WEAVE SPRINT · PAPER II

Schizophrenia

Aetiology, phenomenology, classification and course, the first clinical chapter in one document. Four bands run from the dopamine and neurodevelopmental models, through the phenomenology of the positive, negative and cognitive domains, to the current criteria and the recent nosological change, then to the differential against its mimics and the question of course, prognosis and outcome.

CONTENTS

- Aetiology and neurobiology
- Clinical features and phenomenology
- Classification, subtypes and nosological change
- Course, prognosis and outcome
- Apply and consolidate

Dr. Wilfred D'souza · Dr. Niharika Reddy

WEAVE · CENTRE FOR INTEGRATIVE PSYCHIATRY

Weave
Centre for Integrative Psychiatry

WEAVE SPRINT
PSYCHIATRY OUTREACH PROGRAMME

Psychiatry that listens before it prescribes.

Therapy-informed psychiatry for adults, children, couples and families. Online across India, in person in Mumbai.





Assessments

ADHD, autism and developmental. Anxiety, mood, attention and personality patterns.



Consultations and sessions

Psychiatric consultations, therapy sessions, medication review and couples sessions.



Family Library

Free plain-language guides for families, in five languages.

`weave.clinic/family`

REFER, OR SEND SOMEONE OUR WAY

Your patient contacts Weave directly and decides whether to book.

You remain the referring clinician. Any coordination between clinicians happens with the patient's permission.

CONTACT

`weave.clinic/contact`
`WhatsApp +91 7625004229`

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

WEAVE.CLINIC

Routine referrals only. This is not an emergency route.

Contents

Concept / rule Key number Trap

Aetiology and neurobiology 5

1 Orientation: what schizophrenia is and the criteria map 5

2 Epidemiology: incidence, prevalence, onset and the mortality gap 10

3 Genetics: heritability, twin and adoption data, CNVs and polygenic risk 14

4 The dopamine hypothesis and aberrant salience 18

5 Glutamate, GABA and the other transmitter systems 22

6 The neurodevelopmental model and environmental risk 27

7 Structural neuroimaging and neuropathology 32

Clinical features and phenomenology 37

8 The symptom domains and the dimensional models 37

9 Positive symptoms: delusions, hallucinations and thought disorder 43

10 Negative symptoms and the deficit syndrome 49

11 Disorganisation: disorganised speech and behaviour 54

12 Schneider's first-rank symptoms and Bleuler's fundamental symptoms 59

13 Cognitive impairment, insight and cognition as a treatment target 64

14 Prodrome, the at-risk mental state and first-episode psychosis 70

Classification, subtypes and nosological change 75

15 The diagnostic criteria: ICD-11, DSM-5-TR and the legacy ICD-10 75

16 History and the abolition of the subtypes 81

17 The schizophrenia spectrum and the dimensional debate 86

18 Discriminate: schizophrenia versus its mimics 91

Course, prognosis and outcome 96

19 The phases, natural course and duration of untreated psychosis 96

20 Prognostic factors, cross-cultural outcome and recovery 102

21 Suicide, the mortality gap and physical comorbidity 108

Apply and consolidate 113

22 Apply: four worked clinical vignettes 113

23 Consolidate: mnemonic, retrieval and synthesis 118

Previously asked 122

Quick review 124

References 127

Index 131

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.

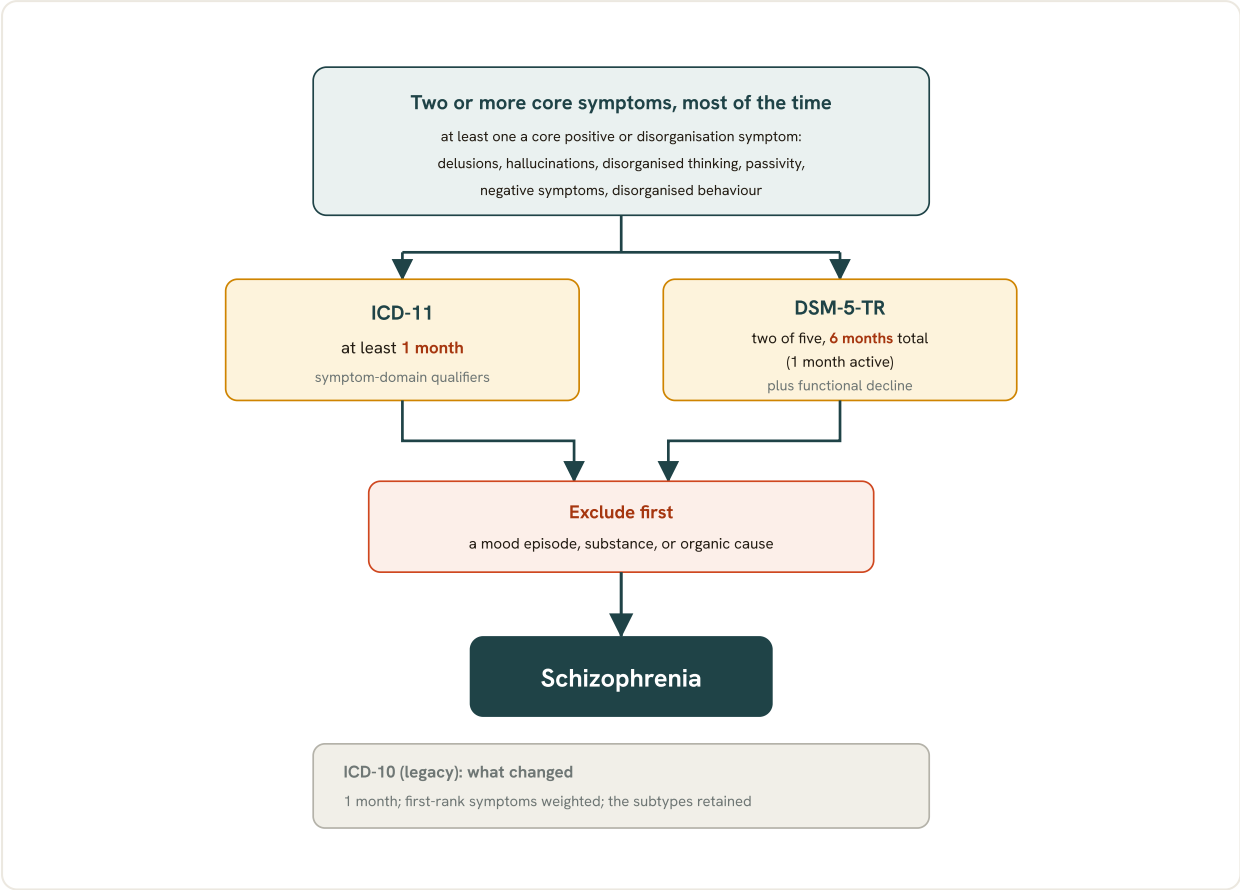


Fig 8.1 The diagnostic criteria as a decision map. Two or more core symptoms, at least one from the positive or disorganisation cluster, must persist for the required duration, ICD-11 asking one month and DSM-5-TR a six-month total with functional decline, and a mood, substance or organic cause must 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).

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).

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.

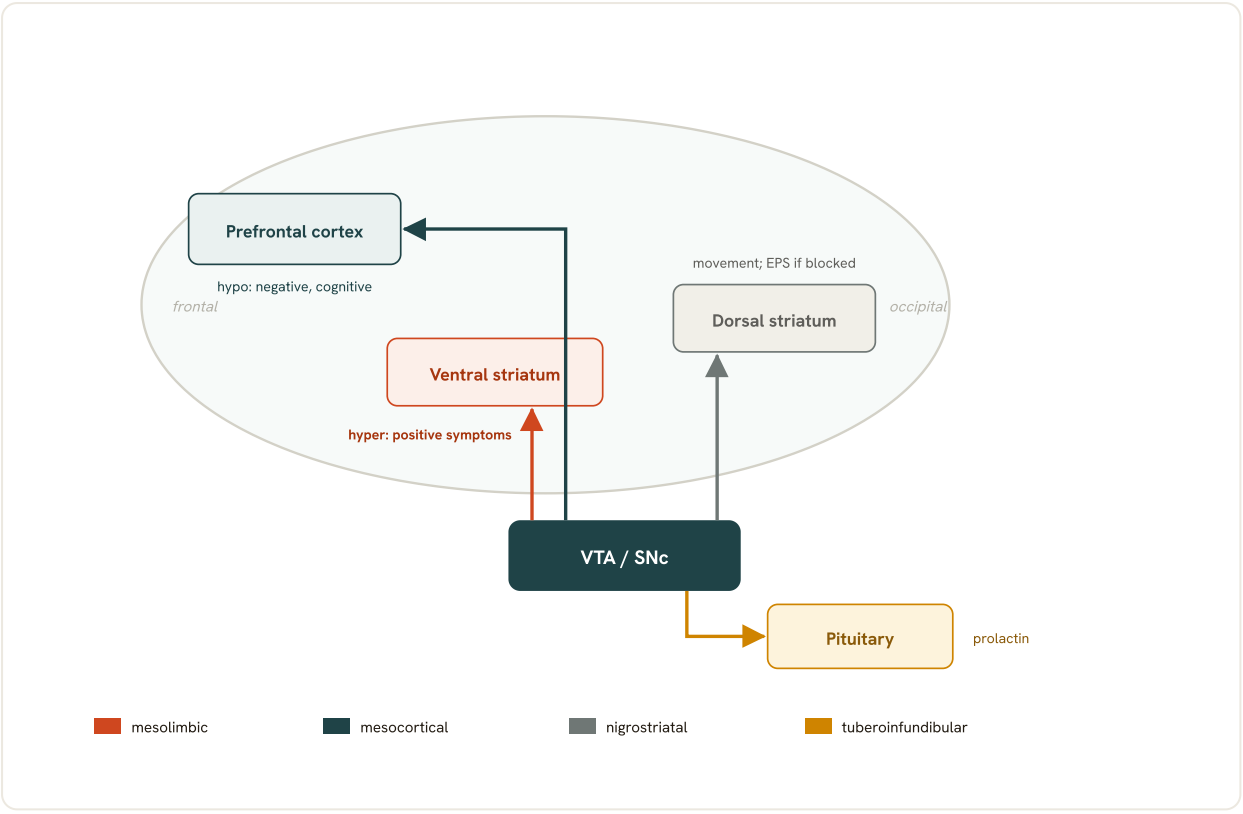


Fig 8.2 The four dopamine pathways on a schematic sagittal brain, colour-coded in the legend. The revised hypothesis is regional: the mesolimbic tract to the ventral striatum is overactive and drives the positive symptoms, while the mesocortical tract to the prefrontal cortex is underactive and underlies 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.

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.

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.

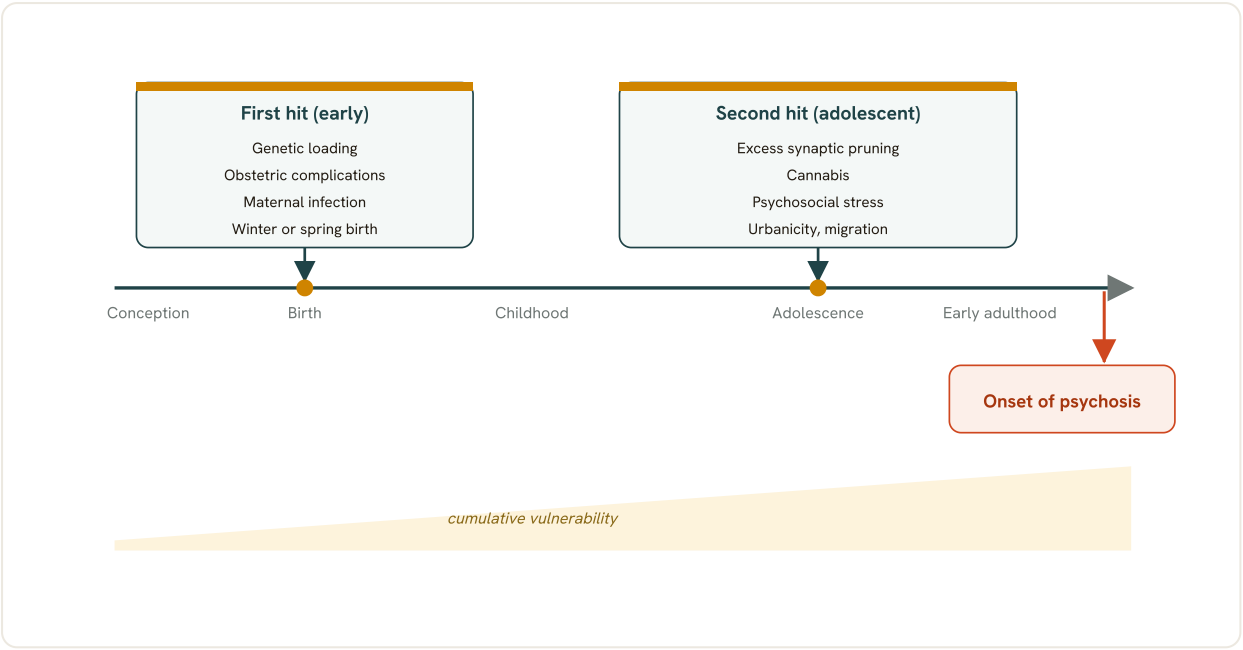


Fig 8.3 The neurodevelopmental two-hit model across the lifespan. An early first hit, genetic and prenatal, primes the vulnerability, which then accumulates until an adolescent second hit, synaptic and psychosocial, precipitates the onset of psychosis as the affected circuits mature. Neither hit alone 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	2.5	1.57	6.7
OR, OBSTETRIC COMPLICATIONS (CANNON 2002)	RR, CANNABIS; ~6X HEAVY (ANDREASSON 1987)	OR, URBANICITY (VAN OS 2003)	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

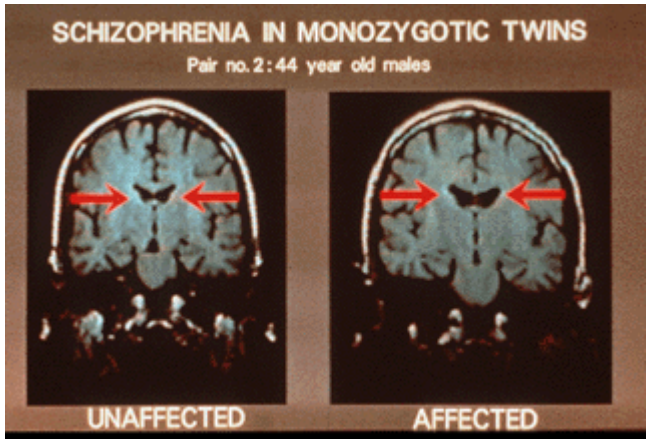
- **Neurodevelopmental hypothesis (Weinberger; Murray & Lewis):** an early fixed lesion of brain development expressed at adolescent circuit maturation; discriminator is the absence of gliosis (developmental, not degenerative).
- **Two-hit model:** first hit = genes plus early neurodevelopmental insult; 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 8.4 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).

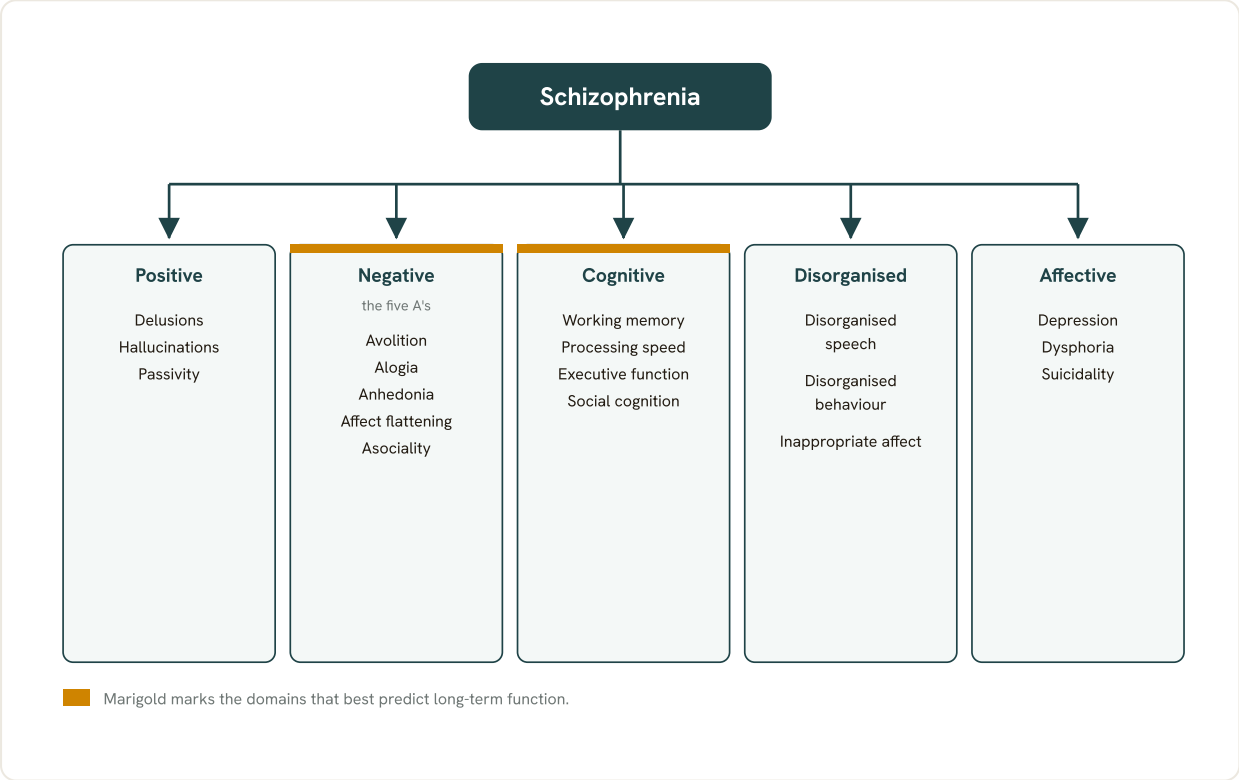


Fig 8.5 The five symptom domains of schizophrenia as one map. A patient is described by a profile across these semi-independent dimensions rather than by a single subtype. The negative and cognitive domains, marked in marigold, carry the greatest weight for long-term functional outcome even though the 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.

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.

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**

SOURCE OF THE NEGATIVE SYMPTOM	MECHANISM	TREATABLE? / ACTION
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).

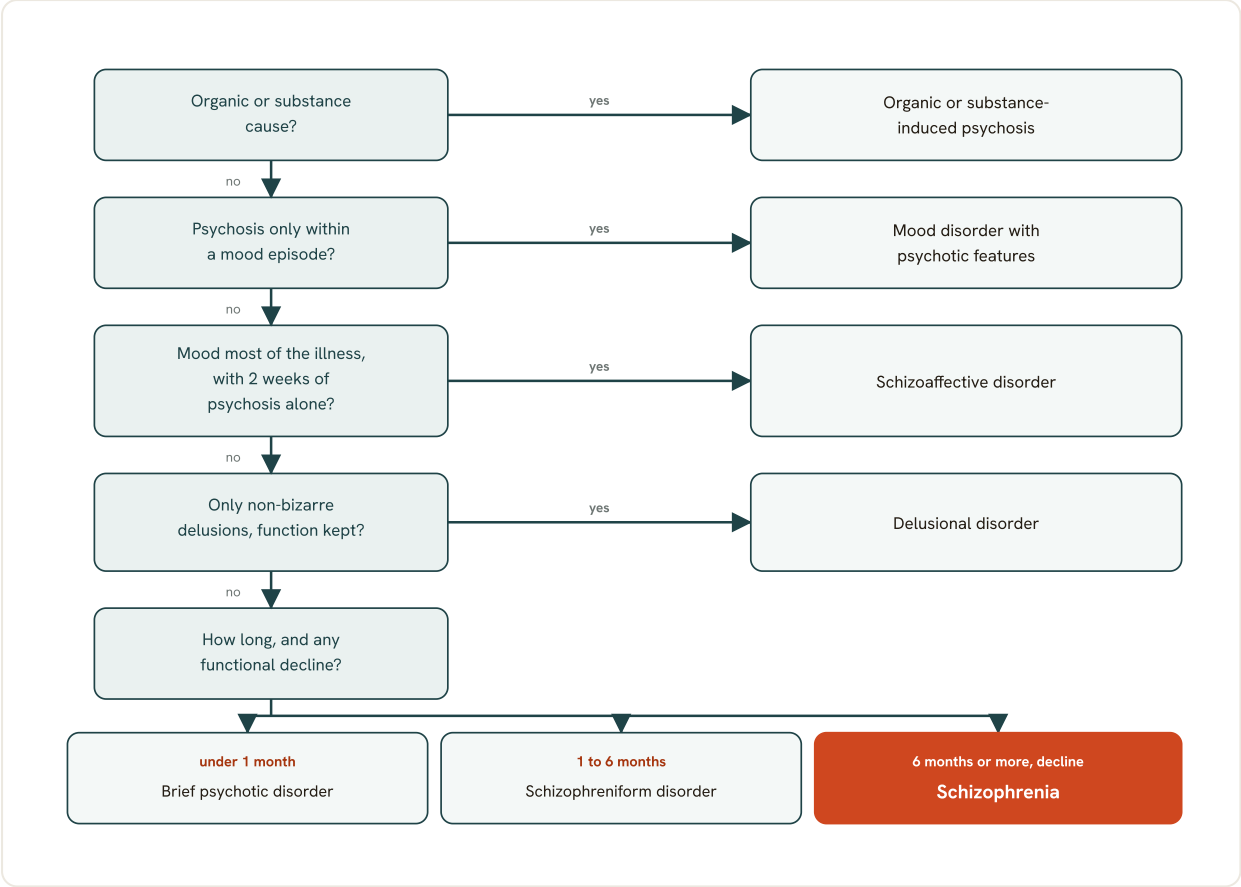


Fig 8.6 The differential decision tree that separates schizophrenia from its mimics. Working down from a first episode of psychosis, each question turns on a single discriminator: rule out an organic or substance cause first, then a mood-confined psychosis, then schizoaffective disorder, then a preserved-function 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 8.6).

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.

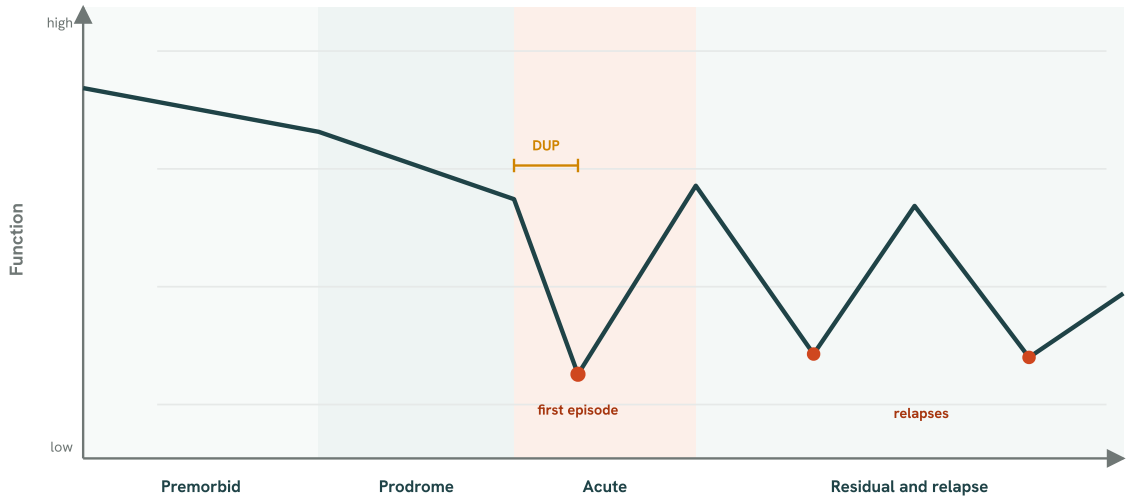


Fig 8.7 The phases and natural course of schizophrenia, plotted as function against time. A near-normal premorbid level declines through the prodrome, drops at the first episode after a duration of untreated psychosis, and then follows a relapsing course with incomplete recovery to a residual baseline. 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 8.8 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.

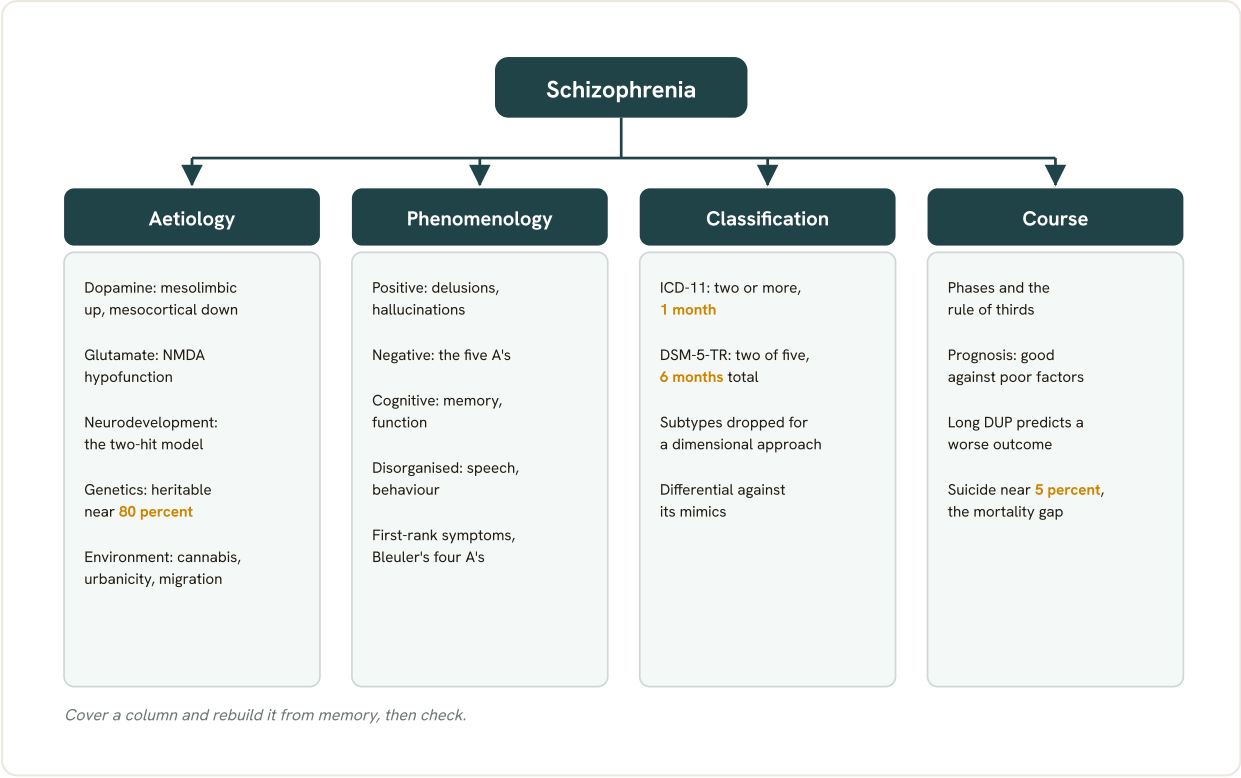


Fig 8.9 The whole chapter as one map, four branches from a single node: aetiology, phenomenology, classification and course. Redraw it from memory, then cover each column and rebuild its contents. The chain runs from cause to phenomenon to criteria to outcome, and holding the four branches together is 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.

SOURCE HIERARCHY (TEXTBOOKS)

1. Boland R, Verduin ML, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 11th ed. Philadelphia: Wolters Kluwer; 2024. [the primary depth bar across aetiology, clinical features, subtypes, course and treatment]
2. Boland R, Verduin ML, eds. Kaplan & Sadock's Synopsis of Psychiatry. 12th ed. Philadelphia: Wolters Kluwer; 2022. [the concise cross-check for definitions and clinical summaries]
3. Geddes JR, Andreasen NC, Goodwin GM, eds. New Oxford Textbook of Psychiatry. 3rd ed. Oxford: Oxford University Press; 2020. [neurobiology, the high-risk state and the neurodevelopmental account]
4. Tasman A, Kay J, Lieberman JA, First MB, Riba MB, eds. Tasman's Psychiatry. Chichester: Wiley-Blackwell; 2024. [phenomenology, epidemiology and the dimensional model of psychosis]
5. Johnstone EC, Owens DGC, Lawrie SM, McIntosh AM, Sharpe M, eds. Companion to Psychiatric Studies. 8th ed. Edinburgh: Churchill Livingstone/Elsevier; 2010. [the structural-imaging and cognitive-deficit evidence base]
6. Harrison P, Cowen P, Burns T, Fazel M. Shorter Oxford Textbook of Psychiatry. 7th ed. Oxford: Oxford University Press; 2018. [course, outcome and the aetiological synthesis]
7. Sims A. Symptoms in the Mind: An Introduction to Descriptive Psychopathology. Oxford: Elsevier; latest ed. [the descriptive-phenomenology definitions of first-rank symptoms, passivity and formal thought disorder]
8. World Health Organization. ICD-11 Clinical Descriptions and Diagnostic Requirements for Mental, Behavioural and Neurodevelopmental Disorders. Geneva: WHO; 2024. [the current international classification and the dimensional symptom specifiers]
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed, text revision (DSM-5-TR). Washington, DC: APA; 2022. [the criteria set, the schizophrenia spectrum and the abandonment of the classical subtypes]
10. Stahl SM. Stahl's Essential Psychopharmacology. 5th ed. Cambridge: Cambridge University Press; 2021. [the dopamine, glutamate and muscarinic circuit models underlying symptoms and treatment]

FOUNDATIONAL SOURCES

1. Kraepelin E. Dementia Praecox and Paraphrenia (Barclay RM, transl; Robertson GM, ed). Edinburgh: E & S Livingstone; 1919. [the original delineation of dementia praecox by early onset and deteriorating course]

2. Bleuler E. Dementia Praecox or the Group of Schizophrenias (Zinkin J, transl). New York: International Universities Press; 1950 (original 1911). [the renaming to schizophrenia and the fundamental versus accessory symptoms, the four A's]
3. Schneider K. Clinical Psychopathology (Hamilton MW, transl). New York: Grune & Stratton; 1959. [the first-rank symptoms as a pragmatic diagnostic emphasis]
4. World Health Organization. The International Pilot Study of Schizophrenia. Geneva: WHO; 1973. [the demonstration that a core syndrome is identifiable across cultures]

JOURNAL REFERENCES (PUBMED-VERIFIED, 51)

1. Heston LL. Psychiatric disorders in foster home reared children of schizophrenic mothers. Br J Psychiatry. 1966;112(489):819-25. PMID: 5966555.
2. Andreasen NC. Thought, language, and communication disorders. I. Clinical assessment, definition of terms, and evaluation of their reliability. Arch Gen Psychiatry. 1979;36(12):1315-21. PMID: 496551.
3. Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet. 1976;2(7992):924-6. PMID: 62160.
4. Seeman P, Lee T, Chau-Wong M, Wong K. Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature. 1976;261(5562):717-9. PMID: 945467.
5. Creese I, Burt DR, Snyder SH. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science. 1976;192(4238):481-3. PMID: 3854.
6. Vaughn CE, Leff JP. The influence of family and social factors on the course of psychiatric illness. A comparison of schizophrenic and depressed neurotic patients. Br J Psychiatry. 1976;129:125-37. PMID: 963348.
7. Crow TJ. Molecular pathology of schizophrenia: more than one disease process? Br Med J. 1980;280(6207):66-8. PMID: 6101544.
8. Andreasen NC. Negative symptoms in schizophrenia. Definition and reliability. Arch Gen Psychiatry. 1982;39(7):784-8. PMID: 7165477.
9. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry. 1987;44(7):660-9. PMID: 3606332.
10. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? Br Med J (Clin Res Ed). 1987;295(6600):681-2. PMID: 3117295.
11. Andreasson S, Allebeck P, Engstrom A, Rydberg U. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. Lancet. 1987;2(8574):1483-6. PMID: 2892048.
12. Liddle PF. The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. Br J Psychiatry. 1987;151:145-51. PMID: 3690102.
13. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76. PMID: 3616518.
14. David AS. Insight and psychosis. Br J Psychiatry. 1990;156:798-808. PMID: 2207510.
15. Liddle PF, Friston KJ, Frith CD, Hirsch SR, Jones T, Frackowiak RS. Patterns of cerebral blood flow in schizophrenia. Br J Psychiatry. 1992;160:179-86. PMID: 1540757.
16. Jablensky A, Sartorius N, Ernberg G, et al. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. Psychol Med Monogr Suppl. 1992;20:1-97. PMID: 1565705.
17. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry. 1994;51(3):199-214. PMID: 8122957.
18. Karayiorgou M, Morris MA, Morrow B, et al. Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. Proc Natl Acad Sci U S A. 1995;92(17):7612-6. PMID: 7644464.
19. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry. 1996;153(3):321-30. PMID: 8610818.
20. Yung AR, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophr Bull. 1996;22(2):353-70. PMID: 8782291.
21. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr Bull. 2000;26(1):119-36. PMID: 10755673.
22. Hopper K, Wanderling J. Revisiting the developed versus developing country distinction in course and outcome in schizophrenia: results from ISoS, the WHO collaborative followup project. Schizophr Bull. 2000;26(4):835-46.

PMID: 11087016.

23. Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. Am J Psychiatry. 2002;159(7):1080-92. PMID: 12091183.
24. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry. 2003;160(1):13-23. PMID: 12505794.
25. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry. 2003;60(12):1187-92. PMID: 14662550.
26. Meltzer HY, Alphs L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen Psychiatry. 2003;60(1):82-91. PMID: 12511175.
27. Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry. 2005;162(3):441-9. PMID: 15741458.
28. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. Arch Gen Psychiatry. 2005;62(9):975-83. PMID: 16143729.
29. Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a reexamination. Arch Gen Psychiatry. 2005;62(3):247-53. PMID: 15753237.
30. Fearon P, Kirkbride JB, Morgan C, et al. Incidence of schizophrenia and other psychoses in ethnic minority groups: results from the MRC AESOP Study. Psychol Med. 2006;36(11):1541-50. PMID: 16938150.
31. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry. 2007;64(10):1123-31. PMID: 17909124.
32. Cohen A, Patel V, Thara R, Gureje O. Questioning an axiom: better prognosis for schizophrenia in the developing world? Schizophr Bull. 2008;34(2):229-44. PMID: 17905787.
33. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008;30:67-76. PMID: 18480098.
34. Cannon TD, Cadenhead K, Cornblatt B, et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Arch Gen Psychiatry. 2008;65(1):28-37. PMID: 18180426.
35. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III, the final common pathway. Schizophr Bull. 2009;35(3):549-62. PMID: 19325164.
36. Large M, Sharma S, Compton MT, Slade T, Nielssen O. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. Arch Gen Psychiatry. 2011;68(6):555-61. PMID: 21300939.
37. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am J Psychiatry. 2011;168(5):472-85. PMID: 21406461.
38. Kirkpatrick B, Strauss GP, Nguyen L, et al. The brief negative symptom scale: psychometric properties. Schizophr Bull. 2011;37(2):300-5. PMID: 20558531.
39. Howes OD, Kambeitz J, Kim E, et al. The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Arch Gen Psychiatry. 2012;69(8):776-86. PMID: 22474070.
40. Fusar-Poli P, Bonoldi I, Yung AR, et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch Gen Psychiatry. 2012;69(3):220-9. PMID: 22393215.
41. Haijma SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. Schizophr Bull. 2013;39(5):1129-38. PMID: 23042112.
42. Jaaskelainen E, Juola P, Hirvonen N, et al. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull. 2013;39(6):1296-306. PMID: 23172003.
43. Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry. 2013;70(1):107-20. PMID: 23165428.
44. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014;511(7510):421-7. PMID: 25056061.
45. Penttila M, Jaaskelainen E, Hirvonen N, Isohanni M, Miettunen J. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. Br J Psychiatry. 2014;205(2):88-94. PMID: 25252316.
46. Kahn RS, Sommer IE, Murray RM, et al. Schizophrenia. Nat Rev Dis Primers. 2015;1:15067. PMID: 27189524.
47. Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet. 2016;388(10039):86-97. PMID: 26777917.
48. Sekar A, Bialas AR, de Rivera H, et al. Schizophrenia risk from complex variation of complement component 4. Nature. 2016;530(7589):177-83. PMID: 26814963.

49. Weinberger DR, Radulescu E. Finding the elusive psychiatric "lesion" with 21st-century neuroanatomy: a note of caution. Am J Psychiatry. 2016;173(1):27-33. PMID: 26315983.

50. Gautham MS, Gururaj G, Varghese M, et al. The National Mental Health Survey of India (2016): Prevalence, socio-demographic correlates and treatment gap of mental morbidity. Int J Soc Psychiatry. 2020;66(4):361-72. PMID: 32126902.

51. Brannan SK, Sawchak S, Miller AC, Lieberman JA, Paul SM, Breier A. Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia. N Engl J Med. 2021;384(8):717-26. PMID: 33626254.

Index

22q11 15
5-HT2A receptor 25
aberrant salience 18
abolition of subtypes 77
absence of gliosis 28
accessory symptoms 62
Acetylcholine 22
acute 6
acute onset 40
adoption 5
affective flattening 50
age of onset 12
alogia 7
Andreasen 53
anhedonia 7
asociality 7
at-risk mental state 70
attenuated psychosis 72
avolition 7
avolition-apathy 51
basic symptoms 71
Bleuler 4
BNSS 53
Brief psychotic 87
Brief psychotic disorder 87
C4 16
CAINS 53
cannabis 17
catatonia 5
Catatonic 7
categorical 76
circumstantiality 55
Clang associations 56
cnv 14
cognitive 4
cognitive hypothesis 66
cognitive impairment 4
cognitive remediation therapy 67
comorbidity 53
copy number 16
course specifier 76
Criterion A 7
cross-cultural 10
Crow 38
cytoarchitecture 32
de-prioritisation 79
de-prioritization 79
decision tree 5
deficit syndrome 20
Delusional disorder 5
Delusional mood 21
Delusional perception 45
dementia praecox 39
Derailment 39
Determinants of Outcome of Severe Mental Disorders 100
developing countries 105
developmental hypothesis 27
differential 4
differential diagnosis 91
dimensional 8
diminished expression 51
DISC1 16
disorganisation 4
disorganisation syndrome 41
Disorganised behaviour 6
disorganised speech 7
domain qualifier 6
dopamine hypothesis 4
dopamine pathway 19
dosmed 100
drift hypothesis 31
DSM-5 4
DSM-5-TR 4
DSM-IV 79
DTNBP1 17
DUP 16
duration 6
duration of untreated psychosis 73
dysconnectivity 35
early onset 50
endophenotype 23
exclusion 7
Expressed emotion 30
extended psychosis phenotype 89
fep 73
First-episode psychosis 70
first-rank symptoms 4
five domain 5
five negative-symptom domains 50

formal thought disorder 5
functional impact 67
Functional outcome 38
fundamental symptoms 4
GABA 22
gamma oscillations 24
glutamate hypothesis 22
glutamic acid decarboxylase 24
good prognosis 103
grey matter 34
GWAS 15
hebephrenia 81
Hebephrenic 8
heritability 4
hippocampal 28
hyperdopaminergia 20
hypofrontality 35
ICD-10 4
ICD-11 4
Inappropriate affect 38
incidence 10
insidious onset 40
insight 39
International Pilot Study of Schizophrenia 97
International Study of Schizophrenia 97
ipss 100
isos 100
KarXT 68
ketamine 23
Kraepelin 39
Kurt Schneider 59
kynurenine 25
legacy 4
Liddle 38
lifetime morbid risk 10
lifetime risk 4
long-term outcome 50
loosening of associations 39
major depressive disorder with psychotic features 115
majority 78
master mnemonic 5
MATRICS Consensus Cognitive Battery 65
mesocortical 19
mesolimbic 19
metabolic screening 109
MHC 16
microglial 25
Migration 17
mnemonic 5
mood 5
mood disorder with psychotic 5
muscarinic 25
National Mental Health Survey 12
natural course 96
negative symptom 4
negative symptoms 4
neologism 46
neurocognition 65
neurodevelopmental hypothesis 27
neuroimaging 4
neuroinflammation 22
neuropathology 4
neuropil 32
nicotinic receptor 25
nigrostriatal 19
NMDA receptor 22
NMDA receptor hypofunction 22
no gliosis 31
not pathognomonic 46
NRG1 16
obstetric complication 17
one month 6
organic 5
organic and substance workup 91
organic psychosis 73
original 4
P50 23
panss 53
Paranoid 8
parvalbumin interneuron 24
passivity 6
passivity phenomena 44
pathognomonic 7
PCP 23
persistent negative symptoms 98
phencyclidine 23
point prevalence 10
polygenic 14
polygenic risk score 16
poor prognosis 52
positive symptom 4
Poverty of content of speech 56
precipitant 99
premature death 110
premorbid 9

premorbid functioning 103
prepulse inhibition 74
Prevalence 6
primary negative symptom 51
prodromal phase 98
prodrome 4
proneness-persistence-impairment model 89
psychomotor poverty 35
psychosis continuum 86
psychotic-like experiences 88
reality distortion 41
Recovery 31
relapse 31
remission 40
remission criteria 106
Remission in Schizophrenia Working Group 106
Residual 8
residual phase 9
revised 4
rule of thirds 97
sans 53
Schedule for the Assessment of Insight 69
Schedule for the Deficit Syndrome 52
Schizoaffective 5
Schizoaffective disorder 5
schizophrenia spectrum 86
Schizophreniform 5
Schizophreniform disorder 8
Schizotypal disorder 87
Schneiderian first-rank symptoms 8
season of birth 29
secondary negative symptom 39
secondary psychosis 94
serious mental illness 109
serotonin 22
severity 42
sex difference 6
Simple schizophrenia 81
six month 8
SMI 4
Social causation 31
social drift 31
Somatic passivity 59
substance-induced 5
substance-induced psychosis 5
subtype 4
subtype removal 79
suicide risk 7
symptom domain 4
symptom-domain 6
synaptic pruning 16
synthesis map 119
Tangentiality 39
temporal confinement 92
thought broadcasting 44
thought insertion 8
three-syndrome 38
time 4
tuberoinfundibular 19
Twin 5
two of five 6
two weeks 45
two-hit 4
Type I 38
Type II 38
ultra-high-risk 70
Undifferentiated 77
Urbanicity 11
ventricular enlargement 28
what changed 5
word approximation 56
Word salad 46
Xanomeline 68

PRINTING AND DISTRIBUTION

Notes Next Door (NND), Delhi is the official printing and distribution partner for Weave Sprint. The soft-copy PDFs and the complete print-ready set are always available at weave.clinic/sprint, should you prefer to print the notes yourself. Weave Sprint is open source and free, and as part of Weave's commitment to residents it will stay that way, forever. We do, however, strongly recommend a printed set from Notes Next Door: in our experience, they have been the most reliable printing partner we have worked with.