-yield nosology point developed with the catatonia material.

Epidemiology and the female preponderance. Late-onset schizophrenia is commoner in women, who are affected between **2 and 10** times more often than men, a robust finding often linked to the loss of estrogen-mediated dopaminergic protection at menopause (Kaplan & Sadock 2024). The International Late-Onset Schizophrenia Group judged late-onset schizophrenia to be broadly a neurodevelopmental disorder differing from early-onset disease more in degree than in kind, whereas very-late-onset schizophrenia-like psychosis showed features (more brain abnormalities and neuropsychological deficits) suggesting a neurodegenerative component (Kaplan & Sadock 2024).

RULE **Split by the two ages.** Onset 40 to 60 is late-onset schizophrenia; onset after 60 is very-late-onset schizophrenia-like psychosis (the old paraphrenia); both are commoner in women.

8.6 The clinical picture: persecutory and partition delusions, preserved affect and cognition

The phenomenology. The late-onset picture is dominated by prominent, well-organised **persecutory** delusions and by partition delusions, the conviction that people, objects or radiation can pass through impermeable structures such as walls, ceilings, doors or windows (Kaplan & Sadock 2024). Hallucinations are common and may be multimodal (auditory, visual, tactile, olfactory). By contrast, formal thought disorder and negative symptoms are infrequent, and affect and cognition are relatively preserved, which is precisely why some doubt whether very-late-onset psychosis belongs under schizophrenia at all (Kaplan & Sadock 2024; Tasman 2015). The raw descriptive definition of the partition delusion is cross-referenced to the Psychometry, Assessment and Descriptive Psychopathology notes.

The predisposing background. The late-onset psychoses are classically associated with **sensory impairment** (especially deafness and visual loss), social isolation, and premorbid schizoid or paranoid personality traits; marriage and fertility rates are lower and social isolation greater than in the general population (Kaplan & Sadock 2024). Cognitive dysfunction, where present, affects frontal-subcortical domains, and, importantly, retention of information is usually preserved, in

contrast to the retention (storage) deficit of a cortical dementia like Alzheimer's disease (Kaplan & Sadock 2024).

FEATURE	LATE-ONSET SCHIZOPHRENIA (40 TO 60)	VERY-LATE-ONSET SCHIZOPHRENIA-LIKE PSYCHOSIS (AFTER 60)
Historical label	Late-onset schizophrenia	**Paraphrenia / late paraphrenia**
Sex	Female preponderance	**Female preponderance, more marked**
Delusions	Prominent persecutory	**Persecutory plus partition delusions**
Thought disorder / negative symptoms	Relatively infrequent	**Infrequent (fuels doubt about the diagnosis)**
Affect and cognition	Relatively preserved	Preserved, but organic cause must be excluded
Postulated mechanism	Largely neurodevelopmental (degree, not kind)	**Possible neurodegenerative component**

The international-consensus split: late-onset schizophrenia versus the very-late-onset schizophrenia-like psychosis that inherits the paraphrenia concept.

8.7 The imperative: exclude a neurodegenerative or organic cause

The discriminator that matters most. Late-life psychotic symptoms can arise de novo or be driven by dementia, delirium, medical illness, polypharmacy, substance misuse or sensory deficit; secondary psychosis (attributable to another medical or neurological disorder) accounts for a large share of late-life cases (Kaplan & Sadock 2024). A very-late-onset presentation in particular must be worked up as potentially the herald of a dementing process: a proportion convert to dementia on follow-up, so a confident diagnosis of very-late-onset schizophrenia-like psychosis can be made only after a sufficient observation period (Kaplan & Sadock 2024). Disorder-specific treatment is low-dose antipsychotic cover (the starting dose is a fraction of the usual adult dose, with careful attention to older-age adverse effects), plus correcting sensory deficits and social isolation; the antipsychotic drug detail is cross-referenced to the Schizophrenia: management, antipsychotics and adverse effects notes.

TRAP **Missing an emerging dementia.** Labelling a first psychosis after 60 as very-late-onset schizophrenia-like psychosis without a neurocognitive workup and follow-up misses the organic or neurodegenerative cause hiding behind it.

PEARL

Preserved retention is the tell: in very-late-onset psychosis the patient can still lay down and hold new memories, so a rapidly failing memory should push you towards a dementia, not towards paraphrenia. Deafness, isolation and a suspicious premorbid personality complete the classic late-onset triad.

GOOD TO REMEMBER

- **Late-onset schizophrenia:** schizophrenia with onset between 40 and 60; the discriminator is the age band with prominent persecutory delusions and relatively preserved affect and cognition; hold the international-consensus split at 40 (Howard et al. 2000).
- **Very-late-onset schizophrenia-like psychosis:** psychosis with onset after 60, the old paraphrenia; the discriminator is partition delusions with a possible neurodegenerative component; hold the number, onset after 60.
- **Paraphrenia:** Kraepelin's paranoid psychosis of later life spared the emotional and volitional decline of dementia praecox, revived by Roth as late paraphrenia; the one feature is well-organised persecutory delusions with preserved personality.
- **Partition delusion:** the belief that people, objects or radiation pass through walls, doors or windows; the discriminating context is very-late-onset schizophrenia-like psychosis; the one association is late-life onset.
- **Associations:** female sex (2 to 10 times commoner), sensory impairment, social isolation, paranoid or schizoid premorbid traits; the imperative is to exclude a neurodegenerative or organic cause.

9 · Attenuated psychosis syndrome

The **attenuated psychosis syndrome** is DSM-5-TR's attempt to give the clinical high-risk state a name inside the manual: sub-threshold positive symptoms, present often enough and distressing enough to bring a young person to attention, but with reality testing still relatively intact and the person still able to doubt the experience. It is not a full psychotic disorder and, importantly, it is not a formal diagnosis: it sits in Section III among the conditions for further study. For the exam it is a small, high-yield item precisely because it is the point where the **at-risk mental state** becomes a candidate category, and where the false-positive problem is the reason it stops short of the main manual.

Why it earns a place. It formalises the prodrome or at-risk mental state that the schizophrenia course chapter describes, and it forces the discrimination examiners want: an at-risk state named for study is not established schizophrenia. The prodrome and the wider at-risk-mental-state material, along with the schizophrenia course it belongs to, are owned by the Schizophrenia: aetiology, phenomenology, classification and course notes and are not re-derived here; this section is deliberately short.

9.1 The DSM-5-TR condition for further study: attenuated, sub-threshold, insight relatively intact

Core definition. Attenuated psychosis syndrome is a DSM-5-TR **condition for further study** (Section III), characterised by **attenuated psychosis**: delusion-like ideas, unusual perceptual experiences or disorganised speech that are psychosis-like but below the threshold of a full psychotic symptom, with reality testing still relatively intact and the person generally still able to appreciate that the perceptions are altered (APA 2022). The symptoms are less severe and more transient than in a psychotic disorder, and skepticism about them can be induced. In effect it is the at-risk mental state formalised into a candidate category (Kaplan & Sadock 2024).

The operational criteria. Criterion A requires at least one of three attenuated symptoms in relatively intact reality testing: attenuated delusions, attenuated hallucinations, or attenuated disorganized speech. The symptom must have been present **at least once per week for the past**

month (Criterion B) and must have **begun or worsened in the past year** (Criterion C). It must be sufficiently distressing or disabling to warrant clinical attention (Criterion D), not better explained by another mental disorder or a substance or medical cause (Criterion E), and the criteria for any psychotic disorder must never have been met (Criterion F) (APA 2022).

RULE **It names the at-risk mental state, but it is not a formal diagnosis.** Attenuated psychosis syndrome is a DSM-5-TR condition for further study, a candidate label for the clinical high-risk state, not an established Section II diagnosis.

HOLD THIS

Attenuated psychosis syndrome = sub-threshold delusion-like ideas, unusual perceptions or disorganised speech with reality testing relatively intact, at least once a week for the past month and worsening in the past year, distressing enough to warrant clinical attention; it is the at-risk mental state as a DSM-5-TR condition for further study, not a formal diagnosis.

9.2 Why it stays "for further study": only a minority transition, so false-positive and stigma risks dominate

The transition problem. The syndrome remains a condition for further study rather than a formal diagnosis because only a minority of those identified go on to a full psychotic disorder. Modern meta-analytic clinical-high-risk data put transition to a full psychotic disorder at roughly **11% at 6 months**, **15% at 1 year** and **20% at 2 years**, with the older ultra-high-risk cohorts reporting higher rates of around a third at one year; across all of them most people meeting criteria never convert, the non-converting group generally improving in symptoms over time (Kaplan & Sadock 2024, citing Fusar-Poli et al.). The at-risk mental state is detected with structured measures: the Comprehensive Assessment of At-Risk Mental State (CAARMS) and the Structured Interview for Psychosis-Risk Syndromes (SIPS) (New Oxford 2020; Kaplan & Sadock 2024).

The cost of a false positive. Because most identified individuals will not become psychotic, formalising the label risks over-diagnosis: labelling large numbers of help-seeking adolescents as pre-psychotic, exposing them to stigma and to potentially unnecessary antipsychotic treatment. That false-positive and stigma calculus is exactly why DSM-5-TR held the syndrome back in Section III for study rather than promoting it to a full diagnosis. Management is therefore watchful clinical attention and monitoring, not routine antipsychotic prescription; where drug treatment is considered, the antipsychotic detail is cross-referenced to the Schizophrenia: management, antipsychotics and adverse effects notes.

TRAP **Labelling an at-risk state as established schizophrenia.** Calling a person with attenuated, sub-threshold symptoms "schizophrenic" mislabels a candidate at-risk state as a lifelong illness that most of them will never develop.

~15% at 1 yr	Section III	most
TRANSITION TO PSYCHOSIS (ABOUT 20% AT 2 YEARS)	DSM-5-TR CONDITION FOR FURTHER STUDY, NOT A FORMAL DIAGNOSIS	DO NOT CONVERT; NON-CONVERTERS GENERALLY IMPROVE

WORKED EXAMPLE

A distressed 17-year-old is brought in with a few months of intermittent suspiciousness that people are talking about him, fleeting shadow-like visual experiences, and speech that his teachers find vague and off-track. He can, when gently challenged, entertain that there might be another explanation and does not act on the ideas. Symptoms are present several times a week, began this year, and are impairing his schooling. Reality testing is relatively intact and full psychotic-disorder criteria have never been met. This fits attenuated psychosis syndrome as a condition for further study: he is monitored and supported, not diagnosed with schizophrenia and not started on an antipsychotic by reflex.

INDIA

Dedicated clinical-high-risk and early-intervention services are still uncommon in routine Indian practice, so young people with attenuated, sub-threshold symptoms are usually seen once frankly psychotic rather than in a formal at-risk clinic. The practical lesson is the same as the syndrome's own caution: hold the at-risk label lightly, monitor over time, and avoid committing an adolescent to a schizophrenia diagnosis, and to long-term antipsychotics, on sub-threshold symptoms alone.

GOOD TO REMEMBER

- **Attenuated psychosis syndrome:** sub-threshold delusion-like ideas, unusual perceptual experiences or disorganised speech with reality testing relatively intact, distressing enough to warrant clinical attention; the one discriminator is preserved insight with symptoms below full psychotic threshold; hold the number: DSM-5-TR Section III condition for further study, symptoms at least once a week for the past month.
- **At-risk mental state / clinical high-risk:** the construct the syndrome formalises; the discriminating feature is help-seeking with sub-threshold symptoms not yet meeting psychotic-disorder criteria; the number to hold is a minority transition (about 15% at one year, 20% at two years), with most never converting.
- **Why "for further study":** only a minority transition, so the false-positive and stigma risks of formalising the label keep it out of the main diagnostic manual; the one point is that it is not a formal diagnosis.

10 · Differentiate: the schizophrenia-spectrum differential

Why this matters. This is the payoff of the whole primary-psychosis band: the examiner does not hand you a label, they hand you a presentation and ask which spectrum diagnosis it is. Every one of these disorders can look identical on a single afternoon of cross-section, a patient who is deluded, hallucinating and functioning poorly. What separates them is almost never the snapshot; it is the **longitudinal architecture**, chiefly two axes: how long the psychosis has run, and how much mood has been loaded onto it. Hold those two axes and the spectrum falls into an orderly grid; forget them and you will misclassify on the strength of a single interview.

This topic does not re-teach any of these disorders. Schizophrenia itself, its phenomenology, aetiology, criteria and course, is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes; the raw descriptive definitions of the delusions live in the Psychometry, Assessment and Descriptive Psychopathology notes; the mood-episode criteria that

schizoaffective leans on are cross-referenced to the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes; and the drug detail belongs to the Schizophrenia: management, antipsychotics and adverse effects notes. Here we do one thing: we **distinguish** the members of the spectrum from one another, keyed on the single discriminator for each pairing.

10.1 The two master axes: duration and mood-loading

Almost the entire spectrum resolves onto two continuous variables. The first is **duration of psychosis**: the DSM-5 ladder runs less than **one month** (brief psychotic disorder), **one to six months** (schizophreniform disorder), and more than **six months** (schizophrenia), with the ICD-11 threshold for schizophrenia set at **one month** or longer (Kaplan & Sadock 2024, DSM-5-TR 2022, ICD-11 CDDR). The second is **mood-loading**: how much of the illness is occupied by a full mood episode, and whether any psychosis ever runs in the absence of a prominent mood episode. Schizoaffective disorder, mood-with-psychosis and schizophrenia are separated almost entirely on this second axis. Learn to place a case on both axes before you reach for a name.

RULE **Duration and mood-loading are the master discriminators across the spectrum.** Duration sorts the short-course psychoses (brief, schizophreniform, schizophrenia); mood-loading sorts schizoaffective from mood-with-psychosis and from schizophrenia. Place the case on both axes first, then name it.

TRAP **Letting a cross-sectional snapshot of psychosis override the longitudinal criteria.** A single florid interview cannot distinguish brief psychotic disorder, schizophreniform disorder, schizophrenia or an acute mood episode with psychosis; only the course over time can. Diagnosing from the snapshot is the classic spectrum error.

10.2 Schizoaffective vs mood-with-psychosis vs schizophrenia: the mood-loading axis

This is the three-way discrimination that turns entirely on mood-loading, and it is the single highest-yield pairing on the spectrum. Two rules do the work (DSM-5-TR 2022, Kaplan & Sadock 2024). First, schizoaffective disorder requires a period of at least **two weeks** of delusions or hallucinations in the absence of a prominent mood episode over the lifetime of the illness (Criterion B): this is the two-weeks-of-psychosis-without-a-prominent-mood-episode rule, and it is what separates schizoaffective disorder from mood-with-psychosis, where psychosis is confined to the mood episode and never runs alone. Second, schizoaffective disorder requires that mood symptoms are present for the majority of the total duration of the active and residual illness (Criterion C): this mood-for-the-majority requirement is what separates it from schizophrenia, which carries no prominent mood for the majority of its course.

So the logic is a fork. If psychosis *only ever* appears inside a mood episode, it is **mood-with-psychosis** (a mood disorder with psychotic features), and its mood-episode criteria are set out in the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes. If psychosis runs for at least two weeks *without* a prominent mood episode, and mood nonetheless occupies the majority of the illness, it is schizoaffective disorder. If psychosis dominates and mood is a minor, non-majority accompaniment, it is schizophrenia. The two-week gate excludes

mood-with-psychosis below; the majority rule excludes schizophrenia above; schizoaffective disorder lives only in the narrow band where both hold.

10.3 Delusional disorder vs paranoid schizophrenia: the breadth axis

Here duration is not the discriminator (both are chronic); breadth of the psychosis is. Delusional disorder is defined by one or more well-systematised, long-lasting delusions on a single circumscribed theme, classically *non-bizarre*, with the rest of mental life and personality relatively intact and social and occupational functioning largely preserved (New Oxford Textbook 2020, Kaplan & Sadock 2024, ICD-11 CDDR). What is *absent* is what makes the diagnosis: no persistent prominent hallucinations, no formal thought disorder or disorganisation, no negative symptoms, no experiences of influence or passivity, no general functional decline. The contrast with **paranoid schizophrenia** is exactly this breadth. Schizophrenia brings the wider syndrome, prominent hallucinations, disorganised thinking and behaviour, negative symptoms and functional deterioration, on top of the delusions; if those broader features are present, the ICD-11 boundary text is explicit that a diagnosis of schizophrenia is made instead of delusional disorder (ICD-11 CDDR). Two further pointers: delusional disorder comes to attention at a later age (onset generally in the mid- to late-30s) and shows far less deterioration over time than schizophrenia (Kaplan & Sadock 2024). Hallucinations may occur in delusional disorder if they are congruent with the delusional theme and not persistent; persistent, prominent hallucinations push the diagnosis over into schizophrenia.

RULE **One theme, preserved function equals delusional disorder; the wider syndrome equals schizophrenia.** A single-theme non-bizarre delusion with otherwise intact personality and function is delusional disorder; add prominent hallucinations, disorganisation, negative symptoms or functional decline and it becomes paranoid schizophrenia.

10.4 ATPD vs brief psychotic disorder vs schizophreniform: the duration ladder

These three are the short-course psychoses, and the discrimination is chiefly the duration ladder plus, for ATPD, a distinctive onset and course. In DSM-5-TR the ladder is clean: brief psychotic disorder lasts at least one day but less than **one month** with eventual full return to premorbid functioning; schizophreniform disorder lasts at least **one month but less than six months** and is otherwise identical to schizophrenia (a diagnosis of exclusion in time, made provisional if recovery has not yet occurred); and beyond six months with functional impairment the diagnosis becomes schizophrenia (DSM-5-TR 2022, Kaplan & Sadock 2024). The ICD-11 counterpart to the acute end is acute and transient psychotic disorder (ATPD, 6A23), and its signature is not merely brevity but the *quality* of the episode: an abrupt onset progressing from a non-psychotic to a clearly psychotic state within **two weeks**, with symptoms that fluctuate rapidly in intensity and type (the content of delusions and hallucinations shifting even on a daily basis), an absence of negative symptoms, a duration that does not exceed **three months** (most often lasting from a few days to one month), and a characteristically good outcome with full recovery (ICD-11 CDDR). This rapidly-shifting, abrupt-onset, short-and-remitting picture is the ATPD fingerprint; the older Scandinavian reactive-psychosis and cycloid-psychosis concepts feed into it.

Two boundary points the examiner likes. A case that meets all schizophrenia requirements but has lasted less than the one-month threshold, with no previous history of schizophrenia, is *not* ATPD in ICD-11: it is assigned to other specified primary psychotic disorder, because ATPD is defined by its fluctuating acute quality, not merely by being schizophrenia-cut-short (ICD-11 CDDR). And because ICD-11 sets the schizophrenia duration at one month, many cases that DSM-5 would call schizophreniform disorder are simply classified as schizophrenia in ICD-11; there is no schizophreniform category in ICD-11 (Kaplan & Sadock 2024).

under 1 mo	1 to 6 mo	up to 3 mo	within 2 wk
BRIEF PSYCHOTIC DISORDER (DSM-5-TR)	SCHIZOPHRENIFORM DISORDER (DSM-5-TR)	ATPD, DOES NOT EXCEED THREE MONTHS (ICD-11)	ATPD ONSET, NON-PSYCHOTIC TO PSYCHOTIC (ICD-11)

10.5 The interleaved spectrum differential

The grid below interleaves all the spectrum members onto the two master axes and names, for each, the one discriminator that settles the pairing. Read it as a single decision tool: place the case by presentation, duration and mood-loading, then read off the discriminator column.

DISORDER	PRESENTATION	DURATION	MOOD-LOADING	THE ONE DISCRIMINATOR
Brief psychotic disorder	Acute florid psychosis, often with a stressor; full return to premorbid function	1 day to under 1 month	None required	**Resolves in under one month with full recovery**
ATPD (ICD-11 6A23)	Abrupt onset, rapidly fluctuating delusions or hallucinations shifting even daily; no negative symptoms; good outcome	Onset within 2 weeks; does not exceed 3 months (often days to 1 month)	Variable, mood may colour the picture but is not the axis	**Abrupt onset plus rapidly shifting content plus short remitting course**
Schizophreniform disorder	Identical to schizophrenia in symptoms; functional decline not required	1 to 6 months	Mood-with-psychosis and schizoaffective ruled out	**Duration one to six months (provisional if recovery not yet occurred)**
Schizophrenia	Full syndrome: delusions, hallucinations, disorganisation, negative symptoms, functional decline	6 months or more (ICD-11: 1 month or more)	No prominent mood for the majority of the illness	**Duration over 6 months (owned by the schizophrenia notes)**

DISORDER	PRESENTATION	DURATION	MOOD-LOADING	THE ONE DISCRIMINATOR
Schizoaffective disorder	Full mood episode concurrent with schizophrenia-criterion psychosis	Chronic	Mood for the majority; at least 2 weeks of psychosis without a prominent mood episode	**Two weeks of psychosis without a prominent mood episode, and mood for the majority**
Mood-with-psychosis	Delusions or hallucinations occurring only within a mood episode	Duration of the mood episode	Maximal, psychosis is confined to the mood episode	**Psychosis only within mood episodes, never for two weeks alone**
Delusional disorder	Single-theme, well-systematised, non-bizarre delusion; personality and function preserved	Chronic, at least 3 months (ICD-11); later onset (mid to late 30s)	Low, mood not the axis	**One non-bizarre theme with preserved function and no wider syndrome**
Paranoid schizophrenia	Persecutory delusions plus prominent hallucinations, disorganisation, negative symptoms, decline	6 months or more	No prominent mood for the majority	**The wider syndrome and functional decline on top of the delusions**

The spectrum keyed on two axes: duration sorts the short-course psychoses; mood-loading sorts schizoaffective from mood-with-psychosis and schizophrenia; breadth sorts delusional disorder from paranoid schizophrenia.

10.6 Working the differential in practice

The examiner rewards a method, not a lucky guess. Take any psychotic presentation and ask, in order: has an organic or substance cause been excluded (a detailed history, examination and, where indicated, toxicology and imaging, since a rapid onset in someone with a substance history should raise substance-induced psychosis)? How long has the psychosis run in its full form (the duration ladder)? Does any psychosis run in the absence of a prominent mood episode, and does mood occupy the majority of the illness (the mood-loading fork)? Is the psychosis a single circumscribed non-bizarre theme with preserved function, or the wider syndrome with decline (the breadth axis)? Is the onset abrupt with rapidly shifting content and a short remitting course (the ATPD fingerprint)? Answer those five in sequence and the spectrum diagnosis is usually forced. The one thing that must never drive the answer is the cross-sectional snapshot alone.

COMMON TRAP

Do not diagnose schizoaffective disorder simply because psychosis and a mood episode co-occur. Concurrent psychotic and mood symptoms are equally compatible with a mood disorder with psychotic features; the diagnosis turns on the two-weeks-of-psychosis-without-a-prominent-mood-episode rule (Criterion B) and the mood-for-the-majority rule (Criterion C). Without the two-week window this is mood-with-psychosis, not schizoaffective disorder.

INDIA

Acute, abrupt-onset, short-course psychoses of the ATPD type are a well-recognised and relatively common presentation in Indian practice, frequently precipitated by an acute stressor and carrying a good outcome, which fits the classic acute-and-transient picture; longitudinal follow-up remains essential because a proportion later declare themselves as schizophrenia or a mood disorder. Delusional disorder is similarly encountered as a late-onset, single-theme, function-preserving condition. Verify any local prevalence claim against a primary source before quoting a figure.

MNEMONIC

DURATION, MOOD, BREADTH

Three questions settle almost the whole spectrum. DURATION sorts the short-course psychoses (under one month brief, one to six months schizophreniform, over six months schizophrenia). MOOD-loading sorts schizoaffective (two weeks of psychosis without a prominent mood episode, plus mood for the majority) from mood-with-psychosis (psychosis only within mood episodes) and schizophrenia (no prominent mood for the majority). BREADTH sorts delusional disorder (one theme, preserved function) from paranoid schizophrenia (the wider syndrome, decline).

HOLD THIS

Never diagnose the spectrum from a cross-sectional snapshot: duration (the under-one-month / one-to-six-month / over-six-month ladder) and mood-loading (two weeks of psychosis without a prominent mood episode, plus mood for the majority) are the master discriminators, and breadth (one non-bizarre theme with preserved function versus the wider syndrome) settles delusional disorder against paranoid schizophrenia.

GOOD TO REMEMBER

- **Schizoaffective vs mood-with-psychosis vs schizophrenia:** schizoaffective needs at least **two weeks** of psychosis without a prominent mood episode (Criterion B, separates it from mood-with-psychosis) and mood for the majority of the illness (Criterion C, separates it from schizophrenia); mood-with-psychosis has psychosis only within mood episodes; the number to hold is two weeks.
- **Delusional disorder vs paranoid schizophrenia:** a single-theme, non-bizarre delusion with preserved personality and function is delusional disorder; add prominent hallucinations, disorganisation, negative symptoms or decline and it is paranoid schizophrenia; delusional disorder onset is later (mid to late 30s).
- **Brief psychotic disorder:** acute psychosis lasting at least one day but less than **one month** with full recovery; the one number is under one month (DSM-5-TR).
- **Schizophreniform disorder:** schizophrenia-identical symptoms lasting **one to six months**; the one eponym is Langfeldt (1939), who introduced the concept; no equivalent in ICD-11.
- **ATPD (ICD-11 6A23):** abrupt onset from non-psychotic to psychotic within **two weeks**, rapidly shifting content, no negative symptoms, duration not exceeding **three months** (often days to one month), good outcome; the discriminator is the abrupt-onset, fluctuating, short-remitting quality, not brevity alone.
- **The two master axes:** duration sorts the short-course psychoses; mood-loading sorts schizoaffective from mood-with-psychosis and schizophrenia; the trap is diagnosing from the cross-sectional snapshot instead of the longitudinal course.

Delusional misidentification and named delusional syndromes

11 · Delusional misidentification syndromes

Why this matters. The **delusional misidentification syndromes** are a small keyed grid the examiner loves precisely because the eponyms are so easy to swap: four named beliefs, each turning on *who* is misidentified and in *which direction*. They are not a disorder in their own right but a recurring content pattern that rides on top of schizophrenia, mood disorder with psychosis, dementia and focal brain disease. The whole topic can be held on two axes: the familiar-versus-stranger axis (Capgras is the familiar seen as an impostor; Fregoli is the stranger seen as a familiar-in-disguise), and the appearance-versus-identity axis (whether the physical face changes, the psychological identity changes, or both).

Because these beliefs so often sit on organic pathology, the topic doubles as a trap about aetiology: a striking eponymous delusion is an invitation to look for a right-hemisphere lesion, a dementia or a metabolic cause, not to reflexively call it functional psychosis. The raw descriptive phenomenology of each belief (how it is elicited and graded at the mental-state level) is cross-referenced to the Psychometry, Assessment and Descriptive Psychopathology notes; here the job is the diagnosis and the discrimination. The **misidentification syndromes** are grouped in ICD-11 and DSM-5-TR under other specified schizophrenia-spectrum and other psychotic disorders when they stand alone (Kaplan & Sadock 2024).

Syndrome	The core misidentification	Typical association
Capgras	A familiar person seen as an identical impostor	commonest; up to 40% organic; right hemisphere
Fregoli	One persecutor disguised inside strangers	persecutory psychosis; rarer; Courbon & Fail 1927
Inter-metamorphosis	Appearance AND identity both swapped	total transformation; rare
Subjective doubles	Doubles of the self, acting on their own	not heautoscopy (self seen)
Reduplicative paramnesia	A place or object believed duplicated	right-hemisphere / frontal lesion

Fig 10.7 The delusional misidentification syndromes, keyed on the core misidentification. Capgras and Fregoli are direction-reversed (the familiar seen as an impostor versus one persecutor seen disguised inside strangers); intermetamorphosis changes both appearance and identity; subjective doubles turns the belief on the self; reduplicative paramnesia is the organic marker of the group. A face-processing disconnection and a high rate of right-hemisphere or organic pathology make excluding an organic cause mandatory.

11.1 Capgras syndrome: the familiar seen as an impostor

Capgras syndrome. The belief that a familiar person, to whom the sufferer is emotionally close (typically a spouse or relative, and sometimes a pet or an object), has been replaced by an identical impostor or double who has assumed that person's role and behaves like them (Companion 2010, Kaplan & Sadock 2024). It is the most common of the group. The conviction can be dangerous: some patients threaten, harm or even kill the supposed impostor, so the recognition of Capgras

carries a real risk assessment. It was described by the French psychiatrist Joseph Capgras (Capgras & Reboul-Lachaux 1923), who called it the "illusion of doubles" (Tasman 2015). The core is a paradox the patient rationalises: the person looks exactly the same but does not *feel* the same, and so must be a substitute.

RULE **Capgras is the familiar seen as an impostor; Fregoli is the stranger seen as a familiar-in-disguise.** Fix the direction first (who is real, who is disguised) and the two eponyms stop swapping.

11.2 Fregoli syndrome: the persecutor disguised as everyone

Fregoli syndrome. The belief that a persecutor is present but disguised as different people the patient meets: a single familiar figure (usually the persecutor) is repeatedly identified inside strangers who bear no physical resemblance, so the doctor is "really" the persecutor, then the nurse is, and so on, yet the persecutor is always one and the same (New Oxford 2020, Shorter Oxford 2018). The direction is the mirror-image of Capgras: the outward appearance is a stranger's, but the inner identity is claimed to be a known person. It was originally described by Courbon and Fail in 1927 and is even rarer than the Capgras delusion (Shorter Oxford 2018), named after Leopoldo Fregoli, the Italian stage actor famous for rapid changes of appearance and character.

TRAP **Attributing misidentification to a functional psychosis without excluding neurological or organic disease.** Up to 40% of Capgras cases carry an organic disorder (head injury, dementia); a striking misidentification delusion mandates an organic screen before it is called schizophrenia.

11.3 Intermetamorphosis and the syndrome of subjective doubles

Intermetamorphosis. The belief that others have been swapped in *both* physical appearance and identity, so that people (and sometimes animals or objects) are transformed into one another; unlike Fregoli, where only the hidden identity changes, here the delusion is of a total transformation, psychological as well as physical (New Oxford 2020, AIIMS Clinical Methods 2024). **Syndrome of subjective doubles.** The belief in doubles of oneself: the patient is convinced that exact physical copies of themselves exist and carry out independent actions, each with a separate psychological identity (New Oxford 2020, AIIMS Clinical Methods 2024). It is distinct from heautoscopy, in which the self is *seen* as a visual double rather than believed to exist as an independent agent.

11.4 The proposed mechanism: a face processing disconnection

The influential cognitive account of Capgras, and by extension the group, is the two-route model of face processing (Ellis & Young 1990). It proposes two routes to facial recognition: one for the identification of the face itself and one that gives the face its affective sense of familiarity. Prosopagnosia is a loss of the first route; Capgras is proposed as its "mirror image", an intact primary recognition route with a disconnection of the second, so the face is recognised as identical but is stripped of the emotional feeling that should accompany a loved one (Ellis & Young 1990). Ellis et al (1997) supported this by showing that Capgras patients fail to show the normal autonomic (skin-conductance) discrimination between familiar and unfamiliar faces. This

account is consistent with the high rate of right-hemisphere and organic pathology in these patients (Companion 2010). The patient mistakes a change in themselves (the missing sense of familiarity) for a change in the other person, and rationalises it as substitution.

The imperative to exclude an organic cause. Because delusional misidentification is so strongly associated with right-hemisphere dysfunction and structural or metabolic brain disease, an organic cause must be actively excluded in every case. Capgras has been reported in central nervous system lesions, dementia (especially dementia with Lewy bodies), vitamin B12 deficiency, hepatic encephalopathy, diabetes and hypothyroidism (AIIMS Clinical Methods 2024, Companion 2010). Right-sided cerebral pathology also produces reduplicative paramnesia, the belief that a familiar place, object or body part has been duplicated, which sits alongside the misidentification group and points the same way, toward the right hemisphere.

up to 40%
OF CAPGRAS CASES CARRY AN ORGANIC DISORDER (COMPANION 2010)

1927
COURBON AND FAIL DESCRIBE FREGOLI SYNDROME

right hemisphere
THE PATHOLOGY TO SUSPECT ACROSS THE GROUP

11.5 The differentiation grid

The grid is the deliverable: each syndrome is defined by *who* is misidentified and in *which* direction (familiar to stranger, or the reverse), and by whether appearance, identity, or both are held to have changed. Read down the "core misidentification" column and the eponyms separate cleanly.

SYNDROME	THE CORE MISIDENTIFICATION	TYPICAL ASSOCIATION
Capgras syndrome	**A familiar person (or pet or object) is believed replaced by an identical impostor or double; looks the same, does not feel the same**	Most common of the group; schizophrenia; organic disease in up to 40%; right-hemisphere pathology
Fregoli syndrome	**A persecutor is present but disguised as different strangers the patient meets; one persecutor inside many faces**	Persecutory psychosis; rarer than Capgras; Courbon and Fail 1927
Intermetamorphosis	**Others are swapped in both physical appearance and identity; a total transformation, not merely a disguise**	Psychotic disorders; rare; may include animals and objects
Syndrome of subjective doubles	**Belief in exact doubles of oneself, acting independently with separate identities**	Psychotic disorders; distinguish from heautoscopy (the self seen, not believed independent)
Reduplicative paramnesia	A familiar place, object or body part is believed duplicated (e.g. the real home moved and replaced by an identical one)	Right-hemisphere and frontal lesions; organic marker rather than functional psychosis

The misidentification grid: Capgras and Fregoli are direction-reversed (familiar-as-impostor versus stranger-as-familiar); intermetamorphosis changes both appearance and identity; subjective doubles turns the belief on the self.

HOLD THIS

Capgras = the familiar person seen as an identical impostor (looks the same, does not feel the same); Fregoli = the one persecutor seen disguised inside many strangers; a face processing disconnection between recognition and the affective sense of familiarity, plus right-hemisphere or organic pathology in a large minority, makes excluding an organic cause mandatory.

PEARL

The two-route face-recognition model gives the group a tidy logic: prosopagnosia loses the recognition route but keeps the feeling of familiarity; Capgras is the mirror image, keeping recognition but losing the feeling, so the face is known yet feels wrong and is rationalised as a substitute (Ellis & Young 1990). One model, two opposite clinical pictures.

INDIA

In Indian practice these syndromes are seen most often as content within schizophrenia and, increasingly, within dementia in older patients; the clinical discipline is identical, an organic and metabolic screen (including B12, thyroid and neuroimaging where a focal or right-hemisphere picture is suspected) before the belief is attributed to a functional psychosis. The named beliefs are managed by treating the underlying disorder, not as entities in themselves.

GOOD TO REMEMBER

- **Capgras syndrome:** a familiar person replaced by an identical impostor; the discriminator is "looks the same, does not feel the same"; the number to hold is up to 40% organic, and the eponym is Joseph Capgras (1923).
- **Fregoli syndrome:** a persecutor disguised as different strangers the patient meets; the discriminator is one identity inside many unfamiliar faces (mirror image of Capgras); the eponym and date are Courbon and Fail, 1927.
- **Intermetamorphosis:** others swapped in both physical appearance and identity; the discriminator is a total transformation (not just a disguise); hold that both appearance and identity change.
- **Syndrome of subjective doubles:** the belief in doubles of oneself acting independently; the discriminator is that the double is of the self and is believed to exist as an agent; distinguish it from heautoscopy.
- **The mechanism:** a face processing disconnection between visual recognition and the affective sense of familiarity; the fact to hold is the high rate of right-hemisphere and organic pathology and the imperative to exclude an organic cause (Ellis & Young 1990, Companion 2010).

12 · Named monothematic delusional syndromes

A handful of delusions carry their own eponyms, and the examiner loves them precisely because they are quick to name and easy to misattribute. Each is a **monothematic** delusion: a single, circumscribed belief that dominates the clinical picture while the rest of thought stays comparatively intact (Coltheart, Langdon & McKay 2007; New Oxford Textbook). The trap built into the whole set is a category error, treating the eponym as a diagnosis in its own right, when almost all of these are **delusional content** that can appear across schizophrenia, delusional disorder, a mood episode or an organic state.

Why it matters. Marks here are won on three moves: attaching each eponym to the correct content without swapping them, stating that the content is transdiagnostic rather than a disorder in itself, and, for one of them, recognising a real forensic danger. The raw descriptive definitions of the delusions themselves belong to the Psychometry, Assessment and Descriptive Psychopathology notes; the task here is to name the content precisely and then find the illness underneath it.

Eponym	Core delusional content	Association or risk
De Clerambault (erotomania)	A higher-status person is secretly in love	solitary women; stalking
Othello (delusional jealousy)	A partner is being unfaithful	violence and homicide risk; commoner in men
Cotard (nihilistic)	Being dead, not existing, or the organs lost	severe psychotic depression; severity marker
Ekbom (infestation)	Infested with parasites under the skin	matchbox sign; presents to dermatology

Fig 10.8 The named monothematic delusional syndromes, keyed on the core delusional content. Each is delusional content that can occur across schizophrenia, delusional disorder, a mood episode or an organic state, not a disorder in itself: name the content, then find the illness. Othello syndrome (delusional jealousy) is the one that carries a genuine forensic risk of violence to the partner.

12.1 Content, not disorder: the governing principle

Name the content, then find the illness. These eponymous syndromes are defined by *what* the patient believes, not by any distinct aetiology or course. Each can occur as the somatocentric, erotocentric or securocentric expression of an underlying condition, so the same named delusion is seen in schizophrenia, in delusional disorder as a monothematic somatic or persecutory belief, in a severe mood episode, and in organic and drug-induced states (New Oxford Textbook; Tasman; Kaplan & Sadock 2024). The clinical move is therefore two-step: recognise the content, attach the eponym, then work out the diagnostic bed it sits in. Only where the belief stands alone, monosymptomatic and monothematic with otherwise preserved functioning, does it become a delusional disorder in its own right (New Oxford Textbook).

RULE **Eponym first, diagnosis second.** Erotomania, morbid jealousy, nihilism and infestation are *content* that occurs across schizophrenia, delusional disorder, mood disorder and organic states; name the content, then find the illness that carries it.

12.2 De Clerambault syndrome: erotomania

The delusion of being loved. In de clerambault syndrome, also written **clerambault**'s syndrome and synonymous with erotomania (psychose passionelle), the patient is imperturbably convinced that another person, usually of higher social status and often a celebrity or a distant figure, is secretly in love with them (New Oxford Textbook; Kaplan & Sadock 2024; AIIMS Clinical Methods 2024). The supposed lover is typically unaware, unattainable and out of reach, and the belief persists even when that person ignores or rejects the patient's contacts (Kaplan & Sadock

2024). It is classically described in solitary, withdrawn, dependent women, though it is not confined to them, and it can drive persistent stalking and unwanted approach behaviour (Kaplan & Sadock 2024; New Oxford Textbook). Erotomanic content is not unique to delusional disorder and occurs as a symptom of other psychotic conditions (Tasman).

GOOD TO REMEMBER

- **De Clerambault syndrome (erotomania):** the delusion that another person, usually of higher status, is secretly in love with the patient. Discriminator: the object is typically unaware and unattainable, yet the conviction is unshakeable. Eponym to hold: de Clerambault (psychose passionelle); classically described in women.

12.3 Othello syndrome: delusional jealousy

The dangerous one. In othello syndrome, also called morbid jealousy, conjugal paranoia or delusional jealousy, the patient holds the fixed, false belief that their sexual partner is being unfaithful, pursued with relentless checking, interrogation and demands for confession (New Oxford Textbook). The name is drawn directly from Shakespeare's Othello, who killed his wife on a false belief of infidelity (New Oxford Textbook). This is the syndrome that carries a genuine forensic risk: the jealous delusion is associated with a real danger of violence, including homicide, toward the accused partner, and morbid jealousy is over-represented in spousal violence and killing (New Oxford Textbook; Companion to Psychiatric Studies). It is reported as more common in men, and, like the others, delusional jealousy is transdiagnostic and can be a symptom of schizophrenia, an organic or alcohol-related state, or delusional disorder (Companion to Psychiatric Studies; New Oxford Textbook).

TRAP **Treating Othello syndrome as benign.** Delusional jealousy is not a quirk of a suspicious marriage; it carries a real risk of harm to the partner, up to homicide, and mandates a formal risk assessment and, often, separation for the partner's safety.

GOOD TO REMEMBER

- **Othello syndrome (delusional jealousy):** the delusion that a partner is unfaithful. Discriminator: fixed, false conviction of infidelity, pursued with checking and demands for confession, distinct from ordinary jealousy. Forensic caveat to hold: genuine risk of violence and homicide toward the partner; reported commoner in men.

12.4 Cotard syndrome: the nihilistic delusion

The delusion of non-existence. Cotard syndrome, the delusion of negation, is the nihilistic delusion that the self, others or the world no longer exist, have been destroyed, or have lost their meaning and value (Shorter Oxford Textbook; AIIMS Clinical Methods 2024). In its fuller forms the patient believes they are dead, do not exist, or have lost or rotted away their internal organs, that the bowels are blocked or the blood has stopped, and it may extend to a delusion that the whole world is about to end (Shorter Oxford Textbook). It is classically seen in severe, often psychotic, depression, and also occurs in schizophrenia and in organic states (Shorter Oxford Textbook; Kaplan & Sadock 2024). It is a marker of severity: the nihilistic-somatic core signals a profound depressive or organic illness rather than a benign hypochondriacal worry.

GOOD TO REMEMBER

- **Cotard syndrome (nihilistic delusion):** the delusion of being dead, not existing, or having lost the internal organs. Discriminator: nihilistic-somatic negation, classically bowels or blood, not merely fear of illness. Association to hold: severe, often psychotic, depression (Jules Cotard, delire de negation).

12.5 Ekbom syndrome: delusional infestation

The delusion of parasites under the skin. Ekbom syndrome, or delusional infestation (delusional parasitosis, acarophobia, monosymptomatic hypochondriacal psychosis), is the fixed belief that one is infested with parasites, insects or small organisms crawling on or under the skin (Kaplan & Sadock 2024; Shorter Oxford Textbook). Thibierge first described the condition in the 1890s; it is now widely termed Ekbom syndrome after Karl-Axel Ekbom (Kaplan & Sadock 2024). The hallmark clinical sign is the **matchbox sign**: the patient brings collected specimens, usually skin, hair or lint, in a small container as proof of the infestation (Kaplan & Sadock 2024). These patients present most often to dermatology rather than psychiatry, and self-treat by washing, excoriating and using insecticides (Kaplan & Sadock 2024). It is the commonest presentation of monosymptomatic hypochondriacal psychosis and, again, can be primary (delusional disorder, somatic type) or secondary to schizophrenia, depression, dementia or drug intoxication such as cocaine (Tasman; Kaplan & Sadock 2024).

PEARL

The matchbox sign (the patient arriving with a container of "specimens", now sometimes the "specimen-jar" or smartphone-photo sign) is near-pathognomonic for delusional infestation and a fast bedside pointer. Before settling on Ekbom syndrome, exclude a real infestation, and screen for the organic and drug causes, cocaine and amphetamine "formication", B12 deficiency, hypothyroidism and dementia, that mimic it.

GOOD TO REMEMBER

- **Ekbom syndrome (delusional infestation):** the delusion of being infested with parasites or small organisms. Discriminator: the matchbox sign, specimens brought as proof; presents to dermatology. Eponym to hold: Karl-Axel Ekbom (first described by Thibierge, 1890s); commonest monosymptomatic hypochondriacal psychosis.

12.6 The keyed grid: eponym, content, association

The four in one table. The classic way to hold these is by their arche-theme: erotocentric (erotomania, jealousy), securocentric (persecutory, misidentification) and somatocentric (infestation, nihilistic-somatic) content (New Oxford Textbook). The grid below pins each eponym to its core delusional content and its single most exam-relevant association or risk. Every row is content that can occur across diagnoses; the eponym names the belief, not the illness.

EPONYM	CORE DELUSIONAL CONTENT	CLASSIC ASSOCIATION OR RISK
De Clerambault syndrome	**Another person, often of higher status, is secretly in love with the patient (erotomania)**	Classically solitary women; stalking and unwanted approach
Othello syndrome	**A partner is being unfaithful (delusional jealousy)**	**Real forensic risk of violence and homicide to the partner; commoner in men**
Cotard syndrome	**One is dead, does not exist, or has lost the internal organs (nihilistic delusion)**	Severe, often psychotic, depression; a severity marker
Ekbom syndrome	**One is infested with parasites or small organisms (delusional infestation)**	Matchbox sign; presents to dermatology; exclude cocaine, B12, dementia

Fig 10.8: the named monothematic delusional syndromes, eponym to content to association; each is delusional content that occurs across diagnoses, not a disorder in itself.

MNEMONIC

JELLI: Jealousy, Erotomania, Loss-of-existence, Little-organisms Infest

Othello = Jealousy; de Clerambault = Erotomania; Cotard = Loss of existence (nihilism); Ekbom = Little organisms Infest the skin. Four eponyms, four contents, in one string.

INDIA

In Indian delusional-disorder series the somatic and jealous subtypes are well represented, and delusional infestation and morbid jealousy are recognisable presentations in general and old-age psychiatry practice; the jealous subtype in particular carries the same domestic-violence risk that mandates a routine risk assessment and, where alcohol is the driver, attention to the alcohol-related state underlying the jealousy. The onset in delusional disorder is typically later than in schizophrenia (Companion to Psychiatric Studies), which fits the older, married patient in whom Othello and Ekbom syndromes are so often seen.

HOLD THIS

De Clerambault (loved by another), Othello (partner unfaithful), Cotard (dead or without organs) and Ekbom (infested) are monothematic delusional *contents* that occur across schizophrenia, delusional disorder, mood disorder and organic states; name the content, find the illness, and never call Othello syndrome benign, it can kill the partner.

Catatonia

13 · Catatonia: the signs and their examination

Catatonia is elicited, not merely observed. **Catatonia** is a syndrome of disturbed motility, volition and reactivity that sits *transdiagnostically* across mood, psychotic, autistic, developmental and organic disease. The examiner who only watches a still patient will miss it; the one who

reaches out, resists, mirrors and instructs will find it. This topic teaches the **catatonic signs** in their classical and modern groupings, the bedside **examination** that elicits them, and the Bush-Francis rating scale that standardises the search. The raw descriptive definitions of the movement and volition disorders are cross-referenced to the Psychometry, Assessment and Descriptive Psychopathology notes; here the target is recognition and the discrimination from the mimics that get catatonia missed.

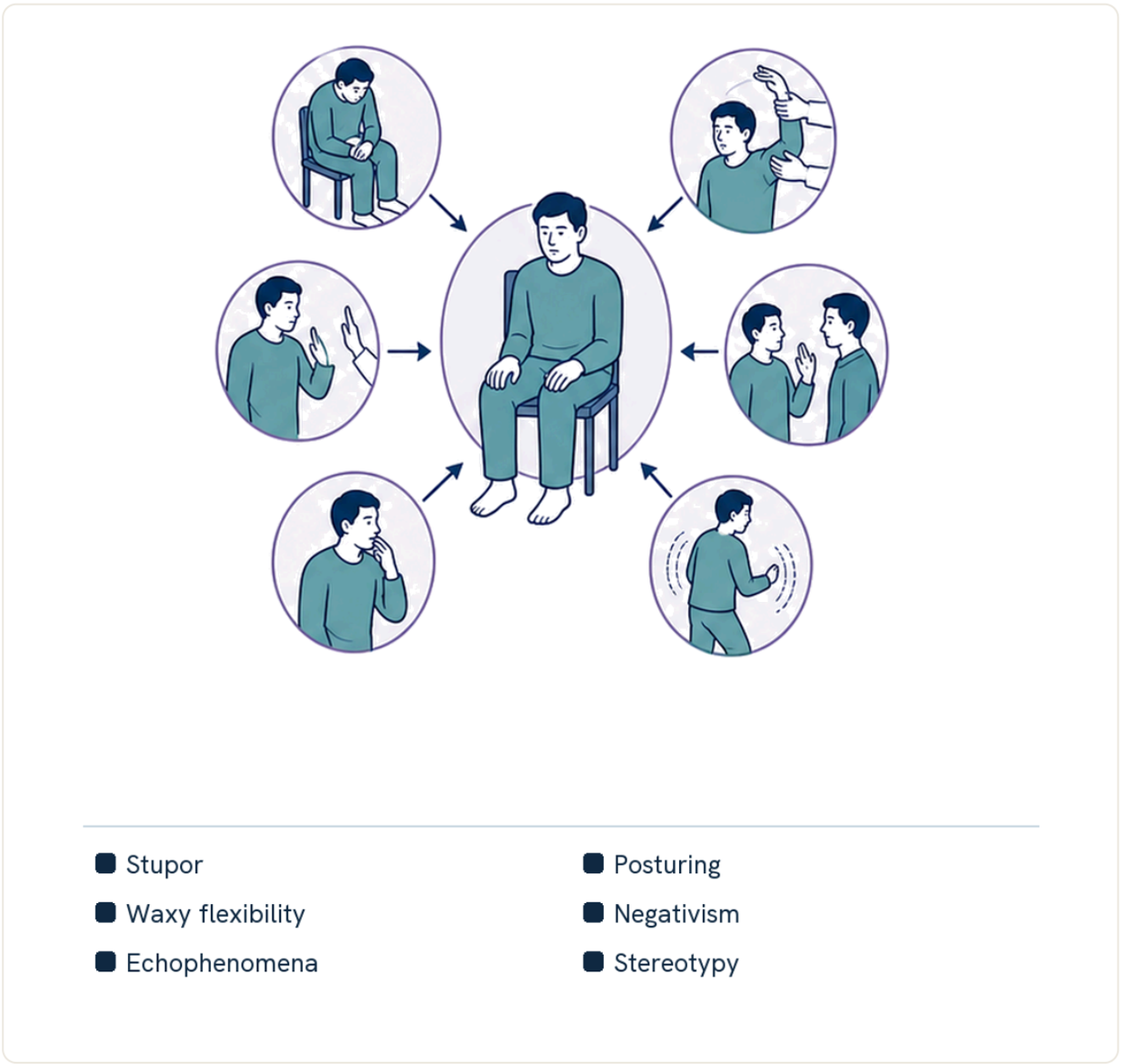

Fig 10.9 A structured examination for catatonia samples reduced movement and interaction, maintained posture, waxy flexibility, resistance or negativism, echophenomena and purposeless repetitive movement.

The high-yield frame for a viva: catatonia is a *clinical* diagnosis made on a defined constellation of signs, most of which must be actively drawn out. Naming the sign, describing how you elicit it, and placing it on the Bush-Francis map is the examiner-pleasing sequence.

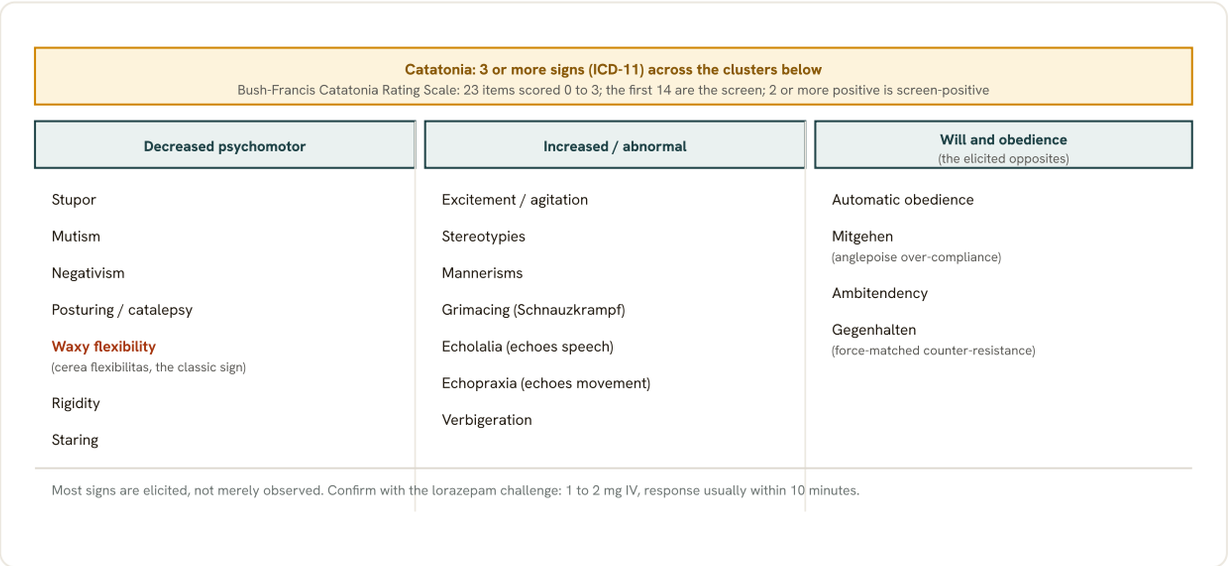

Fig 10.10 The catatonic signs grouped across the three ICD-11 psychomotor clusters, mapped onto the Bush-Francis rating scale. Waxy flexibility (cerea flexibilitas) is the classic elicited sign. Most signs must be actively drawn out at the bedside, which is why stuporous catatonia is so easily missed as depression or non-cooperation; three or more signs meet the ICD-11 threshold, and a lorazepam challenge confirms.

13.1 The Kahlbaum picture and the transdiagnostic modern concept

Origin. Kahlbaum described catatonia (*Die Katatonie oder das Spannungsirresein*, the "tension insanity") in 1874 as a cyclical illness passing through melancholic, manic, stuporous and, ultimately, dementing phases (Kahlbaum 1874). Kraepelin then folded it into dementia praecox as a subtype, and catatonia was for a century treated as a form of schizophrenia. That is the error the modern concept corrects.

The modern reframe. Catatonia is a *transdiagnostic* motor syndrome: in a New York cohort of catatonic inpatients only a small minority met criteria for schizophrenia, while more than two-thirds had affective disorders, usually mania (Kaplan & Sadock 2024). The disorder schizophrenia itself is not re-taught here; its phenomenology and criteria are owned by the Schizophrenia: aetiology, phenomenology, classification and course notes. What matters for catatonia is that a mood episode, an organic or medical illness, autism or substances are each more likely than schizophrenia to be the substrate.

RULE **Catatonia is a syndrome, not a subtype.** Diagnose the sign-constellation first, then hunt the cause; mood and medical illness outrank schizophrenia as the substrate.

13.2 The ICD-11 placement and diagnostic requirement

Nosology (ICD-11 primary). ICD-11 makes catatonia a free-standing, cross-cutting entity with its own grouping: 6A40 Catatonia associated with another mental disorder, 6A41 Catatonia induced by substances or medications, 6E69 Secondary catatonia syndrome, and 6A4Z Catatonia, unspecified (ICD-11 CDDR 2024). This is a genuinely high-yield point: catatonia is coded independently of the underlying disorder.

The threshold. ICD-11 requires **three or more** symptoms of decreased, increased or abnormal psychomotor activity, drawn from any combination of three clusters, typically lasting **at least several hours** (ICD-11 CDDR 2024). DSM-5-TR cross-maps closely, requiring **three or more** of

twelve psychomotor features (DSM-5-TR 2022). ICD-10 flagged the older habit of counting catatonia as a schizophrenia subtype, which both current systems abandon.

three or more	3 clusters	6A40
SIGNS FOR ICD-11 / DSM-5-TR CATATONIA	DECREASED, INCREASED, ABNORMAL PSYCHOMOTOR	ICD-11 CODE, ASSOCIATED WITH ANOTHER DISORDER

13.3 The motor and volitional signs

The core cluster. These are the hypokinetic and postural signs that dominate the classical stuporous picture.

Stupor

Immobility with no or markedly reduced psychomotor activity, minimally responsive to external stimuli, yet the patient is often aware of the surroundings (Fish, in Companion 2010).

Mutism

No or very little verbal response; speech hushed to unintelligibility. Do not count if due to a nervous-system disease or a speech/language disorder (ICD-11 CDDR 2024).

Negativism

Motiveless resistance to instruction; the patient does the reverse of what is asked, holding the breath when told to breathe deeply, resisting being stood up then refusing to lie down (Sims 2015).

Posturing / catalepsy

Posturing: spontaneous active maintenance of a posture against gravity. Catalepsy: passive induction of a posture by the examiner that is then held against gravity (ICD-11 CDDR 2024).

Waxy flexibility (cerea flexibilitas)

Slight, even, plastic resistance to positioning, "like bending a warm candle wax," the limb then held in the new position (ICD-11 CDDR 2024).

Rigidity

Resistance from increased tone, from mild to severe "lead-pipe" rigidity; requires examination (ICD-11 CDDR 2024).

Staring

Fixed gaze with decreased blinking, often with widely opened eyes (ICD-11 CDDR 2024).

Waxy flexibility is the classic teaching sign of catatonia: the examiner moulds the limb and it stays. It is distinct from *catalepsy* (posture held without the plastic resistance) and from lead-pipe *rigidity* (uniform resistance with no "give").

> **HOLD THIS**
> Waxy flexibility (cerea flexibilitas) is the classic catatonic sign: mould the limb like warm wax and it holds the new position against gravity.

13.4 The echo phenomena, and the disorders of will and obedience

Echo phenomena. Echolalia is the automatic mirroring of the examiner's speech; echopraxia is the mirroring of the examiner's movements. ICD-11 groups them as "echophenomena" under abnormal psychomotor activity (ICD-11 CDDR 2024).

Disorders of will and obedience. These paired opposites are the volitional heart of catatonia and are pure elicited signs.

Automatic obedience

Every instruction is carried out regardless of consequence. Kraepelin's demonstration was to ask the patient to put out the tongue and prick it with a pin; the patient kept protruding it despite the repeated prick.

Mitgehen

Extreme cooperation: the limb moves in the direction of the examiner's slightest pressure ("anglepoise-lamp" sign), then returns, despite instruction to resist (Companion 2010).

Ambitendency

The patient appears "motorically stuck," alternating between starting and stopping a movement in indecisive, hesitant fashion (ICD-11 CDDR 2024).

Gegenhalten (opposition)

The opposite of mitgehen: springy resistance to passive movement that increases in proportion to the force the examiner applies (Sims 2015; Companion 2010).

The clinical elegance is the pairing: mitgehen is over-compliance with passive movement, gegenhalten is motiveless counter-resistance to it, and both can appear in the same patient.

13.5 Mannerisms, stereotypies, grimacing and verbigeration

The abnormal-activity cluster. These are the "odd but active" signs.

Mannerisms

Odd, purposeful, goal-directed acts executed in an idiosyncratic, exaggerated-caricature way (e.g. a bizarre style of washing or dressing) (ICD-11 CDDR 2024; Companion 2010).

Stereotypies

Repetitive, non-goal-directed motor activity (finger-play, patting or rubbing the self). The abnormality is not in the action but in its frequency (ICD-11 CDDR 2024).

Grimacing

Odd or distorted facial expressions inappropriate to the situation. The exaggerated forward-thrusting of the lips (Schnauzkrampf, snout spasm) is a related facial sign that the AIIMS Clinical Methods text files as a facial stereotypy (ICD-11 CDDR 2024; AIIMS 2024).

Verbigeration

Continuous, directionless repetition of words, phrases or sentences; the senseless repetition of sounds or words (ICD-11 CDDR 2024; Shorter Oxford 2018).

In practice mannerisms and stereotypies shade into one another; both are motor behaviour rendered abnormal by repetitiveness, purposelessness or stiltedness. Mannerisms retain a goal (a distorted *way* of doing a normal act); stereotypies have no goal at all.

13.6 The bedside examination: catatonia is elicited

Observe, then elicit. A structured examination splits the signs into those you simply observe (staring, mutism, grimacing, stupor, excitement, stereotypy, mannerism, verbigeration, spontaneous echo) and those you must actively draw out (rigidity, negativism, posturing, waxy

flexibility, catalepsy, automatic obedience, mitgehen, mitmachen, ambitendency, echo phenomena) (AIIMS 2024). The whole discipline of the topic is that most catatonic signs live in the second column.

How to elicit the key signs.

- **Posturing and waxy flexibility.** Passively move the neck, jaw, shoulders, elbows, fingers and lower limbs; feel for the even, plastic "candle-wax" resistance and watch whether the induced posture is held against gravity (catalepsy). Look for the "psychological pillow," where the head is held elevated as if on a pillow (AIIMS 2024).
- **Negativism and gegenhalten.** Instruct simple actions and note reversal; then move a limb passively and feel for springy resistance that grows to match your force (AIIMS 2024).
- **Automatic obedience and mitgehen.** Instruct the patient to resist your manipulation; if the limb nonetheless rises with the slightest upward pressure of your finger and returns when released, that is mitgehen. The pin-prick tongue test is the historical automatic-obedience manoeuvre; instructing the patient to "resist" is the humane modern substitute (AIIMS 2024).
- **Echo phenomena.** Perform a gesture or a phrase and watch for spontaneous mirroring (echopraxia, echolalia).

WORKED EXAMPLE

A mute, immobile young man on the ward is written up as "uncooperative." You lift his arm; it offers the even plastic resistance of warm wax and stays raised (waxy flexibility, catalepsy). You press a finger under his forearm having told him to keep still; the arm floats upward and returns when you let go (mitgehen). You now have two elicited signs, staring and mutism observed: four signs, well over the three-sign threshold. This is catatonia, not obstinacy.

13.7 The Bush-Francis rating scale: domains and screen

The standard instrument. The Bush-Francis Catatonia Rating Scale (BFCRS) is the preferred scale for routine use for its validity, reliability and ease of administration (Bush 1996; AIIMS 2024). It has 23 items rated 0 to 3 for severity, and the presence or absence of the first 14 items forms the standardised *screening* examination (the Bush-Francis Catatonia Screening Instrument, BFCSI) (Bush 1996; AIIMS 2024).

The screen. By convention, **two or more** of the first 14 signs identify probable catatonia and warrant the full 23-item rating and a lorazepam challenge (a widely-applied screening cutoff; the standardised instrument is Bush 1996). The 14 screening items span the same clusters covered above: the standardised examination proceeds observe-then-elicit, exactly as in 13.6. FIG 10.7 maps the catatonic signs onto the Bush-Francis domains.

23 items	first 14	two or more
FULL BFCRS, SCORED 0 TO 3	SCREENING INSTRUMENT (BFCSI)	SCREEN-POSITIVE THRESHOLD (BUSH 1996)

Confirmation, cross-referenced. Once catatonia is identified, the intravenous lorazepam challenge helps confirm it and predicts treatment response: 1 to 2 mg IV over two minutes, with reassessment at 5 minutes and a favourable response usually within 10 minutes (AIIMS 2024). The therapeutics of benzodiazepines and ECT are disorder-specific pointers here; ECT technique points to the ECT and neurostimulation notes.

TRAP **Do not read hypokinetic catatonia as "just severe depression."** A mute, staring, immobile, food-refusing patient is easily filed as retarded depression or an "uncooperative" patient; examine for the elicited signs before you settle for either.

COMMON TRAP

Stuporous (hypokinetic) catatonia hides in plain sight. Because the patient looks passively unwell, teams label it depression, negativistic personality, or non-cooperation and never lay hands on the limbs. Several catatonic signs (waxy flexibility, gegenhalten, mitgehen, catalepsy) exist only when elicited, so a purely observational assessment will systematically miss them.

INDIA

Catatonia remains common in Indian inpatient practice and is a mainstay indication for ECT, which is widely available in government and teaching hospitals; the AIIMS Clinical Methods text codifies the observe-and-elicit examination taught in Indian residencies (AIIMS 2024). Benzodiazepine (lorazepam) first-line and ECT for lorazepam-non-response are the standard Indian pathway, with the lorazepam challenge used at the bedside to confirm.

PEARL

Malignant catatonia (hyperthermia, autonomic instability, rigidity, raised creatine phosphokinase) is clinically near-identical to neuroleptic malignant syndrome and shares management logic; NMS as an entity is owned by the Schizophrenia: management, antipsychotics and adverse effects notes and appears here only as this differential. If antipsychotics were recently given, you cannot separate the two on signs alone: stop the antipsychotic, support in intensive care, and treat as malignant catatonia.

MNEMONIC

WRENCHES-M: Waxy flexibility, Rigidity, Echophenomena, Negativism, Catalepsy/posturing, Automatic obedience/Mitgehen, Stupor/mutism, Stereotypy/mannerism

A rough hook for the sign families across the three ICD-11 clusters; the "M" tail flags mitgehen and mannerisms as the easily forgotten elicited/abnormal-activity signs.

GOOD TO REMEMBER

- **Catatonia:** transdiagnostic psychomotor syndrome; ICD-11 needs three or more signs from decreased, increased and abnormal-activity clusters; coded free-standing (6A40 associated with another disorder).
- **Kahlbaum:** first described catatonia (the "tension insanity") in 1874; hold the eponym and the year.
- **Waxy flexibility (cerea flexibilitas):** even plastic "warm-wax" resistance with the limb held in the new position; the classic catatonic sign, an elicited sign.
- **Catalepsy vs rigidity:** catalepsy is a passively induced posture held against gravity; rigidity is uniform increased tone ("lead-pipe"), no plastic give; waxy flexibility sits between as plastic resistance.
- **Negativism:** motiveless doing-the-reverse of instruction; discriminator from apathy is the active opposition.
- **Mitgehen vs gegenhalten:** mitgehen is anglepoise-lamp over-compliance to slight passive pressure; gegenhalten is force-matched springy counter-resistance; the elicited opposites of obedience/opposition.
- **Echophenomena:** echolalia (mirrors speech), echopraxia (mirrors movement); the discriminator is automatic, uninstructed mimicry.
- **Verbigeration:** senseless directionless repetition of words or phrases; a speech-level stereotypy.
- **Bush-Francis (BFCRS):** 23 items scored 0 to 3; first 14 form the screen; two or more screen-positive signs identify probable catatonia (Bush 1996).
- **Lorazepam challenge:** 1 to 2 mg IV over two minutes, reassess at 5 minutes, favourable response usually within 10 minutes; confirms and predicts response (AIIMS 2024).

14 · Aetiology and the transdiagnostic placement of catatonia

Catatonia is the syndrome that most reliably catches the resident out, because its causes are wide and its nosology has just moved under the examiner's feet. The old teaching, that catatonia is a subtype of schizophrenia, is wrong on both counts: the commonest psychiatric cause is a mood disorder, not schizophrenia, and a large minority of cases are driven by a neurological or medical process that will be missed unless it is actively sought. This is a clinical-disorder topic, so it teaches the two things a viva tests: the *causes* (which three groups, and which is commonest), and the *discrimination* (why an organic cause must be excluded, and where ICD-11 now places the syndrome). The descriptive definitions of the individual catatonic signs (stupor, mutism, negativism, waxy flexibility, echophenomena) are owned by the Psychometry, Assessment and Descriptive Psychopathology notes and are not re-derived here; the schizophrenia disorder itself is owned by the Schizophrenia: aetiology, phenomenology, classification and course notes.

How to use this page. Hold three cause groups (**psychiatric**, **neurological**, **medical**), then one principle (**organic catatonia** must always be excluded in new or atypical presentations), then one nosological shift (**ICD-11** codes catatonia as a **transdiagnostic** syndrome that many conditions can share, not a schizophrenia subtype). The single fact most often swapped is which psychiatric disorder is the commonest cause: it is the *mood* disorders, not schizophrenia (DSM-5-TR 2022).

14.1 The aetiology of catatonia in three groups

Causes are widespread and cut across the whole of medicine. The **aetiology of catatonia** is best carried as three groups (Kaplan & Sadock 2024, ICD-11 CDDR). The first is **psychiatric**: the

mood disorders (both depressive and bipolar episodes) and schizophrenia and other primary psychotic disorders, with neurodevelopmental disorders (especially autism spectrum disorder) a third psychiatric home. The crucial exam point is that, taken together, the mood disorders are a *commoner psychiatric cause than schizophrenia*: catatonia occurs in up to **35%** of individuals with schizophrenia, but the majority of catatonia cases arise in depressive or bipolar disorders (DSM-5-TR 2022). The second group is a **neurological cause**: encephalitis, in particular anti-NMDA-receptor encephalitis, seizures and the postictal state, stroke (cerebrovascular disease), and space-occupying lesions (neoplasms), alongside head trauma. The third group is **medical causes**: metabolic and electrolyte derangement (diabetic ketoacidosis, hypercalcaemia, hyponatraemia, hepatic encephalopathy, homocystinuria), infection (typhoid, HIV, infectious mononucleosis), autoimmune disease (systemic lupus erythematosus, Hashimoto/autoimmune encephalopathy, PANDAS), and drug-related or withdrawal states (antipsychotics, benzodiazepines, steroids, disulfiram, ciprofloxacin; and intoxication with or withdrawal from PCP, cannabis, cocaine, MDMA, LSD or opioids) (ICD-11 CDDR).

GROUP	REPRESENTATIVE CAUSES	THE ONE POINT TO HOLD
Psychiatric	Mood disorders (depressive and bipolar); schizophrenia and other primary psychotic disorders; autism spectrum disorder	**The *mood disorders are the commonest psychiatric cause*, not schizophrenia; catatonia in up to 35% of schizophrenia but most cases are mood**
Neurological cause	Encephalitis (esp. anti-NMDA-receptor encephalitis); seizures and the postictal state; stroke; space-occupying lesions; head trauma	**Anti-NMDA-receptor encephalitis is the archetypal treatable neurological cause and classically presents with psychiatric features then catatonia**
Medical causes	Metabolic and electrolyte derangement; infection; autoimmune disease; drug-related or withdrawal states	**Any of these produces catatonia indistinguishable from the psychiatric form; screening bloods, imaging and (if encephalitis is suspected) lumbar puncture are how they are found**

The three cause groups of catatonia; the trap is to stop at the psychiatric group and, within it, to assume schizophrenia rather than a mood disorder (Kaplan & Sadock 2024, DSM-5-TR 2022, ICD-11 CDDR).

RULE **Always exclude a medical or neurological cause of new catatonia, and remember the mood disorders are the commonest psychiatric cause.** New or atypical catatonia is organic until proven otherwise; among psychiatric causes, think mood first, not schizophrenia.

TRAP **Assuming catatonia means schizophrenia.** Catatonic signs are nonspecific: the commonest psychiatric cause is a mood disorder, and a substantial share of cases are neurological or medical; treating catatonia as pathognomonic of schizophrenia misses both the mood disorder and the organic cause.

14.2 The organic catatonia principle

Exclude a physical cause before you land on a psychiatric one. The **organic catatonia** principle is the governing safety rule of the syndrome: a medical or neurological cause must *always* be excluded, especially in new or atypical catatonia, because so many treatable physical illnesses reproduce it exactly and because an untreated organic driver can be lethal (Kaplan & Sadock 2024). Several pointers raise the prior for an organic cause: a first-ever episode, an atypical picture, older age (secondary catatonia syndrome becomes more likely after 40 and rises sharply after 65), very early onset (before 20, which associates with nervous-system disease or a neurodevelopmental disorder), co-occurring delirium or fluctuating consciousness, focal neurological signs, or autonomic instability. Catatonia itself has *no* specific laboratory, imaging or EEG signature, so the workup is aimed at the underlying cause and at complications: complete blood count, a complete metabolic panel, serum creatine kinase (markedly raised in malignant catatonia and NMS, and a warning of rhabdomyolysis), neuroimaging for a lesion, EEG (diffuse slowing points to delirium or encephalitis rather than a primary psychiatric cause), and, where encephalitis is suspected, a lumbar puncture with an autoimmune-encephalitis panel (Kaplan & Sadock 2024). If the entire workup is unremarkable, a psychiatric cause becomes the likely explanation, but only by exclusion.

WORKED EXAMPLE

A previously well 24-year-old woman is admitted with two weeks of mutism, negativism and waxy flexibility, preceded by headache, low-grade fever and a few days of odd, fearful behaviour. She meets the criteria for catatonia. Because this is a *first, atypical* episode in a young person with a prodrome suggesting encephalitis, the organic catatonia principle applies: alongside a lorazepam challenge for the catatonia, she needs neuroimaging and a lumbar puncture with an autoimmune-encephalitis panel. Anti-NMDA-receptor encephalitis is the target diagnosis (it classically opens with psychiatric symptoms and catatonia before seizures and dysautonomia appear), and immunotherapy, not an antipsychotic, is the definitive treatment. Reaching for schizophrenia here would be the cardinal error.

14.3 The ICD-11 transdiagnostic placement

Catatonia is now a syndrome of its own, not a schizophrenia subtype. The important nosological shift is that **ICD-11** treats catatonia as a **transdiagnostic** syndrome of primarily psychomotor disturbance that **catatonia can accompany** many conditions (ICD-11 CDDR). It is given its own grouping with four categories rather than being buried as a form of schizophrenia: 6A40 catatonia associated with another mental disorder (the associated disorder, whether a mood disorder, schizophrenia or another primary psychotic disorder, or autism spectrum disorder, is coded separately), 6A41 catatonia induced by substances or medications, 6E69 secondary catatonia syndrome (the direct pathophysiological consequence of a medical or neurological condition), and 6A4Z catatonia, unspecified. So the syndrome sits above any single diagnosis: it is defined once (three or more psychomotor symptoms from decreased, increased or abnormal activity) and then attributed to whatever underlies it. This is the important shift from the older ICD-10 view, in which catatonic schizophrenia (F20.2) was a named schizophrenia subtype and

the organic form (F06.1, organic catatonic disorder, which maps onto ICD-11's 6E69) sat apart; ICD-11 dissolves the subtype and makes the transdiagnostic syndrome primary (ICD-11 CDDR).

PEARL

The examiner's favourite one-liner is the direction of the shift. ICD-10 had a *catatonic subtype of schizophrenia* (F20.2); ICD-11 abolishes the schizophrenia subtypes and codes catatonia as a standalone transdiagnostic syndrome (6A40 / 6A41 / 6E69 / 6A4Z) that can accompany many disorders. If asked "where does catatonia live in ICD-11?", the answer is "its own grouping, coded to whatever it accompanies", not "under schizophrenia".

14.4 DSM-5-TR: a specifier and an associated syndrome, not a subtype

DSM-5-TR reaches the same destination by a different route. DSM-5 similarly stopped treating catatonia as a subtype of schizophrenia and instead handles it three ways: as a *specifier* ("with catatonia") that can be appended to a neurodevelopmental, psychotic, bipolar or depressive disorder; as **catatonia associated with another mental disorder** (the catatonia specifier, coded F06.1) when it is the focus; and as two standalone entities, *catatonic disorder due to another medical condition* and *unspecified catatonia* (DSM-5-TR 2022). Catatonia is defined by three or more of twelve psychomotor features. DSM-5-TR is explicit that although catatonia has historically been associated with schizophrenia, the symptoms are *nonspecific* and occur across mood, neurodevelopmental and medical conditions, and that "the majority of catatonia cases involve individuals with depressive or bipolar disorders" (DSM-5-TR 2022). So both major systems now converge: catatonia is a transdiagnostic syndrome, commonest in mood disorders, and never assumed to mean schizophrenia.

SYSTEM	HOW CATATONIA IS PLACED	THE DISCRIMINATING POINT
ICD-10 (older view)	Catatonic schizophrenia F20.2 as a named subtype; organic catatonic disorder F06.1 separate	**Catatonia partly owned *within* schizophrenia as a subtype: the view now superseded**
ICD-11	Own grouping: 6A40 associated with another mental disorder, 6A41 substance/medication-induced, 6E69 secondary catatonia syndrome, 6A4Z unspecified	**A transdiagnostic syndrome coded to whatever it accompanies; schizophrenia subtypes abolished**
DSM-5-TR	"With catatonia" specifier; catatonia associated with another mental disorder (F06.1); catatonic disorder due to another medical condition; unspecified catatonia	**A specifier or an associated syndrome, *not* a subtype; 3 of 12 features; explicitly nonspecific**

The nosological placement of catatonia across systems: the shared modern message is transdiagnostic, and the ICD-10 catatonic-schizophrenia subtype is the view being left behind (ICD-11 CDDR, DSM-5-TR 2022).

14.5 Why the placement changed: the aetiological and neurobiological logic

The nosology followed the biology and the epidemiology. Two lines of evidence made the schizophrenia subtype untenable. The first is epidemiological: once catatonia was rated

systematically (with scales such as the Bush-Francis Catatonia Rating Scale, Bush 1996), it was found across mood, neurodevelopmental, medical and neurological conditions, with mood disorders supplying more cases than schizophrenia (a clinical-sample meta-analysis put the pooled prevalence of catatonia at about **9%**) (Bush 1996, DSM-5-TR 2022). The second is neurobiological: catatonic features arise from disruption of cortical-subcortical (basal-ganglia-thalamocortical) circuits regulating cortical function, producing reduced dopaminergic and GABA-A activity and upregulation of NMDA activity, and this final common pathway can be reached from many upstream causes (Kaplan & Sadock 2024). The same model explains the diagnostic-and-therapeutic lorazepam challenge (a GABA-A agonist disinhibits striatal dopamine and reverses the state) and why glutamate antagonists such as amantadine help in refractory cases. A shared circuit-level endpoint entered from many directions is exactly a transdiagnostic syndrome, which is what the classifications now encode.

up to 35%	**~9%**	**3 of 12**
OF SCHIZOPHRENIA SHOWS CATATONIA	POOLED PREVALENCE IN CLINICAL SAMPLES	FEATURES REQUIRED (DSM-5-TR)

14.6 The one differential the placement forces: malignant catatonia versus NMS

The organic-exclusion rule has one high-stakes special case. When catatonia is accompanied by autonomic instability and hyperthermia it becomes malignant catatonia, a life-threatening state that carried a **75% to 100%** mortality before modern treatment and around **10%** with benzodiazepines and ECT (Kaplan & Sadock 2024). Its near-twin is neuroleptic malignant syndrome, which shares rigidity, hyperthermia, dysautonomia and a raised creatine kinase; the practical distinction is the drug history (NMS follows dopamine-antagonist exposure or dopamine-agonist withdrawal), and the two are increasingly regarded as variants of the same catatonic spectrum. NMS as an entity is owned by the Schizophrenia: management, antipsychotics and adverse effects notes and is taught in full there; it appears here only as the differential that malignant catatonia forces. The management principle is that antipsychotics can worsen catatonia and precipitate the malignant form, so in a catatonic patient they are used cautiously and covered by lorazepam; the ECT technique itself points to the ECT and neurostimulation notes.

TRAP **Mistaking malignant catatonia for NMS (or giving a catatonic patient an antipsychotic).** The two overlap almost completely; the drug history separates them, and reaching for an antipsychotic in catatonia can tip a patient into the malignant, potentially fatal form.

INDIA

Catatonia is a familiar presentation in Indian practice, where a substantial share is mood-related and organic causes (post-infective, metabolic, autoimmune encephalitis) are actively sought given the local infectious and nutritional burden; the ICD-11 (and long-familiar ICD-10) framework is standard in Indian teaching texts. A practical advantage is that ECT, the definitive treatment for severe and malignant catatonia, is comparatively well established and available across Indian psychiatric units, and lorazepam is cheap and generic, so the diagnostic-therapeutic lorazepam challenge is readily performed at the bedside. The system-wide rule that no diagnosis is named to the patient sits comfortably here: the family is engaged around the psychomotor state and its urgency rather than a label. Where a brand is needed, lead with the Indian generic and verify locally rather than inventing one.

GOOD TO REMEMBER

- **Aetiology of catatonia (three groups):** psychiatric (mood disorders and schizophrenia/primary psychotic disorders, plus autism), neurological (encephalitis including anti-NMDA-receptor encephalitis, seizures/postictal state, stroke, space-occupying lesions) and medical (metabolic/electrolyte, infective, autoimmune, drug/withdrawal); the number to hold is that the mood disorders are the commonest psychiatric cause, with catatonia in up to 35% of schizophrenia but most cases being mood.
- **Organic catatonia principle:** a medical or neurological cause must always be excluded, especially in new or atypical catatonia; the discriminator prompting a physical workup is a first, atypical, older-onset or delirium-associated episode; the workup to hold is CBC, CMP, creatine kinase, neuroimaging, EEG and (if encephalitis suspected) lumbar puncture.
- **Anti-NMDA-receptor encephalitis:** the archetypal treatable neurological cause; the discriminator is a young patient with a psychiatric-then-catatonic prodrome progressing to seizures and dysautonomia; the point to hold is that CSF autoimmune-encephalitis testing and immunotherapy, not an antipsychotic, are definitive.
- **ICD-11 transdiagnostic placement:** catatonia is its own grouping, coded to whatever it accompanies; the discriminator from the old view is that the schizophrenia subtype (ICD-10 F20.2) is abolished; the codes to hold are 6A40 (associated with another mental disorder), 6A41 (substance/medication-induced), 6E69 (secondary catatonia syndrome) and 6A4Z (unspecified).
- **DSM-5-TR placement:** a "with catatonia" specifier, catatonia associated with another mental disorder (F06.1), catatonic disorder due to another medical condition and unspecified catatonia; the discriminator is that it is a specifier or associated syndrome, not a subtype; the number to hold is 3 of 12 psychomotor features.
- **Malignant catatonia:** catatonia plus hyperthermia and autonomic instability; the discriminator from NMS is the drug history (NMS follows dopamine antagonism); the number to hold is the mortality, 75% to 100% untreated, about 10% with benzodiazepines and ECT.

HOLD THIS

Catatonia is a transdiagnostic psychomotor syndrome, not a schizophrenia subtype: its commonest psychiatric cause is a mood disorder (catatonia occurs in up to 35% of schizophrenia but most cases are mood), it is frequently neurological or medical (encephalitis, especially anti-NMDA-receptor encephalitis, seizures, stroke, metabolic, autoimmune, drug or withdrawal), so a medical or neurological cause must always be excluded in new or atypical catatonia; ICD-11 codes it in its own grouping (6A40 / 6A41 / 6E69 / 6A4Z) that catatonia can accompany many conditions, and DSM-5-TR treats it as a specifier or associated syndrome rather than a subtype.

15 · Catatonia management: the lorazepam challenge and benzodiazepines

Why this matters. Catatonia is the one psychiatric syndrome where a single bedside manoeuvre is at once the diagnostic test and the first dose of treatment. The **lorazepam challenge** lets you confirm the syndrome and start reversing it in the same act, and the examiner rewards the resident who states the drug, the route, the dose and the response window, and who knows why a high-potency antipsychotic is the wrong reflex. The raw descriptive signs of catatonia (stupor, mutism, negativism, waxy flexibility, echophenomena) are set out in the Psychometry, Assessment and Descriptive Psychopathology notes and are not re-derived here; this topic teaches what you *do* once the syndrome is recognised.

Fig 10.11 Catatonia management begins with recognition and urgent medical assessment, followed by a benzodiazepine challenge; severe, malignant or non-responsive illness requires prompt electroconvulsive therapy.

The governing principle is simple and heavily tested: benzodiazepines, opened by the lorazepam challenge and then titrated, are first-line for catatonia regardless of the underlying cause, and antipsychotics are the classic trap. Two facts anchor the topic: a **benzodiazepine** reduces catatonic symptoms in roughly 70% to 80% of patients (Kaplan & Sadock 2024), and the

antipsychotic reflex can worsen catatonia or tip it into malignant catatonia. Supportive care and treatment of the cause run alongside from the outset; ECT is the definitive treatment where the drug fails or the picture is malignant, with its technique cross-referenced to the ECT and neurostimulation notes.

15.1 The lorazepam challenge: one act, two purposes

The lorazepam challenge is a test dose of **lorazepam** given to a patient with suspected catatonia, watched for a rapid reduction in catatonic features. It is diagnostic and therapeutic in the same stroke: a positive response (increased interaction, reduction of catatonic features) is confirmatory of catatonia and is simultaneously the first therapeutic dose (Kaplan & Sadock 2024). The standard adult dose is **2 mg**, commonly quoted as **1 to 2 mg** given intravenously or intramuscularly; IV is preferred for its quick onset and because a stuporous patient may be unable to swallow the oral formulation, with IM or sublingual used when IV access is unavailable (Kaplan & Sadock 2024). Lower doses suit paediatric and frail older adults, but 2 mg is recommended for most adults to avoid an equivocal result.

The **response** is often dramatic and quick: a robust "Lazarus" response may be seen within 30 minutes of a 2 mg dose, though some patients need up to 120 minutes; the AIIMS bedside protocol gives 1 to 2 mg IV over two minutes and reassesses at 5 to 10 minutes (Kaplan & Sadock 2024, Clinical Methods in Psychiatry AIIMS 2024). Interpretation has a trap of its own: a positive response confirms catatonia, but a negative response (sedation, or no change) does *not* rule it out, so if suspicion stays high a further dose is given and the patient reassessed. Monitor the change with a standardised scale rather than by impression.

RULE **The lorazepam challenge is diagnosis and treatment in one.** A test dose of lorazepam (2 mg, IV preferred) that produces a marked partial or full response both confirms catatonia and begins reversing it.

TRAP **Reading a negative challenge as excluding catatonia.** A positive response confirms the syndrome; sedation or no change does not rule it out. If clinical suspicion remains, repeat the dose rather than abandon the diagnosis.

15.2 Benzodiazepines as first-line: titration after the challenge

Once the challenge is positive, **lorazepam** is the first-line treatment irrespective of aetiology, carrying an efficacy of **70% to 80%** for symptom reduction (Kaplan & Sadock 2024). The drug is then scheduled and titrated upward, often to higher-than-usual doses. A typical regimen schedules lorazepam (for example 2 mg every 6 hours) for at least the first 24 to 48 hours, moving to a titrated total daily dose that controls symptoms without excessive sedation; some patients need a total of 30 mg or more per day (Kaplan & Sadock 2024). Nursing must give scheduled doses even when the patient appears to sleep, because that "sleep" may be stupor returning as the last dose wears off. Once symptoms have clearly improved, taper slowly (a 10% to 25% reduction per day).

Second-line and adjunctive agents exist but are not the answer to hold first: zolpidem 5 to 10 mg, GABA-active antiepileptics (valproate, topiramate, carbamazepine), and NMDA-receptor antagonists (amantadine 100 to 600 mg/day, memantine 10 to 20 mg/day) are used as adjuncts to lorazepam rather than as monotherapy, chiefly in lorazepam-refractory cases (Kaplan & Sadock 2024).

RULE **Benzodiazepines, not antipsychotics, are first-line for catatonia.** Lorazepam challenge, then titration (often to higher-than-usual doses), reverses roughly 70% to 80% of cases whatever the cause.

15.3 Supportive care and treating the cause

Catatonia is a medical emergency of immobility, so supportive care runs in parallel from the outset and is examinable in its own right. The stuporous, immobile patient is at risk of dehydration, malnutrition, aspiration pneumonia, pressure sores, contractures, urinary retention, rhabdomyolysis with renal failure, and venous thromboembolism. Management therefore includes hydration and nutrition (IV fluids, nasogastric or PEG feeding), VTE prophylaxis (anticoagulation), pressure care and mobilisation, aspiration precautions, urinary catheterisation, and monitoring of vitals and fluid balance (Kaplan & Sadock 2024, Clinical Methods AIIMS 2024). In parallel, the underlying cause is investigated and treated: catatonia is transdiagnostic, so a medical, neurological or substance cause must be actively excluded and managed, and treatment must not be delayed merely because the cause has not yet been found. Serum creatine kinase is tracked because marked elevation flags malignant catatonia or neuroleptic malignant syndrome and predicts renal risk.

WORKED EXAMPLE

A young man with schizophrenia is mute, immobile and holds imposed postures; he is not eating or drinking. You give 2 mg lorazepam IV over two minutes and at 8 minutes he begins to speak and move: the challenge is positive, confirming catatonia and starting treatment. You schedule lorazepam 2 mg every 6 hours, start IV fluids, VTE prophylaxis and pressure care, send CK and a metabolic screen, and arrange ECT cover in case of incomplete response. You do *not* reach for haloperidol to treat his psychosis while he is catatonic.

15.4 The antipsychotic caution: precipitating malignant catatonia

Antipsychotics were historically used to treat catatonia, but in many cases this worsened symptoms and increased mortality (Kaplan & Sadock 2024). The mechanistic reason fits the model: catatonia involves reduced GABA-A activity and a resulting hypodopaminergic state, so a dopamine-blocking drug can deepen the very dysfunction that drives the syndrome. The clinical danger is that a high-potency antipsychotic given to a catatonic patient can precipitate malignant catatonia or neuroleptic malignant syndrome (NMS), both life-threatening. Where the underlying psychosis genuinely needs antipsychotic cover, it should be given alongside lorazepam, and a second-generation agent, especially one with partial D2-agonist activity such as aripiprazole, is preferred over a high-potency D2 blocker (Kaplan & Sadock 2024). The drug detail and NMS as

an entity are owned by the Schizophrenia: management, antipsychotics and adverse effects notes; here NMS appears only as the malignant-catatonia differential.

TRAP **Giving a high-potency antipsychotic to a catatonic patient.** It can fail to help, worsen the catatonia, and precipitate malignant catatonia or neuroleptic malignant syndrome. Treat the catatonia with a benzodiazepine first; if antipsychotic cover is needed, add it to lorazepam and prefer a partial D2 agonist.

15.5 Malignant catatonia versus NMS, and where ECT comes in

Malignant catatonia (the older terms lethal catatonia and malignant catatonia are used interchangeably) is catatonic stupor accompanied by hyperthermia and autonomic instability, a potentially fatal state that on presentation may be clinically and biochemically indistinguishable from neuroleptic malignant syndrome, which has led to the view that NMS is best regarded as a drug-induced variant of malignant catatonia (Maudsley Prescribing Guidelines 2021, DSM-5-TR 2022). The practical consequence for management is that antipsychotics must be stopped and benzodiazepines and ECT brought forward urgently. **ECT** is the definitive treatment: it is the gold-standard for catatonia with about 90% efficacy, has no absolute contraindications, and is the treatment of choice when the patient is lorazepam-refractory or has progressed to malignant catatonia (Kaplan & Sadock 2024). Because malignant catatonia can evolve fast, ECT should be considered and consent sought early rather than after the drug has clearly failed. The ECT technique itself is set out in the ECT and neurostimulation notes and is not taught here.

FEATURE	MALIGNANT CATATONIA	NEUROLEPTIC MALIGNANT SYNDROME
Nature	Severe catatonia with hyperthermia and autonomic instability	**Antipsychotic-induced; often viewed as a drug-triggered variant of malignant catatonia**
Trigger	**Any cause of catatonia; may arise without any drug**	Onset after starting or increasing a dopamine antagonist
Core signs	Stupor, rigidity, fever, autonomic instability; raised CK	Fever, "lead-pipe" rigidity, altered mental state, autonomic instability; raised CK
The offending drug	**Antipsychotics can precipitate or worsen it: stop them**	Antipsychotic is the cause: withdraw immediately
Treatment overlap	Benzodiazepines and ECT; stop antipsychotics	**Supportive care, dantrolene/bromocriptine, benzodiazepines; ECT if refractory (see the Schizophrenia: management, antipsychotics and adverse effects notes)**

Malignant catatonia and NMS may be indistinguishable at the bedside; the discriminator is the drug history, and either way antipsychotics come off and benzodiazepines plus ECT go on. NMS as an entity is owned by the Schizophrenia: management, antipsychotics and adverse effects notes.

TRAP **Chasing the malignant-catatonia versus NMS label instead of acting.** The two overlap so closely they may be one spectrum; do not delay stopping the antipsychotic and starting benzodiazepines and ECT while you argue the name.

15.6 ICD-11 and the transdiagnostic frame

The nosology carries a high-yield point that shapes management. ICD-11 treats catatonia as a separate transdiagnostic grouping of primarily psychomotor disturbance that can arise across schizophrenia and other primary psychotic disorders, mood disorders, neurodevelopmental disorders (especially autism), with substances or medications, and with medical conditions (ICD-11 CDDR). The grouping codes are 6A40 catatonia associated with another mental disorder, 6A41 catatonia induced by substances or medications, and 6E69 secondary catatonia syndrome (a medical cause), with 6A4Z unspecified. Because catatonia crosses diagnoses, the management principle is the same whatever the parent: treat the syndrome with a benzodiazepine and, where needed, ECT, while identifying and treating the cause. DSM-5-TR maps the same idea through a "with catatonia" specifier and catatonia due to another medical condition; ICD-10 lacked the clean transdiagnostic grouping and is flagged as the older frame.

INDIA

Indian practice fits the standard picture and adds two local realities. The lorazepam-based approach is the AIIMS bedside standard: 1 to 2 mg IV over two minutes, reassessed at 5 to 10 minutes, with at least 6 mg given over 24 hours if the response is partial, then scheduled IV lorazepam continued (Clinical Methods in Psychiatry AIIMS 2024). Lorazepam is widely available and inexpensive, so benzodiazepine-first is fully practicable. ECT is comparatively accessible and heavily used in Indian tertiary centres, and modified ECT (mECT) is explicitly recommended as an urgent, life-saving intervention in malignant catatonia, with consent sought as early as possible; maintenance mECT is used in some cases (Clinical Methods AIIMS 2024). The 2025 Indian Psychiatric Society schizophrenia Clinical Practice Guideline (IPS 2025, Sahoo et al., Indian J Psychiatry 2026;68:94-121) is concordant: it endorses the lorazepam challenge test as serving both a diagnostic and a therapeutic purpose in catatonia, with benzodiazepines (lorazepam or clonazepam) used short-term and their long-term use avoided because of tolerance and dependence risk. This material is largely generic; lorazepam is prescribed by generic name.

70% to 80%	**2 mg**	**~90%**
RESPOND TO A BENZODIAZEPINE (LORAZEPAM), FIRST-LINE	STANDARD ADULT LORAZEPAM CHALLENGE DOSE (1 TO 2 MG IV/IM)	ECT EFFICACY, THE DEFINITIVE TREATMENT

MNEMONIC

CHALLENGE, THEN CLIMB, NEVER BLOCK

CHALLENGE: 2 mg lorazepam confirms and starts treatment. CLIMB: titrate the benzodiazepine up, often to higher-than-usual doses, with supportive care and cause-treatment alongside. NEVER BLOCK: avoid a high-potency antipsychotic, which can precipitate malignant catatonia or NMS; ECT is the definitive step.

HOLD THIS

Catatonia is treated benzodiazepine-first: a 2 mg lorazepam challenge that produces a rapid response both confirms the diagnosis and begins treatment, then lorazepam is titrated up (roughly 70% to 80% respond); antipsychotics are the trap because they can precipitate malignant catatonia or NMS, and ECT is the definitive treatment.

GOOD TO REMEMBER

- **Lorazepam challenge:** a test dose of lorazepam, **2 mg** (1 to 2 mg IV or IM), watched for a rapid partial or full response that both confirms catatonia and starts treatment; a negative response does not exclude catatonia; response often within 30 minutes ("Lazarus" response).
- **Benzodiazepine, first-line:** lorazepam titrated up after a positive challenge, often to higher-than-usual doses (up to 30 mg/day or more); efficacy for symptom reduction is **70% to 80%** (Kaplan & Sadock 2024).
- **Antipsychotic caution:** may not help and can worsen catatonia or precipitate malignant catatonia or NMS; if antipsychotic cover is needed, add it to lorazepam and prefer a partial D2 agonist (aripiprazole).
- **Malignant catatonia:** catatonic stupor with hyperthermia and autonomic instability, potentially fatal; may be indistinguishable from NMS (which is viewed as a drug-induced variant); stop antipsychotics, give benzodiazepines and urgent ECT.
- **ECT:** the definitive, gold-standard treatment, about **90%** efficacy, for lorazepam-refractory or malignant catatonia; technique in the ECT and neurostimulation notes.
- **Bush-Francis Catatonia Rating Scale:** the 23-item scale (Bush 1996) used to identify and monitor catatonic signs and to track response to the challenge and titration.
- **ICD-11 placement:** catatonia is a separate transdiagnostic grouping, 6A40 (with another mental disorder), 6A41 (substance/medication-induced), 6E69 (secondary), so the management principle holds across every parent diagnosis.

16 · Malignant catatonia and the differential from NMS

Why this matters. This is the emergency at the far end of the catatonia spectrum and the closer of the schizophrenia-spectrum block: an untreated catatonia that tips into fever, autonomic storm and rigidity is a life-threatening state with a high mortality if it is missed. The examiner's favourite pivot here is the differential from neuroleptic malignant syndrome, because the two are so alike that many authors treat them as one entity, and the resident who can say what leans the picture one way or the other, and who knows that the first move is the same for both, scores. The raw descriptive catatonic signs (stupor, mutism, negativism, waxy flexibility) are set out in the Psychometry, Assessment and Descriptive Psychopathology notes and are not re-derived here.

Two things carry the topic. First, malignant catatonia is a diagnosis of the whole picture, not of a single sign: it is catatonia complicated by hyperthermia and autonomic instability, and it can grow out of an ordinary catatonia that was not treated in time. Second, the differential from NMS is more a matter of leaning than of a clean line, and the safe reflex is identical whichever way you lean: stop any antipsychotic, give benzodiazepines, and move to ECT early. The neuroleptic malignant syndrome as an entity is owned by the Schizophrenia: management, antipsychotics and adverse effects notes and appears here only for this differential; the ECT technique points to the ECT and neurostimulation notes.

	Malignant catatonia (lethal catatonia, Stauder 1934)	Neuroleptic malignant syndrome (owned by the management notes)
Preceding picture	catatonic signs come first	on recent antipsychotic
Drug trigger	none needed (may follow catatonia)	antipsychotic start or dose rise
Rigidity	rigidity within a catatonic picture	lead-pipe rigidity
Fever, autonomic	present (shared)	present (shared)
Creatine kinase	raised (shared)	raised, often marked (shared)
First move (same)	**stop the drug, benzodiazepines, ECT**	**identical: stop, benzodiazepines, ECT**

Almost every cross-sectional feature is shared; the preceding picture and drug history lean the label, and NMS is often held to be a drug-induced malignant catatonia.

Fig 10.12 Malignant catatonia versus neuroleptic malignant syndrome. Fever, rigidity, autonomic instability and a raised creatine kinase are shared, so the discriminators are the preceding picture (catatonic signs first, without a necessary antipsychotic trigger, lean to malignant catatonia; a recent antipsychotic with lead-pipe rigidity leans to NMS). The first management move is the same for both: stop the antipsychotic, give benzodiazepines, and move to ECT early.

16.1 The entity: catatonia plus fever, dysautonomia and rigidity

Malignant catatonia, historically named lethal catatonia, is catatonic stupor accompanied by hyperthermia and autonomic instability, a potentially fatal emergency (Maudsley Prescribing Guidelines 2021). The fatal, hyperpyrexial form of catatonia was described by Karl Heinz Stauder at the Munich University Psychiatric Hospital in 1934 (Kaplan & Sadock 2024), which is why the older literature speaks of Stauder's lethal catatonia. The defining move from ordinary to malignant catatonia is the arrival of autonomic and thermoregulatory failure: on top of the immobility, mutism, posturing and rigidity of catatonia the patient develops fever, labile blood pressure and pulse, tachycardia, sweating, and often a raised serum creatine kinase. It is important that this is not always a fresh presentation: a catatonia that was recognised late or treated inadequately can progress into malignant catatonia, so the state is partly a failure to intervene in time (Kaplan & Sadock 2024).

The **stakes** are what make it examinable as an emergency. Untreated, malignant catatonia carries a high mortality, historically very high before benzodiazepines and ECT, driven by the complications of prolonged immobility and dysautonomia: hyperthermia, dehydration and malnutrition, rhabdomyolysis with acute renal failure, aspiration pneumonia, venous thromboembolism and cardiovascular collapse (Kaplan & Sadock 2024). The practical reading is that malignant catatonia is treated as a medical emergency in parallel with, not after, the diagnostic workup, and that recognising the febrile, rigid, autonomically unstable catatonic patient early is the whole game.

RULE **Fever plus autonomic instability turns catatonia into an emergency.** Malignant catatonia is catatonic stupor complicated by hyperthermia and dysautonomia, it can evolve from an untreated catatonia, and it kills if it is not treated.

16.2 The overlap with NMS: two names, arguably one entity

The heart of the topic is the differential from neuroleptic malignant syndrome, the NMS. The problem is that the two states share almost every feature: fever, rigidity, altered consciousness, autonomic instability and a raised creatine kinase all appear in both, and malignant catatonia may not be distinguishable from NMS either clinically or by laboratory testing (Maudsley Prescribing Guidelines 2021). This near-identity has produced a genuine nosological view rather than a mere resemblance: a symposium at the American Psychiatric Association meeting in 2000 concluded that NMS and malignant catatonia were the same (Kaplan & Sadock 2024), and the widely quoted formulation is that NMS is best regarded as a drug-induced form of malignant catatonia, that is, a malignant catatonia whose trigger happens to be a dopamine antagonist (Maudsley Prescribing Guidelines 2021). DSM-5-TR lists the two together precisely as a differential-diagnostic pair, malignant catatonia versus neuroleptic malignant syndrome (DSM-5-TR 2022).

Because the states overlap, the **discriminating leaning** rests less on the cross-sectional signs than on the preceding picture and the drug history. Catatonic signs that came first, in a patient who has not necessarily had an antipsychotic trigger, favour malignant catatonia: NMS can probably be ruled out in the absence of any prior or recent administration of a dopamine antagonist (Maudsley Prescribing Guidelines 2021). Conversely, a recent antipsychotic start or a dose rise, with lead-pipe rigidity emerging in that context, favours NMS. The leaning is a lean, not a proof, and the examiner wants it framed that way: the drug history tilts the label, the two may in truth be one spectrum, and the management does not wait on the argument.

TRAP **Treating malignant catatonia and NMS as cleanly separable.** They overlap so closely that they may be one entity; the drug history only leans the label, and chasing the name must never delay stopping the antipsychotic and starting benzodiazepines and ECT.

16.3 The differential grid: what leans which way

The discriminators are best held as a grid, because the point is exactly which features overlap (almost all of them) and which few lean the diagnosis. The shared column is large: fever, rigidity, autonomic instability and raised creatine kinase sit in both. The leaning column is small and is dominated by the temporal and pharmacological sequence.

FEATURE	LEANS TO MALIGNANT CATATONIA	LEANS TO NMS
Preceding picture	**Catatonic signs first (stupor, mutism, negativism, posturing), then fever and dysautonomia**	Rigidity and fever emerge on a background of recent antipsychotic exposure
Drug trigger	**No antipsychotic trigger necessary; may arise from an untreated catatonia**	**Recent antipsychotic start or dose rise (a dopamine antagonist)**
Character of the rigidity	Rigidity within a catatonic picture (posturing, waxy flexibility may be present)	**"Lead-pipe" rigidity is the classic descriptor**
Fever and autonomic instability	Present (defining the malignant state)	Present (shared, non-discriminating)
Creatine kinase	Often raised	Often markedly raised (shared, non-discriminating)
Nosological view	The primary entity	**Often regarded as a drug-induced form of malignant catatonia**
First management move	Stop any antipsychotic, benzodiazepines, ECT early	**Identical: stop the antipsychotic, benzodiazepines, ECT early (see the Schizophrenia: management, antipsychotics and adverse effects notes)**

The malignant catatonia versus NMS differential: almost every cross-sectional feature is shared, so the discriminators are the preceding picture and the antipsychotic history, and the first management move is the same either way.

16.4 Management: stop the drug, benzodiazepines, ECT early, intensive care

The management is deliberately the same whichever side of the differential the patient sits, because the states overlap and delay is what kills. The steps are: **stop any antipsychotic** (it can precipitate or worsen the state, and if the diagnosis is NMS the antipsychotic is the cause); **give benzodiazepines**, with lorazepam first-line and the lorazepam challenge as the entry point; **move to ECT early**, which treats both malignant catatonia and NMS and is the definitive step; and run **intensive supportive care** in parallel (hydration and nutrition, cooling, VTE prophylaxis, monitoring of vitals, creatine kinase and renal function, aspiration precautions) (Maudsley Prescribing Guidelines 2021, Kaplan & Sadock 2024). ECT is the gold-standard treatment for catatonia with about **90%** efficacy (Kaplan & Sadock 2024), and because malignant catatonia can evolve fast it should be considered and consent sought early rather than after benzodiazepines have clearly failed. In malignant catatonia every effort is made to maximise the effect of ECT by using liberal stimulus dosing to induce well-generalised seizures (Maudsley Prescribing Guidelines 2021); the technique itself is set out in the ECT and neurostimulation notes and is not taught here.

WORKED EXAMPLE

A woman with a two-week history of progressive mutism, immobility and imposed posturing, never started on an antipsychotic, now spikes a temperature of 39.5 C with labile blood pressure, tachycardia and a creatine kinase of several thousand. The catatonic picture came first and there is no dopamine antagonist in the history, so this leans to malignant catatonia rather than NMS, but the management does not depend on settling the label: no antipsychotic is given, lorazepam is started (2 mg challenge, then scheduled), ECT is arranged urgently, and she is managed with IV fluids, cooling, VTE prophylaxis and renal monitoring on a medical or high-dependency setting. Had she instead deteriorated days after a haloperidol start with lead-pipe rigidity, the lean would be to NMS, and the first moves would be identical.

RULE **Malignant catatonia and NMS overlap, so treat both the same.** Stop the antipsychotic, reach for benzodiazepines, and move to ECT early, with intensive supportive care alongside.

TRAP **Giving more antipsychotic to a febrile, rigid, catatonic patient.** Adding or increasing a dopamine antagonist here can precipitate or deepen malignant catatonia or NMS; the antipsychotic comes off, it does not go up.

~90%	2 mg	1934
ECT EFFICACY IN CATATONIA, THE DEFINITIVE STEP, TREATS BOTH	LORAZEPAM CHALLENGE, BENZODIAZEPINE ENTRY POINT	STAUDER DESCRIBES FATAL HYPERPYREXIAL (LETHAL) CATATONIA

INDIA

Indian tertiary practice fits the standard picture and is well placed for it. Lorazepam is widely available and inexpensive, so a benzodiazepine-first approach is fully practicable, and ECT is comparatively accessible and heavily used in Indian centres. Modified ECT is explicitly recommended as an urgent, life-saving intervention in malignant catatonia, with consent sought as early as possible (Clinical Methods in Psychiatry AIIMS 2024). The message for the Indian resident is that the definitive treatment for this emergency is within reach and should not be delayed while the malignant catatonia versus NMS label is debated.

MNEMONIC

STOP, SEDATE, SHOCK

STOP the antipsychotic (it can precipitate or is the cause). SEDATE with benzodiazepines (lorazepam, the challenge then titration). SHOCK, that is ECT, early, because it treats both malignant catatonia and NMS. All three run with intensive supportive care.

HOLD THIS

Malignant (lethal) catatonia is catatonic stupor plus fever and autonomic instability, and it overlaps so completely with NMS that they may be one entity; the drug history only leans the label (catatonia-first without a drug leans malignant catatonia, a recent antipsychotic with lead-pipe rigidity leans NMS), so for both you stop the antipsychotic, give benzodiazepines, and move to ECT early.

GOOD TO REMEMBER

- **Malignant catatonia (lethal catatonia):** catatonic stupor complicated by hyperthermia and autonomic instability, a life-threatening emergency that can evolve from an untreated catatonia; the fatal hyperpyrexial form was described by Stauder in 1934.
- **The one discriminator from NMS:** the preceding picture and drug history, catatonic signs first without a necessary antipsychotic trigger lean to malignant catatonia, a recent antipsychotic start or dose rise with lead-pipe rigidity leans to NMS; the states otherwise overlap and NMS is often regarded as a drug-induced form of malignant catatonia.
- **The first step, the same for both:** stop any antipsychotic, give benzodiazepines (lorazepam), move to ECT early (which treats both), with intensive supportive care; ECT is the gold-standard with about **90%** efficacy (Kaplan & Sadock 2024).

17 · ECT in catatonia and the Bush-Francis rating scale

Catatonia is treatable, and knowing the ladder is the exam point. Once catatonia is recognised as a syndrome (its signs and the raw descriptive definitions are cross-referenced to **the Psychometry, Assessment and Descriptive Psychopathology notes**, and its transdiagnostic nosology sits under ICD-11 6A40), management runs a short, fixed sequence: withdraw dopamine antagonists, correct the medical substrate, give a lorazepam challenge, and move to **electroconvulsive** therapy where the benzodiazepine fails or the picture turns malignant. This topic covers the place of **ect in catatonia** and the one instrument every resident is asked to name, the Bush-Francis Catatonia Rating Scale.

The examiner will not ask you to re-teach schizophrenia (that is owned by **the Schizophrenia: aetiology, phenomenology, classification and course notes**); the discriminator here is knowing *when not to delay* ECT, and knowing what the scale is for. The technique of ECT (electrode placement, stimulus dosing, the course itself) belongs to **the ECT and neurostimulation notes** and is cross-referenced, not taught here.

17.1 The place of ECT: gold standard, and definitive

Highly effective. Electroconvulsive therapy is the gold standard treatment for catatonia, with an efficacy around **90%** in catatonia (Kaplan & Sadock 2024). It has no absolute contraindications and is well tolerated even in medically ill patients, which matters because catatonia often presents in the acutely unwell. Most patients improve within the first **two to three** treatments (Kaplan & Sadock 2024). Lorazepam is best framed as a temporary bridge to definitive ECT: in many cases the benzodiazepine buys time while ECT is arranged, and some patients need monthly maintenance ECT to prevent relapse into catatonia.

RULE **Do not delay it.** ECT is the treatment for malignant or benzodiazepine-non-responsive catatonia; arrange it early, do not wait out a deteriorating patient.

17.2 When ECT is definitive: malignant and benzodiazepine-non-responsive catatonia

Two clear indications. ECT is specifically the treatment for **benzodiazepine-non-responsive** catatonia and for malignant catatonia. In malignant catatonia (also called lethal or pernicious catatonia, described by Stauder), the syndrome is acute in onset with stupor or excitement,

hyperthermia, autonomic instability, rigidity and altered consciousness; it is potentially fatal and, clinically and by laboratory testing, may be indistinguishable from neuroleptic malignant syndrome (Maudsley 2021). Here ECT can be lifesaving and should not be delayed. The same holds for **benzodiazepine non-responsive** catatonia: once an adequate lorazepam challenge has failed, escalating benzodiazepines or, worse, antipsychotics wastes time. Anticipating this, the clinician arranges ECT while the challenge is still running, so that a non-response or a slide into malignant catatonia does not cost days (Kaplan & Sadock 2024).

TRAP **Persisting with benzodiazepines alone.** In a deteriorating malignant catatonia, staying on lorazepam and hoping is the classic error; the patient needs urgent ECT.

WORKED EXAMPLE

A young man in catatonic stupor, mute and rigid, spikes a fever to 39.5 with labile blood pressure and a rising creatine kinase. He had a partial response to 2 mg lorazepam yesterday but is now worse. This is malignant catatonia (indistinguishable from NMS if he was recently on an antipsychotic). The move is not more lorazepam: it is to stop any dopamine antagonist, support vitals, and arrange urgent ECT the same day.

17.3 The lorazepam challenge: the step before ECT

Diagnostic and therapeutic. The lorazepam challenge is given both to confirm catatonia and to treat it. An initial dose of **2 mg** lorazepam is standard for most adults (lower in frail older adults and children), used for both diagnostic and treatment purposes (Kaplan & Sadock 2024). Indian practice describes an intravenous injection of **1 to 2 mg** lorazepam given over two minutes, with catatonic features reassessed shortly after (AIIMS Clinical Methods 2024). The patient is observed over roughly **30 to 60** minutes to see whether the catatonia dissipates; a positive response supports both diagnosis and the plan, and daily lorazepam then holds the symptoms at bay (Practical Psychopharmacology). A positive challenge is also a signal to arrange ECT, because a good lorazepam response predicts a good ECT response.

2 mg	30 to 60 min	around 90%
INITIAL LORAZEPAM CHALLENGE DOSE	OBSERVATION WINDOW	ECT EFFICACY IN CATATONIA

17.4 The Bush-Francis Catatonia Rating Scale: structure

The standard instrument. The **bush-francis catatonia rating scale** (Bush, Fink, Petrides, Dowling & Francis 1996) is the most used scale to identify catatonia and to grade its severity. It is a 23-item scale with two parts that map onto its two jobs (AIIMS Clinical Methods 2024):

The 14-item screen

The presence or absence of items 1 to 14 (the screening subscale) is scored to flag whether catatonia is present.

The severity scale

All 23 items are then rated 0 to 3 to grade severity, based on behaviour observed during a standardised examination.

Ratings are made on observed behaviour during the examination, with withdrawal and autonomic abnormality drawing on chart and collateral. The scale earns its keep at the bedside because catatonia often goes undetected or is mistaken for psychotic agitation, and it does not respond to escalating antipsychotic dosing (Practical Psychopharmacology).

17.5 Using the scale to monitor response

Serial scoring tracks treatment. Beyond identifying catatonia, the Bush-Francis Catatonia Rating Scale is used to monitor the response to the lorazepam challenge and to ECT: the same 0 to 3 severity ratings, repeated before and after the challenge and across the ECT course, give an objective measure of whether the catatonic burden is falling. This is why the instrument is paired with the challenge and the course rather than used once. It is not diagnostic on its own; the ICD-11 or DSM-5-TR criteria (with the anchoring signs cross-referenced to **the Psychometry, Assessment and Descriptive Psychopathology notes**) make the diagnosis, and the scale quantifies it.

MNEMONIC

SCREEN 14, SCORE 23

Items 1 to 14 are the presence/absence screen; all 23 items rated 0 to 3 give the severity score you track across the lorazepam challenge and ECT.

17.6 Malignant catatonia versus NMS: the differential that decides urgency

The one that changes management. The reason malignant catatonia is worth a row of its own is that it can be indistinguishable from neuroleptic malignant syndrome, and mistaking one for the other is a classic error. Both show hyperthermia, autonomic instability and rigidity; a 2000 American Psychiatric Association meeting concluded the two are the same entity, and NMS is often viewed as a drug-induced (antipsychotic-precipitated) variant of malignant catatonia (Kaplan & Sadock 2024; Maudsley 2021). NMS as a discrete entity is owned by **the Schizophrenia: management, antipsychotics and adverse effects notes**; it appears here only as the mirror of malignant catatonia. The practical convergence is the same: stop the offending dopamine antagonist, support the patient, and both respond to ECT.

FEATURE	MALIGNANT CATATONIA	NMS
Core state	Stupor or excitement, then hyperthermia, autonomic instability, rigidity	Hyperthermia, lead-pipe rigidity, autonomic instability, altered consciousness
Trigger	**May arise primary to the psychiatric illness, without a drug trigger**	**Drug-induced: follows a dopamine antagonist, often after a dose increase**
Relationship	Often clinically and biochemically indistinguishable; widely held to be the same syndrome, with NMS a drug-induced variant	
Decisive treatment	**Urgent ECT; do not delay**	Stop the antipsychotic, support, dantrolene/bromocriptine; ECT if refractory

Malignant catatonia and NMS overlap so completely that the same first moves apply; the discriminator is the drug history, not the presentation.

INDIA

ECT for catatonia is well established in Indian practice. AIIMS Clinical Methods in Psychiatry (2024) sets out that urgent modified ECT (mECT) is administered in malignant catatonia, so consent for mECT is taken as soon as possible; mECT may be given daily in severe cases and then reduced to alternate days or twice weekly as the catatonic syndrome declines, with maintenance mECT where needed. The lorazepam challenge (intravenous 1 to 2 mg over two minutes) is the standard first step, and the Bush-Francis Catatonia Rating Scale is named as the most used instrument to monitor catatonic signs. Overall prognosis is good, but delay in diagnosis and treatment raises morbidity, which is exactly why ECT is not delayed.

PEARL

ICD-11 places catatonia as a transdiagnostic grouping, not a subtype of schizophrenia: 6A40 catatonia associated with another mental disorder, 6A41 catatonia induced by substances or medications, and 6E69 secondary catatonia syndrome. This nosological move (catatonia can accompany mood disorders, psychoses or medical illness) is the high-yield point and reinforces the search for a treatable substrate before ECT.

HOLD THIS

ECT is the gold standard for catatonia (around 90% efficacy) and the definitive treatment for malignant or benzodiazepine-non-responsive catatonia; do not delay it, and track the response with the Bush-Francis scale.

GOOD TO REMEMBER

- **ECT in catatonia:** gold standard, efficacy around 90%; definitive for malignant and benzodiazepine-non-responsive catatonia; most improve within two to three treatments; maintenance ECT prevents relapse. Technique lives in the ECT and neurostimulation notes.
- **Lorazepam challenge:** initial 2 mg (IV 1 to 2 mg over two minutes in Indian practice), diagnostic and therapeutic; observe over 30 to 60 minutes; a positive response is the cue to arrange ECT.
- **Bush-Francis Catatonia Rating Scale (Bush 1996):** 23-item scale; items 1 to 14 = presence/absence screen; all 23 rated 0 to 3 for severity; used to identify catatonia and monitor response to the lorazepam challenge and ECT.
- **Malignant (lethal/pernicious) catatonia:** acute stupor or excitement with hyperthermia, autonomic instability, rigidity; often indistinguishable from NMS; urgent ECT can be lifesaving. Stauder eponym.
- **ICD-11 placement:** transdiagnostic grouping, 6A40 (with another mental disorder), 6A41 (substance/medication-induced), 6E69 (secondary catatonia syndrome).

Apply and consolidate

18 · Apply: four worked vignettes

Why this matters. Everything in these notes converges on a small number of bedside decisions, and the examiner tests them through short cases, not through recall of a criterion list. This closing topic runs four **worked vignettes**, each a brief scenario, the reasoning, then the resolution, that reassemble the moves already taught: the schizoaffective versus mood-with-psychosis gate, the delusional-disorder read, the catatonia lorazepam challenge, and the malignant-catatonia versus NMS emergency. Nothing new is introduced; the raw criteria live in the sibling topics and are cross-referenced, not re-derived.

Each vignette is deliberately compact and ends on the single discriminator that settles it, because that is how the case discussion is scored: not on how many features you can list, but on whether you name the one rule that decides the diagnosis. Treat every "Case:" below as a **worked example** to rehearse aloud, and hold the four clinical moves in the good-to-remember box at the close.

18.1 Vignette one: schizoaffective disorder versus mood with psychotic features

The commonest trap in the whole spectrum is to see psychosis and a mood episode together and reach for the schizoaffective label. The decision turns entirely on the two DSM-5-TR rules (Kaplan & Sadock 2024, DSM-5-TR 2022): Criterion B, a period of at least **two weeks** of delusions or hallucinations in the absence of a prominent mood episode; and Criterion C, mood-episode symptoms present for the majority of the total duration of the illness. The full mood-episode criteria are cross-referenced to the Mood disorders: classification, depressive and bipolar syndromes, neurobiology notes, and the disorder architecture to the Schizophrenia: aetiology, phenomenology, classification and course notes.

WORKED EXAMPLE

Case: A 34-year-old woman is admitted with a four-month history. For the first two months she had persecutory delusions and third-person auditory hallucinations with no disturbance of mood; over the following two months a full major depressive episode developed, and psychosis and depression have run together since.

Reasoning. Both phenomena are present, so the question is not "is there psychosis and mood" but "is the temporal architecture met". Criterion B asks for at least two weeks of psychosis without a prominent mood episode: here there were a full two months of pure psychosis before any mood change, so the gate is cleared. Criterion C asks that mood dominate the majority of the illness: depression has been present for two of the four months and continues, which is at least half. Both rules hold.

Resolution. Schizoaffective disorder, depressive type. Contrast the counter-case that resolves the other way: if psychosis had appeared only once the depressive episode began and had cleared when mood lifted, Criterion B would fail, there would be no two-week window of pure psychosis, and the diagnosis would be a major depressive episode with psychotic features, where psychosis is confined to the mood episode.

RULE **Two weeks of psychosis without a prominent mood episode is the gate.** Criterion B excludes mood-with-psychosis; Criterion C (mood for the majority of the illness) excludes schizophrenia; both must hold.

TRAP **Diagnosing schizoaffective from concurrent psychosis and mood alone.** Without the two-week pure-psychosis window, co-occurring psychosis and a mood episode are a mood disorder with psychotic features, not schizoaffective disorder.

18.2 Vignette two: delusional disorder versus paranoid schizophrenia

The delusional-disorder read is a discrimination against schizophrenia by what is *absent*. The positive requirement is a single-theme, characteristically non-bizarre delusional system present for at least one month in DSM-5-TR (three months in ICD-11 6A24), with functioning outside the delusion largely preserved and none of the other schizophrenia features (Kaplan & Sadock 2024, DSM-5-TR 2022, ICD-11 CDDR). The raw descriptive definition of a non-bizarre delusion is cross-referenced to the Psychometry, Assessment and Descriptive Psychopathology notes.

WORKED EXAMPLE

Case: A 42-year-old accountant is brought by his wife. For eight months he has been convinced that a colleague is quietly sabotaging his promotion, checking his emails and turning management against him. He is otherwise working, dressing and relating normally; there are no hallucinations, no thought disorder, no negative symptoms, and outside this one theme his conversation and affect are unremarkable.

Reasoning. The belief is plausible-in-kind, a non-bizarre persecutory theme, single and encapsulated, and it has run well beyond the one-month DSM-5-TR (and three-month ICD-11) threshold. The decisive point against paranoid schizophrenia is the preserved picture around the delusion: no prominent hallucinations, no formal thought disorder, no functional collapse. Schizophrenia would show a broader psychotic syndrome and deterioration; here there is a walled garden of one belief in an otherwise intact person.

Resolution. Delusional disorder, persecutory type. Had there been prominent ongoing auditory hallucinations, disorganisation or global functional decline, the diagnosis would shift to schizophrenia, whose criteria and course are owned by the Schizophrenia: aetiology, phenomenology, classification and course notes.

TRAP **Escalating an encapsulated non-bizarre delusion to schizophrenia.** A single-theme delusion with preserved function and no other psychotic features is delusional disorder; do not upgrade it on the strength of the delusion's conviction alone.

INDIA

Indian teaching leans on the ICD tradition, so the three-month non-bizarre-delusion template is the one most residents carry, and morbid jealousy and persecutory presentations are the delusional-disorder subtypes seen most often in clinic. The discrimination against schizophrenia is made the same way: preserved function outside the delusion and the absence of a wider psychotic syndrome.

18.3 Vignette three: catatonia and the lorazepam challenge

Catatonia is the syndrome the examiner most wants worked as a sequence: examine for the signs, exclude an organic cause, give the challenge, then treat with benzodiazepines. ICD-11 codes catatonia as a free-standing, transdiagnostic entity (6A40) requiring three or more signs from the decreased, increased and abnormal-activity clusters; DSM-5-TR cross-maps as three or more of twelve signs (ICD-11 CDDR, DSM-5-TR 2022). The individual signs, catalepsy, waxy flexibility (cerea flexibilitas), mutism, negativism, posturing, echophenomena, are set out with the Bush-Francis scale in the catatonia signs notes and not re-listed here.

WORKED EXAMPLE

Case: A 27-year-old man with known bipolar disorder is admitted mute and immobile. On examination he holds an arm where it is placed (catalepsy), resists passive movement, and shows waxy flexibility. Vitals are stable and he is afebrile.

Reasoning. Three or more signs are present, so the syndromic threshold is met. Before treating, exclude an organic or medical cause, the sign cluster is transdiagnostic and can be driven by encephalitis, metabolic derangement or medication, so a focused work-up (temperature, bloods including creatine kinase, and a screen for an organic driver) comes first. With no red flag for an organic emergency, proceed to the lorazepam challenge: 2 mg IV (1 to 2 mg in adults, lower in children and frail older adults) as a single diagnostic-and-therapeutic dose (Kaplan & Sadock 2024, Clinical Methods in Psychiatry 2024).

Resolution. A marked partial or full response, increased interaction and reduction of catatonic signs, typically within **30 minutes**, both confirms catatonia and opens treatment. Benzodiazepines are then first-line: scheduled lorazepam, titrated from the challenge dose. A positive response confirms the syndrome; sedation or no change does not rule it out. If catatonia is lorazepam-refractory or malignant, ECT is the definitive step, its technique cross-referenced to the ECT and neurostimulation notes.

2 mg IV	within 30 min	70 to 80%
STANDARD ADULT LORAZEPAM CHALLENGE DOSE	RESPONSE WINDOW THAT CONFIRMS CATATONIA	BENZODIAZEPINE EFFICACY FOR SYMPTOM REDUCTION

RULE **The lorazepam challenge is diagnosis and treatment in one.** A 2 mg IV dose that produces a marked response confirms catatonia and starts the benzodiazepine; response is judged by at least 50% improvement.

TRAP **Missing the organic cause.** Catatonia is transdiagnostic: exclude encephalitis, a metabolic cause and medication effects before assuming a primary psychiatric driver, and never reflexively reach for a high-potency antipsychotic.

18.4 Vignette four: malignant catatonia versus neuroleptic malignant syndrome

The emergency vignette is a febrile, rigid, dysautonomic patient, and the task is to reason to the discriminator and the first steps. Malignant catatonia is catatonic stupor with hyperthermia and autonomic instability, a potentially fatal state that at the bedside may be clinically indistinguishable from neuroleptic malignant syndrome, itself best regarded as a drug-induced variant of malignant catatonia (Maudsley Prescribing Guidelines 2021, DSM-5-TR 2022). NMS as an entity is owned by the Schizophrenia: management, antipsychotics and adverse effects notes and appears here only inside this differential.

WORKED EXAMPLE

Case: A 30-year-old man, three days into haloperidol for an acute psychosis, becomes febrile at 39.5 C with lead-pipe rigidity, fluctuating consciousness, labile blood pressure and a creatine kinase of several thousand units.

Reasoning. Fever, rigidity, autonomic instability and a raised CK are common to both malignant catatonia and NMS, so the syndromes overlap at the bedside. The discriminator that settles this presentation is the drug history: recent exposure to a dopamine-blocking antipsychotic points to NMS as the mechanism. Either way the immediate management is the same, because the two are on one continuum.

Resolution. Stop the antipsychotic first. Give a benzodiazepine (lorazepam) and start supportive care, IV fluids, cooling, monitoring, with ECT brought forward urgently if there is incomplete response or progression, since malignant catatonia can evolve fast. Where the underlying psychosis genuinely needs cover once the crisis settles, avoid a high-potency agent; the drug choice belongs to the management notes and the ECT technique to the ECT and neurostimulation notes.

RULE **The discriminator is the drug history; the first three moves are shared.** Recent antipsychotic exposure points to NMS, but for both: stop the antipsychotic, give a benzodiazepine, and move to urgent ECT if it does not settle.

TRAP **Treating malignant catatonia as if it were something other than NMS.** They sit on one continuum; do not withhold benzodiazepines or delay ECT while arguing the label, and never add a high-potency antipsychotic.

HOLD THIS

Four moves, four one-liners: schizoaffective needs at least two weeks of psychosis without a prominent mood episode plus mood for the majority; delusional disorder is a non-bizarre single-theme delusion with preserved function and nothing else; catatonia is three or more signs, exclude an organic cause, then a 2 mg IV lorazepam challenge; malignant catatonia and NMS are one continuum, so stop the antipsychotic, give a benzodiazepine and use urgent ECT.

GOOD TO REMEMBER

- **Schizoaffective versus mood-with-psychosis:** the move is the two-week gate. Diagnose schizoaffective only with at least **two weeks** of psychosis in the absence of a prominent mood episode (Criterion B) plus mood for the majority of the illness (Criterion C); otherwise it is a mood disorder with psychotic features.
- **Delusional disorder versus paranoid schizophrenia:** the move is to diagnose by what is absent. A non-bizarre single-theme delusion, at least one month (DSM-5-TR; three months in ICD-11), with preserved function and no other psychotic features; the number to hold is the one-month (ICD-11 three-month) threshold.
- **Catatonia and the lorazepam challenge:** the move is examine, exclude organic, challenge, treat. Three or more signs (ICD-11 6A40, transdiagnostic; DSM-5-TR three of twelve), then a **2 mg IV** lorazepam challenge with response in about **30 minutes**; benzodiazepines are first-line, symptom reduction **70 to 80%** (Kaplan & Sadock 2024).
- **Malignant catatonia versus NMS:** the move is treat the continuum, not the label. The discriminator is the antipsychotic drug history (NMS is the drug-induced variant); for both, stop the antipsychotic, give a benzodiazepine and use urgent ECT.

19 · Consolidate: mnemonic, retrieval and synthesis

Why this matters. A chapter this long is only as useful as the single thread the reader can pull at midnight before the case discussion. This closing topic does three things and nothing else: it hands over one **master mnemonic** that chains every entity in the block into an ordered walk, it sets a bank of answer-free recall prompts to force **active recall** rather than re-reading, and it names the whole-chapter **synthesis map** to be redrawn from memory. Nothing new is taught here. Every criterion, eponym and number below is owned and verified in the sibling topics and is compressed, not re-derived; the raw descriptive definitions of the delusions and misidentification phenomena stay cross-referenced to the Psychometry, Assessment and Descriptive Psychopathology notes, and the illness schizophrenia itself to the Schizophrenia: aetiology, phenomenology, classification and course notes.

Consolidation is a study step with an evidence base, not a decoration: chaining discrete facts onto one retrieval structure, then testing that structure against blank paper, is how a large block moves from recognition to recall. Treat the mnemonic as the spine, the retrieval prompts as the test, and the synthesis map as the object you must be able to draw with the book shut.

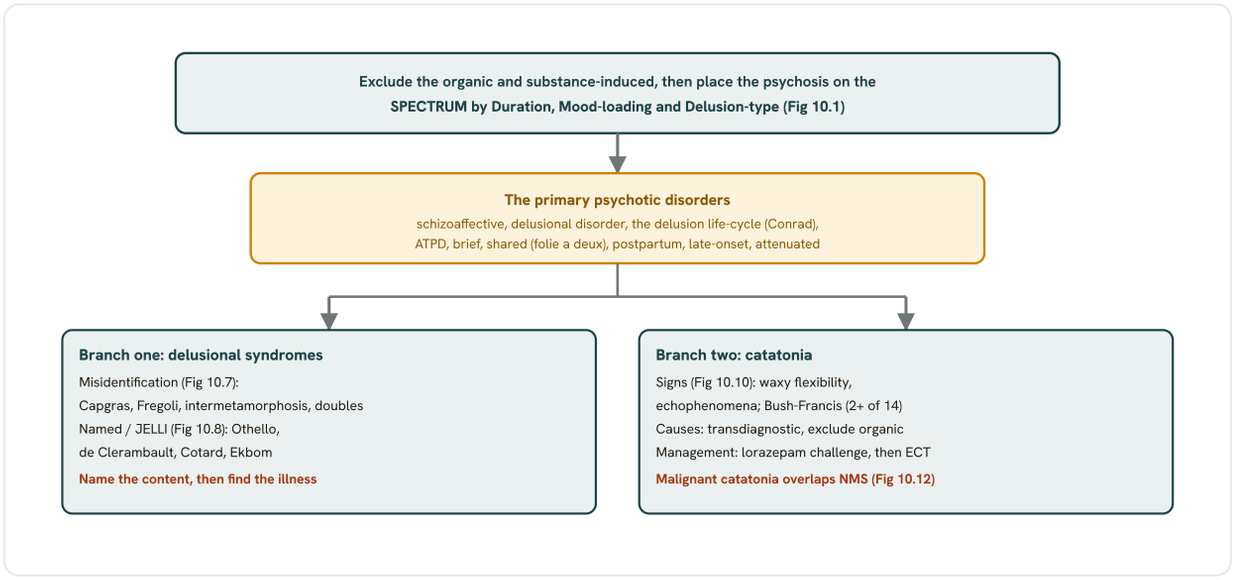

Fig 10.13 The whole-chapter synthesis map, to redraw from memory. The trunk is the spectrum decision tree and its primary psychotic disorders; branch one is the delusional syndromes (misidentification and the named monothematic set), held by content and direction; branch two is catatonia, run as a sequence from signs to causes to management to its malignant form. The gaps you cannot draw are the topics to revisit.

19.1 The master mnemonic: the whole chapter on one chain

The chain seeded at the orientation step now carries its full payload. The three-axis core (place the psychosis on the SPECTRUM by **D**uration, **M**ood-loading and **D**elusion-type) is the trunk; the named delusional syndromes and catatonia hang off it as the two branches the examiner tests by eponym and by sequence. Unpack every letter and the block is recoverable from a single string.

MNEMONIC

"SPECTRUM by D-M-D; then the DELUSIONAL syndromes; then CATATONIA MOVES."

SPECTRUM (the decision tree). First exclude the organic and substance-induced (the silent branch), then place the psychosis on the spectrum by the three axes. **D = Duration:** brief psychotic disorder under one month, schizophreniform one to six months (DSM-5-TR), schizophrenia six months or more (DSM-5-TR) or one month or more (ICD-11), with the acute and transient psychotic disorder (ATPD, ICD-11 6A23) off to the side, acute onset to the full picture within two weeks. **M = Mood-loading:** schizoaffective disorder needs a mood episode for the majority of the illness plus at least two weeks of psychosis without a prominent mood episode; psychosis only within mood episodes is a mood disorder with psychotic features. **D = Delusion-type:** a single non-bizarre delusion in an otherwise preserved person is delusional disorder.

The LIFE-CYCLE and the OTHER PRESENTATIONS. A primary delusion forms through Conrad's stages (Trema to Apophany to Apocalypse) and resolves by integration or sealing-over; and the block carries the compact presentations, the ACUTE and transient psychosis (bouffee delirante, cycloid psychosis), the BRIEF psychotic disorder, the SHARED delusion (folie a deux and its variants: imposee, communiquee, induite, simultanee), the PERINATAL (postpartum) psychosis, the LATE-onset and very-late-onset pictures (paraphrenia, partition delusions), and the ATTENUATED psychosis syndrome.

DELUSIONAL syndromes (branch two). The MISIDENTIFICATION set (Capgras, Fregoli, intermetamorphosis, subjective doubles, reduplicative paramnesia) and the named MONOTHEMATIC set (JELLI: Jealousy = Othello, Erotomania = de Clerambault, Loss-of-existence = Cotard, Little-organisms-Infest = Ekbom). Name the content, then find the illness.

CATATONIA MOVES (branch three). Read it as a sequence: the SIGNS (Kahlbaum's stupor, catalepsy, waxy flexibility, mutism, negativism, echophenomena; scored on the Bush-Francis Catatonia Rating Scale), the CAUSES (transdiagnostic, ICD-11 6A40/6A41/6E69, so exclude an organic driver), the MANAGEMENT (the lorazepam challenge, then benzodiazepines first-line, ECT if refractory), and the MALIGNANT form (Stauder's lethal catatonia, sitting on one continuum with NMS). "Moves" is the reminder that catatonia is the psychomotor syndrome that cuts across the whole grouping. D-M-D is the three-axis core the examiner rewards.

RULE **Walk the mnemonic in order, never by feature-count.** Exclude organic first, place on the spectrum by the three axes, then decide whether the picture is a named delusional content or catatonia; the order is the answer.

TRAP **Memorising the eponyms without the discriminators.** The chain is worthless if Capgras and Fregoli swap, or if Othello is called benign, or if a lorazepam-responsive catatonia is missed for want of the challenge; the letter must recall the rule, not just the name.

HOLD THIS

One string carries the block: place every psychosis on the SPECTRUM by Duration, Mood-loading and Delusion-type after excluding the organic; then work the named DELUSIONAL syndromes (misidentification and JELLI monothematic); then run CATATONIA as signs to causes to management to malignant form.

19.2 Retrieval practice: test the chain against blank paper

Reading the notes again feels like learning and mostly is not. The step that moves this block into recall is **retrieval practice**: shut the book, answer from memory, then check. The prompts below span the three bands (the spectrum and the primary psychotic disorders; the named delusional syndromes; catatonia). Work them as **active recall**, out loud or on paper, before you look anything up. The answers are deliberately absent; every prompt is answered somewhere in the sibling topics of this block.

RETRIEVAL PRACTICE, COVER THE ANSWERS

1. Name the three axes that separate every member of the schizophrenia spectrum, and state the silent branch you apply before you enter the tree.
2. Give the two DSM-5-TR criteria (B and C) that make a diagnosis schizoaffective disorder, and the one that separates it from a mood disorder with psychotic features.
3. State the duration thresholds that split brief psychotic disorder, schizophreniform disorder and schizophrenia in DSM-5-TR, and say where ICD-11 draws the schizophrenia line differently.
4. Define the acute and transient psychotic disorder (ICD-11 6A23) by its onset speed and course, and name its two classical antecedents in the European literature.
5. Give the positive criteria for delusional disorder and the single discriminator that separates it from paranoid schizophrenia.
6. Trace the life-cycle of a primary delusion through its named formation stages, and name the two ways it can resolve.
7. Name the shared-delusion syndrome and its four subtypes by the Latin terms, and state which member is the inducer versus the recipient.
8. State the incidence of postpartum psychosis per deliveries, the window in which most cases begin, and the single highest recurrence-risk factor.
9. Distinguish late-onset schizophrenia from very-late-onset schizophrenia-like psychosis, and name the delusion type classically tied to the older presentation.
10. Match each misidentification eponym (Capgras, Fregoli, intermetamorphosis, subjective doubles) to its core belief and its direction, and state the proportion of Capgras cases with an organic cause.
11. Unpack the JELLI monothematic set: give each eponym, its delusional content, and the one association or forensic risk to hold for each.
12. List the core catatonic signs and name the scale used to score them; then define waxy flexibility and negativism precisely.
13. Describe the lorazepam challenge: drug, dose, route, the response window that confirms catatonia, and the first-line treatment it opens.
14. State where catatonia lives in ICD-11 and why that placement is high-yield, and name the three organic categories you must exclude before calling it primary.
15. Give the one bedside discriminator between malignant catatonia and neuroleptic malignant syndrome, and the first three management moves the two share.

RULE **Answer before you check.** A prompt you can answer from memory is learned; a prompt you can only recognise once you read the answer is not, and re-reading will not fix it, only retrieval will.

19.3 The synthesis map: redraw the block from memory

The final consolidation object is a whole-chapter **synthesis map** to **redraw from memory**: a single figure with one trunk and three branches that you should be able to reproduce on blank paper without the notes open. The **trunk** is the spectrum decision tree, the primary psychotic disorders placed by the three axes (duration, mood-loading, delusion-type) after the organic and substance-induced are excluded, with schizoaffective, delusional disorder and the compact

presentations (acute and transient, brief, shared, perinatal, late-onset, attenuated) as its leaves. **Branch one** is the misidentification and named monothematic delusional syndromes, held by content and direction (Capgras versus Fregoli; the JELLI four). **Branch two** is catatonia as a sequence, signs to causes to management to the malignant form, drawn as the psychomotor syndrome that cuts transdiagnostically across the whole trunk. Redraw it, then check each branch against the good-to-remember boxes of the sibling topics; the gaps you find are the topics to revisit. This is the concept figure for the whole block (Fig 10.13), and drawing it from memory, not reading it, is the last consolidation step.

GOOD TO REMEMBER

- **The master mnemonic:** "SPECTRUM by D-M-D; then the DELUSIONAL syndromes; then CATATONIA MOVES." The whole-chapter chain: exclude organic, place on the spectrum by Duration, Mood-loading and Delusion-type, then the named delusional syndromes, then catatonia signs to causes to management to malignant form. The three-axis core (D-M-D) is the load-bearing part.
- **Retrieval practice:** the study move is to answer the 15 prompts from memory with the answers covered, out loud or on paper, then check; retrieval, not re-reading, is what fixes a large block. Every prompt is answered within the sibling topics of this block.
- **The synthesis map (Fig 10.13):** the object to redraw from memory is one trunk (the spectrum tree and primary disorders, by the three axes) and two branches (the misidentification and JELLI delusional syndromes; catatonia as signs to causes to management to malignant form). The gaps you cannot draw are the topics to revisit.
- **The high-yield anchors to carry:** schizoaffective needs at least **two weeks** of psychosis without prominent mood plus mood for the majority; delusional disorder is at least **one month** (ICD-11 **three months**) of a single non-bizarre delusion; up to **40%** of Capgras cases are organic; catatonia is the **2 mg IV** lorazepam challenge with response in about **30 minutes** and **70% to 80%** benzodiazepine efficacy; malignant catatonia and NMS are one continuum.

Previously asked

This territory is examined less as the long diagnose-and-manage essay of the schizophrenia papers and more as a steady stream of short notes and definitions: a named syndrome, a single disorder, or a discriminating feature. Catatonia is the most examinable single topic and has come as a full short note on its clinical features and, in the neuropsychiatry papers, as organic catatonia; postpartum psychosis and bouffee delirante have each been asked as named short notes. The delusional and misidentification syndromes recur as the definition-and-differentiate items the descriptive-psychopathology and clinical papers favour. The genuine questions on record are grouped by band below.

HOW THIS TERRITORY IS ACTUALLY TESTED

Q **Other primary psychotic disorders.** These come as named short notes rather than long essays. "Postpartum psychosis" has been asked as a 10-mark note, and "bouffee delirante" as a 10-mark note that rewards knowing the acute-and-transient category it seeds. Schizoaffective disorder, delusional disorder and its subtypes, the acute and transient psychotic disorders, and the late-onset psychoses are the definition-and-criteria short notes this band yields; prepare each to be defined, placed on the spectrum by duration and mood-loading, and separated from schizophrenia. short note, recurring

Q **Delusional misidentification and named syndromes.** The eponymous syndromes are classic short-note and viva territory: define Capgras, Fregoli, De Clerambault (erotomania), Othello (delusional jealousy), Cotard and Ekbom, and name the core delusional content and the one association or risk. Othello syndrome carries a forensic angle worth stating. Prepare these as crisp keyed definitions, not essays. **short note and viva, recurring**

Q **Catatonia.** The most examinable single topic of the block. "Clinical features of catatonia" has been asked as a 10-mark note, and "organic catatonia" as a 10-mark note in the neuropsychiatry papers, rewarding the aetiological work-up and the exclusion of a medical or neurological cause. Build the signs, the lorazepam challenge, the transdiagnostic placement, and malignant catatonia and its differential from neuroleptic malignant syndrome to answer the note and the emergency question. **short note, recurring**

Prepare this material to be defined and discriminated, not just recited: the spectrum decision tree, the misidentification and named-syndrome grids, and the malignant-catatonia-versus-NMS differential in these notes are built to the way the topic is examined. The phenomenology, aetiology, criteria and course of schizophrenia itself are developed in the Schizophrenia: aetiology, phenomenology, classification and course notes; the antipsychotic drugs and neuroleptic malignant syndrome as an entity live in the Schizophrenia: management, antipsychotics and adverse effects notes; these notes own the other psychotic disorders, the delusional syndromes, and catatonia.

Quick review

The whole subject in one table	
THE SPECTRUM DECISION TREE	Exclude the organic and substance-induced first, then place the psychosis on three axes: duration, mood-loading and delusion-type. A prominent mood episode pulls out schizoaffective and mood-with-psychosis; a single non-bizarre delusion with preserved function is delusional disorder; the rest go on the duration ruler.
SCHIZOAFFECTIVE DISORDER	At least two weeks of psychosis in the absence of a prominent mood episode (DSM-5-TR Criterion B, excludes mood-with-psychosis) plus mood symptoms for the majority of the total illness (Criterion C, excludes schizophrenia). Bipolar type (F25.0) or depressive type (F25.1). A diagnosis of debated validity: at two years only about a third keep the label. Coined by Kasanin (1933).
DELUSIONAL DISORDER	One or more non-bizarre delusions for at least one month (DSM-5-TR; three months in ICD-11 6A24), function otherwise preserved, no other schizophrenia symptoms. Subtypes by theme: persecutory (commonest), grandiose, jealous (male-predominant, Othello), erotomanic (De Clerambault), somatic (Ekbom), mixed. Onset mid- to late-30s. Kendler's original five dimensions (conviction, extension, bizarreness, disorganisation, pressure) rate form, not content.
THE LIFE-CYCLE OF A DELUSION	Formation through Conrad's phases: trema (delusional mood, an uncanny atmosphere) precedes apophany (the crystallised delusional perception), then anastrophe and apocalypse. Jaspers' primary forms: delusional mood, delusional perception (Schneider's two-memberedness), the sudden autochthonous idea, delusional memory. Dissolution: Bleuler's double bookkeeping and double orientation, encapsulation, and the recovery styles sealing-over versus integration.
ACUTE AND TRANSIENT PSYCHOTIC DISORDER	ICD-11 6A23: abrupt onset to full psychosis within two weeks, no prodrome, a rapidly shifting polymorphic picture, no negative symptoms, duration not over three months, with a characteristically good outcome. The acute polymorphic form (with or without schizophrenia symptoms) is the prototype; bouffee delirante (the Magnan and Legrain tradition) is the French antecedent. Follow up: a minority become schizophrenia or a mood disorder.
BRIEF PSYCHOTIC AND SHARED DISORDERS	Brief psychotic disorder (DSM-5-TR): at least a day, under one month, full recovery, often post-stressor. Induced or shared delusional disorder (folie a deux): a delusion transferred from a dominant psychotic primary to a passive, isolated secondary; separation of the pair usually resolves the secondary's delusion.
PERINATAL AND LATE-ONSET PSYCHOSES	Postpartum psychosis: an acute, often bipolar-spectrum, fluctuating psychosis of the first two weeks, a psychiatric emergency for suicide and

The whole subject in one table	
	infanticide risk; admit, ideally with the baby. Late-onset schizophrenia-like psychosis (onset after 40) and very-late-onset (after 60, the old paraphrenia): commoner in women, with sensory impairment, isolation and partition delusions; exclude a neurodegenerative cause.
ATTENUATED PSYCHOSIS SYNDROME	A DSM-5-TR condition for further study (Section III), not a formal diagnosis: sub-threshold delusion-like ideas, unusual perceptions or disorganised speech with reality testing relatively intact. It names the at-risk mental state (detected by CAARMS or SIPS); only a minority transition (about 15% at one year, 20% at two years), so false-positive and stigma risks keep it out of the main manual.
THE SPECTRUM DIFFERENTIAL	Duration and mood-loading are the master discriminators: brief psychotic under one month, schizophreniform one to six months, schizophrenia six months or more (one month in ICD-11). Schizoaffective needs the two-week pure-psychosis window and mood for the majority; delusional disorder is a single non-bizarre delusion in an otherwise preserved person, against the broader decline of paranoid schizophrenia.
MISIDENTIFICATION SYNDROMES	Keyed on the core misidentification: Capgras (a familiar person seen as an identical impostor), Fregoli (one persecutor disguised inside strangers, the mirror image), intermetamorphosis (both appearance and identity swapped), subjective doubles (doubles of the self). A face-processing disconnection between recognition and the affective sense of familiarity, with a high rate of right-hemisphere or organic pathology (up to 40% of Capgras cases), so exclude an organic cause.
NAMED MONOTHEMATIC SYNDROMES	Content, not disorder (JELLI): De Clerambault (erotomania, another of higher status secretly in love), Othello (delusional jealousy, a real forensic risk of violence, commoner in men), Cotard (nihilistic, being dead or the organs lost, in severe psychotic depression), Ekbom (delusional infestation, the matchbox sign, presents to dermatology). Name the content, then find the illness.
CATATONIA: THE SIGNS	A transdiagnostic psychomotor syndrome, elicited not just observed. The classical Kahlbaum and modern signs across three clusters: decreased (stupor, mutism, negativism, posturing, catalepsy, waxy flexibility), increased or abnormal (stereotypies, mannerisms, echolalia, echopraxia, verbigeration), and the elicited opposites of will (automatic obedience, mitgehen, gegenhalten, ambitendency). Waxy flexibility is the classic sign. Bush-Francis scale: 23 items, first 14 the screen, two or more positive.
CATATONIA: AETIOLOGY	Psychiatric (mood disorders are commoner than schizophrenia), neurological (encephalitis, especially anti-NMDA-receptor encephalitis, seizures, stroke) and medical (metabolic, autoimmune, drug-related) causes; always exclude an organic cause. ICD-11 codes it transdiagnostically (6A40 with another

The whole subject in one table	
	disorder, 6A41 substance-induced, 6E69 secondary), not as a subtype of schizophrenia, which is the shift from ICD-10.
CATATONIA: MANAGEMENT	The lorazepam challenge (1 to 2 mg IV, response usually within 10 minutes) is diagnostic and therapeutic; benzodiazepines are first-line (70 to 80% efficacy), with supportive care and treatment of the cause. Antipsychotics can worsen catatonia and precipitate the malignant form, so they are used with caution. ECT for lorazepam-refractory or malignant catatonia (about 90% efficacy).
MALIGNANT CATATONIA AND NMS	Malignant (lethal) catatonia is catatonic stupor plus fever and autonomic instability, a fatal emergency described by Stauder (1934). It overlaps so completely with neuroleptic malignant syndrome that many treat them as one entity (NMS a drug-induced malignant catatonia). The drug history only leans the label: catatonic signs first, no antipsychotic needed, lean to malignant catatonia; a recent antipsychotic with lead-pipe rigidity leans to NMS. For both: stop the antipsychotic, benzodiazepines, ECT early.
ECT AND THE RATING SCALE	ECT is the treatment for malignant and benzodiazepine-non-responsive catatonia and should not be delayed; the technique is developed in the ECT and neurostimulation notes. The Bush-Francis Catatonia Rating Scale (a 14-item screen and a fuller severity scale) identifies catatonia and monitors the response to the lorazepam challenge and to ECT.
APPLY AND CONSOLIDATE	Four worked cases: schizoaffective versus mood-with-psychosis by the two-week gate, a delusional-disorder read against paranoid schizophrenia, a catatonia worked through the lorazepam challenge, and a malignant-catatonia versus NMS emergency. Then the master mnemonic (place on the spectrum by duration, mood-loading and delusion-type, then the delusional syndromes, then catatonia), answer-free retrieval prompts, and the three-branch synthesis map to redraw from memory.

References

The content is grounded in the standard clinical and descriptive-psychopathology texts (the source hierarchy below), which anchor the settled facts on the criteria, the delusional syndromes and catatonia; the nosology follows ICD-11 (CDDR) primary with DSM-5-TR cross-mapped. Every diagnostic criterion, duration threshold, eponym attribution and named figure has been checked against these sources. Each journal PMID here was verified against PubMed this build, matched on title, first author and year; any identifier that did not resolve to the cited paper was corrected or dropped rather than guessed. The classic historical papers that seed the syndromes (Kasanin, Langfeldt, Conrad, Kahlbaum, Capgras and Reboul-Lachaux, Courbon and Fail, Stauder, Schneider) have no stable PubMed record and are cited by author, title and year.

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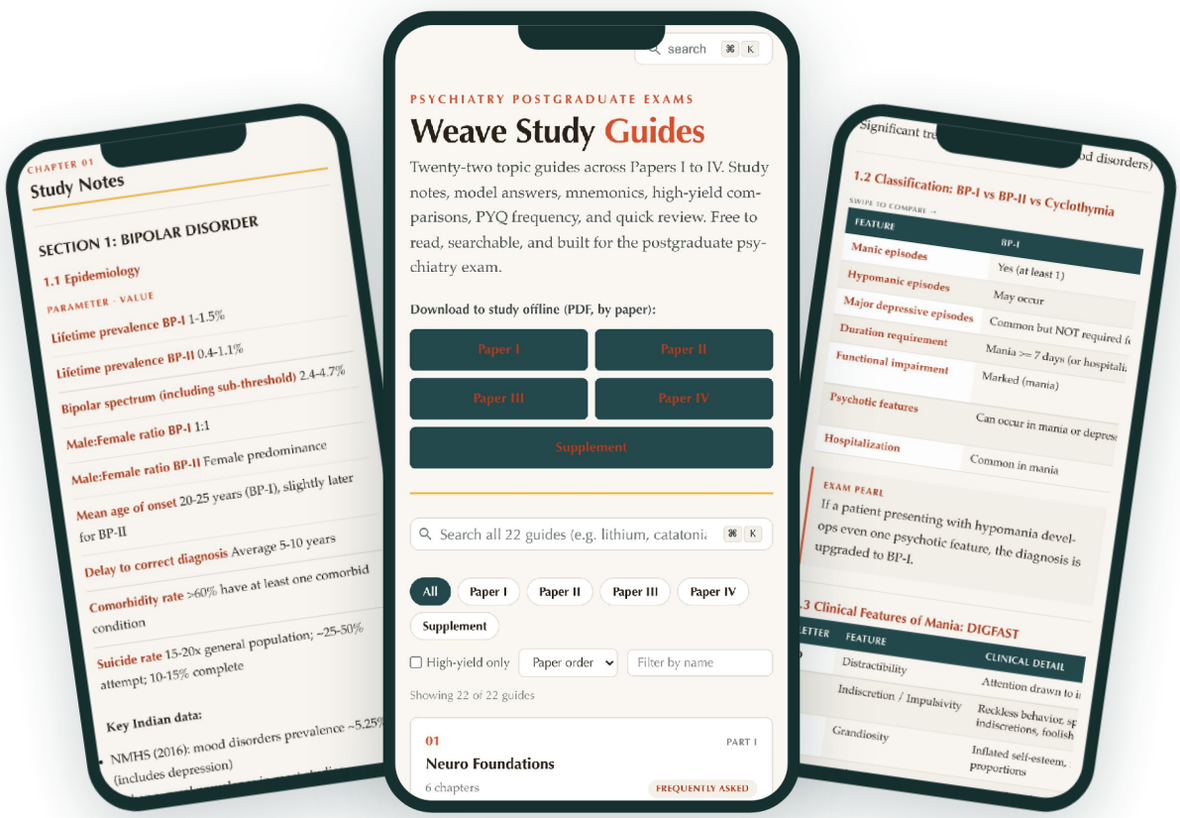

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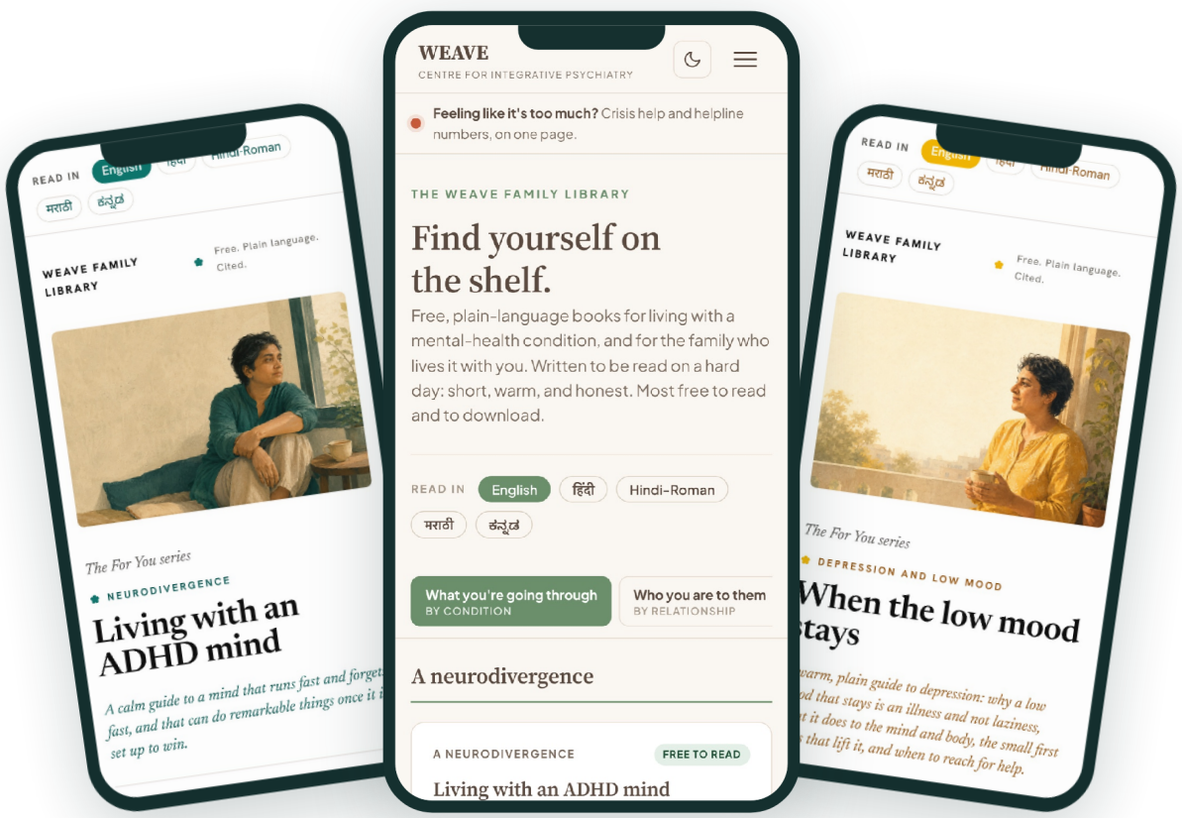

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