WEAVE SPRINT · PAPER I

Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology

The chemical brain the exam tests: the transmitter systems, the hormonal axes, how we image the machinery, and how drugs move it. One complete set of notes, read systems not molecules.

CONTENTS

- Neurochemistry
- Neuroendocrinology
- Neuroimaging
- Basic psychopharmacology
- 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

Neurochemistry 4

1 Orientation: the chemical brain from molecule to syndrome 4

2 Dopamine pathways and clinical correlates 9

3 Serotonin system and receptor subtypes 17

4 Noradrenergic system 24

5 Glutamate and NMDA receptor subtypes (hypofunction model) 30

6 GABA receptor subtypes and pharmacology 37

7 Cholinergic systems 43

8 Neuropeptides (substance P, CRF, oxytocin and others) 50

9 Novel and gasotransmitters: endocannabinoids, nitric oxide, trace amines 57

10 Second messengers and signal transduction 62

11 Neurodevelopment: migration, pruning, critical periods 69

12 Neurotrophins and BDNF 77

Neuroendocrinology 83

13 HPA axis, stress and cortisol 83

14 HPT and HPG axes in psychiatry 91

15 Circadian rhythms and melatonin 98

Neuroimaging 105

16 Structural imaging (CT/MRI) findings in psychiatric disorders 105

17 Functional imaging (fMRI/PET/SPECT) principles and findings 116

Basic psychopharmacology 126

18 Pharmacokinetics (ADME) 126

19 Pharmacodynamics, receptor theory and dose-response 133

20 CYP450 system and drug metabolism 140

21 Receptor up/down-regulation, tolerance and sensitisation 146

Apply and consolidate 153

22 Apply: four mechanism-to-bedside vignettes 153

23 Consolidate: mnemonic total, retrieval and synthesis 157

Previously asked 163

Quick review 165

References 166

Index 172

Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology

Five sections · 23 topics · one complete notes document

the Functional Neuroanatomy & Neurophysiology notes built the wiring. This material builds what runs through it: the handful of neurotransmitter systems the brain actually uses, the three hormonal axes that set its tone, the imaging that lets us see the machinery, and the pharmacology that lets us move it. **Read systems, not molecules.** Almost every answer in this territory rewards the candidate who names the receptor, the pathway and the clinical read-out together, rather than reciting a synthesis chain. These notes run in the order a drug does its work: which chemical, at which receptor, through which second messenger, changing which circuit, producing which clinical effect.

HOW TO USE THESE NOTES

Every figure declares one clinical axis and codes it in colour and shape, with a small legend. The colours are consistent throughout: **petrol** marks structure, the receptor and the relay or executive role, **coral** marks danger, pathology or an excess or deficit state, and **marigold** highlights the drive, reward or facilitatory element. Learn the key once and every diagram reads faster.

Neurochemistry

1 · Orientation: the chemical brain from molecule to syndrome

Before the detail, the frame. the Functional Neuroanatomy & Neurophysiology notes mapped *where* the brain sits and *how* its structures wire together. Today is the layer on top: *how the wiring signals*, and how a molecule, once you follow it far enough, becomes a syndrome and then a drug target. This whole chapter runs on one move, repeated throughout: **trace the molecule to the syndrome to the drug**. A transmitter is made, released, meets a receptor, and reads out through a second messenger; a hormone axis sets the background tone; imaging is how the machinery is seen; and pharmacokinetics-pharmacodynamics is how a drug is pushed into that circuit. Hold that chain and every topic below has a place to land.

The brain does not use hundreds of signals. It runs on a small, examinable set: the **monoamines** (dopamine, serotonin, noradrenaline, and their cousins adrenaline and histamine), the fast amino acids (**glutamate** excitatory, **GABA** and glycine inhibitory), **acetylcholine**, and the slow, modulatory **neuropeptides** (including the endogenous opioids). Newer entrants, the gasotransmitters and the lipid-derived endocannabinoids, break the classical rules and are examined precisely because they do. Every one of these is read out downstream through second messengers and neurotrophic signalling, and three neuroendocrine axes (the HPA stress axis, the HPT and HPG hormonal axes, and the circadian clock) set the hormonal weather in which they all operate. That is the whole territory.

HOLD THIS

Answer with the receptor, the pathway and the clinical read-out together, never a bare synthesis chain. Almost every mark in this territory rewards trace-the-molecule-to-syndrome-to-drug over reciting a biosynthesis pathway.

1.1 The four sub-areas, bound in one frame

This chapter is four connected territories, not four silos. Learn them as a single sentence: *the chemistry does the signalling, the endocrine axes set the tone, imaging shows the machinery, and pharmacology is how we move it*. Each later topic slots under one of these four.

Neurochemistry

The transmitter systems (monoamines, amino acids, acetylcholine, neuropeptides, and the novel gaso- and lipid transmitters), their receptors, and the intracellular second-messenger and neurotrophic cascades they trigger. This is the engine of the chapter.

Neuroendocrinology

The three axes that set the hormonal background: the hypothalamic-pituitary-adrenal (HPA) stress axis, the thyroid and gonadal axes (HPT and HPG), and the circadian and pineal-melatonin clock. The interface where transmitter and hormone meet.

Neuroimaging

How the machinery is seen: structural (CT, MRI), functional (fMRI, PET, SPECT), and the molecular readouts (receptor and transporter occupancy, spectroscopy) that make a transmitter hypothesis testable in a living patient.

Basic psychopharmacology

Pharmacokinetics (how the drug moves: absorption, distribution, metabolism, excretion) and pharmacodynamics (what the drug does at the receptor: agonist, antagonist, partial agonist, inverse agonist). This is how the whole system is deliberately pushed.

1.2 Classification of neurotransmitters: the same list read on five different axes

Examiners ask you to *classify the neurotransmitters*, and the discriminating answer is that there is no single classification: the same set of molecules is sorted differently depending on the question you ask of it. Kaplan and Sadock frame the historical arc that produces this (Kaplan & Sadock 2024): the first transmitters found were small chemicals (acetylcholine, then the biogenic amines), then amino acids and peptides were recognised, then in the 1990s a lipid-derived signal (the endocannabinoids) and even a gas (nitric oxide) qualified, each bending the old definition. So instead of one list, hold five axes. Read the table across each row as one lens on the same molecules.

CLASSIFYING AXIS	CATEGORIES	MEMBERS AND THE DISCRIMINATOR THAT DEFINES EACH
(a) Chemical structure / class	Small-molecule vs neuropeptide vs gasotransmitter vs lipid messenger	**Small-molecule splits into monoamine (dopamine, serotonin, noradrenaline, adrenaline, histamine), amino-acid (glutamate, GABA, glycine) and acetylcholine; then neuropeptides (endorphins, substance P, CRH, oxytocin), gasotransmitters (NO, CO, H2S) and lipid endocannabinoids (anandamide, 2-AG)**
(b) Functional effect	Excitatory vs inhibitory vs modulatory	**Glutamate is the main excitatory workhorse; GABA and glycine are the main inhibitory brakes; the monoamines are chiefly *modulatory*, tuning gain rather than driving firing directly**
(c) Signalling and speed	Ionotropic vs metabotropic	**Ionotropic = a ligand-gated ion channel, fast (milliseconds): NMDA/AMPA, GABA-A, nicotinic, 5-HT3. Metabotropic = a G-protein-coupled receptor, slow (seconds and up) via a second messenger: all monoamine receptors, muscarinic, GABA-B, mGluR**
(d) Synthesis and storage	Classical vesicular vs non-classical made-on-demand	**Classical transmitters are pre-synthesised, packaged in vesicles and released by exocytosis; the gasotransmitters and endocannabinoids are *made on demand* and released *retrogradely* from the post-synaptic cell back onto the pre-synaptic terminal, with no vesicle and, for gases, no membrane receptor**
(e) Dale's principle and co-transmission	One-transmitter model vs co-transmission	**Dale's principle (one neuron, one transmitter) is an oversimplification; most neurons *co-transmit*, typically a fast small-molecule transmitter plus a slow modulatory neuropeptide released from the same terminal (for example noradrenaline with NPY)**

The high-yield insight is that axes (c) and (d) cut across axis (a): acetylcholine, glutamate, GABA and serotonin each act at *both* ionotropic and metabotropic receptors, so "fast or slow" is a property of the receptor, not the transmitter. The made-

on-demand, retrograde, non-vesicular pattern of the gases and endocannabinoids is the single most examined "exception" in the classification.

RULE **Fast-or-slow is a property of the receptor, not the transmitter.** ACh, glutamate, GABA and serotonin each act at both an ionotropic and a metabotropic receptor.

1.3 The made-on-demand exceptions: gasotransmitters and endocannabinoids

Why they matter. These two families break every rule a classical transmitter obeys, which is exactly why a Paper-1 stem singles them out. The **gasotransmitters** are nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H2S). Take NO as the model (Kaplan & Sadock 2024): it is not stored in vesicles but synthesised on demand by nitric oxide synthase from the amino acid arginine (yielding citrulline as a byproduct); being a small gas it diffuses freely across membranes rather than binding a surface receptor, acting directly on an intracellular target (soluble guanylyl cyclase, raising cyclic GMP); it has no reuptake mechanism and a half-life of only a few seconds. Functionally NO is tied to long-term potentiation and memory (it is generated post-synaptically after NMDA-receptor calcium entry and signals retrogradely), and its peripheral cGMP pathway is the target of the phosphodiesterase-5 inhibitors sildenafil and tadalafil. CO, made by heme oxygenase, activates the same guanylyl cyclase pathway more weakly.

The **endocannabinoids**, anandamide and 2-arachidonoylglycerol (2-AG), are the lipid-messenger class: derived from membrane lipids, synthesised on demand in the post-synaptic neuron, and released *retrogradely* onto pre-synaptic CB1 receptors to dampen further transmitter release (a feedback brake). Delta-9-THC is a partial agonist at CB1; rimonabant is a CB1 inverse agonist. Note the parallel with the gases: no vesicle, made when needed, and signalling backwards across the synapse.

COMMON TRAP

Do not call nitric oxide an "inhibitory" or "excitatory" transmitter in the amino-acid sense, and do not say it binds a membrane receptor. NO has no cell-surface receptor and no reuptake; it diffuses in and acts on an intracellular enzyme. Equally, the endocannabinoids are *retrograde* messengers (post-synaptic to pre-synaptic), the reverse of the classical direction, and they are not stored in vesicles.

1.4 The map in one schema: transmitter to receptor family to clinical signature

Before these notes fan out into one system per topic, bind each transmitter to its receptor family and the one clinical role that makes it examinable. This pearl is the spine to redraw from memory; every later topic pays it back in detail.

THE MAP, IN ONE SCHEMA

Dopamine (metabotropic D1 to D5): the psychosis-and-reward transmitter; four pathways, the mesolimbic drives positive symptoms. **Serotonin** (metabotropic, plus the one ionotropic 5-HT3): mood, anxiety, and the SSRI target; 5-HT3 is the emesis and gut receptor. **Noradrenaline** (metabotropic alpha and beta): arousal, attention and the stress response. **Glutamate** (ionotropic NMDA/AMPA/kainate, plus metabotropic mGluR): the main excitatory drive; NMDA hypofunction is the modern schizophrenia and ketamine story, and its overactivity is excitotoxicity. **GABA** (ionotropic GABA-A, metabotropic GABA-B): the main inhibitory brake and the benzodiazepine, barbiturate, alcohol and neurosteroid site. **Acetylcholine** (ionotropic nicotinic, metabotropic muscarinic): memory and the cholinergic hypothesis of Alzheimer disease. **Neuropeptides** (metabotropic): slow modulators, co-released with the classics; the opioid peptides run analgesia and reward. **Gases and endocannabinoids:** the made-on-demand, retrograde exceptions.

1.5 The master mnemonic, seeded now

The consolidation block at the end pays this schema back as a whole synthesis map. Seed the master mnemonic now so the material builds toward it: **"Some Modulators Are Nicely Guiding Growth And Neuroendocrine Physiology."** Unpacked, it walks the systems in order: **S**ignalling (the transmitter systems), **M**onoamines, **A**mino acids, **N**europeptides and **G**ases, then the second-messenger and neurotrophic **G**rowth signalling, **A**xes (HPA, HPT-HPG, circadian) as the **N**euroendocrine tone, and finally **P**harmacology (kinetics and dynamics) as how the whole thing is imaged and moved. The one-line spine to build toward: *a handful of transmitters signal fast or slow, second messengers and neurotrophins read them out, three axes set the tone, imaging shows it, and pharmacology moves it*.

1.6 Cross-references to the Functional Neuroanatomy & Neurophysiology notes: what is already yours

This chapter deliberately does *not* re-teach the anatomy that the Functional Neuroanatomy & Neurophysiology notes established; it builds the chemistry on top of it. Three things are already yours from the Functional Neuroanatomy & Neurophysiology notes and are only cross-referenced here.

Nuclei of origin

The discrete brainstem sources of the ascending modulatory pathways, covered on the Functional Neuroanatomy & Neurophysiology notes: the ventral tegmental area and substantia nigra (dopamine), the raphe nuclei (serotonin), the locus coeruleus (noradrenaline), and the basal forebrain and pedunculopontine nuclei (acetylcholine). Today assumes you can name where each transmitter comes from.

The stress circuit

The limbic-hypothalamic drive of the stress response (amygdala to paraventricular nucleus) was drawn on the Functional Neuroanatomy & Neurophysiology notes; today adds the endocrine arm, the HPA axis and its cortisol feedback, on top of it.

The large-scale networks

The default-mode, salience and executive networks (the Functional Neuroanatomy & Neurophysiology notes) are the substrate that today's neuroimaging topic reads out functionally.

CLINICAL ANCHOR

Neuroinflammation stays on the Functional Neuroanatomy & Neurophysiology notes. The cytokine and microglial story (the inflammatory hypothesis of depression, IL-6 and TNF-alpha, microglial activation) is owned by the Functional Neuroanatomy & Neurophysiology notes and is only cross-referenced today. When a topic here touches an immune signal, point back to the Functional Neuroanatomy & Neurophysiology notes rather than re-teaching it; this chapter's remit is the transmitter, endocrine, imaging and pharmacology layers.

2 · Dopamine pathways and clinical correlates

Dopamine is the neurotransmitter examiners return to more than any other, because a single molecule ties together the phenomenology of psychosis, the whole architecture of antipsychotic drug action, the neurology of Parkinson disease, the pathophysiology of addiction, and the pharmacology of stimulants in ADHD. The trick to owning this topic is to hold three layers in register at once: the **biochemical layer** (how dopamine is made, stored and broken down), the **receptor layer** (two G-protein families with opposite second-messenger signs), and the **anatomical layer** (four projection systems, each with one signature clinical consequence). Almost every single-best-answer item is really asking you to connect a drug action at one layer to a symptom at another.

Exam framing. The four-pathway map is the spine of the topic and the reason Stahl's antipsychotic logic works: an antipsychotic given for a mesolimbic problem inevitably blocks D2 in three other pathways it never meant to touch, and each unwanted blockade is a named side effect. Learn the pathways as a system of trade-offs, not four isolated facts. Cross-reference the the Functional Neuroanatomy & Neurophysiology notes material on the midbrain dopaminergic nuclei: the **ventral tegmental area (VTA)** is the cell body of origin for the two mesocorticolimbic pathways, and the **substantia nigra pars compacta (SNc)** is the origin of the nigrostriatal pathway.

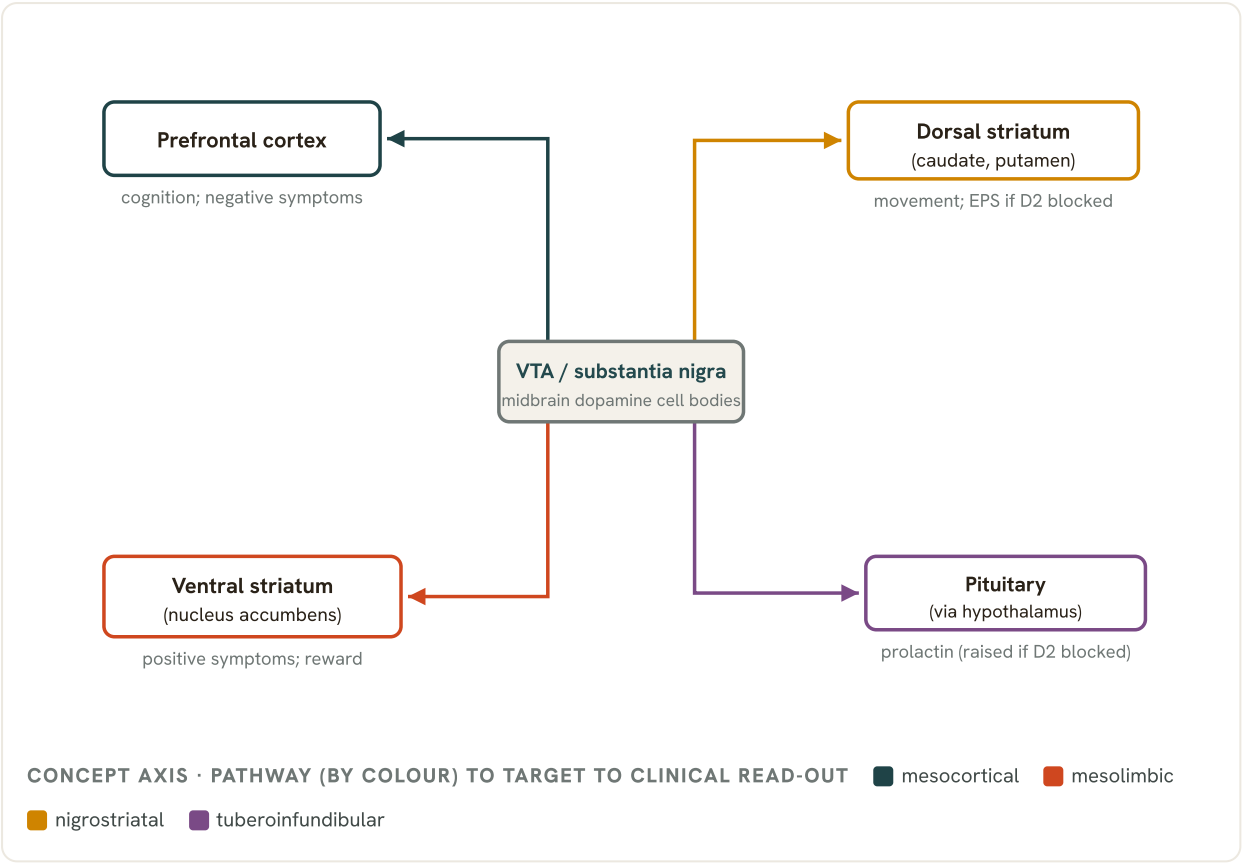


Fig 2.1 The four dopamine pathways from the midbrain nuclei (VTA and substantia nigra), each ending at its target with the clinical read-out a D2 blocker produces there. Mesocortical (petrol) runs to prefrontal cortex, mesolimbic (coral) to ventral striatum, nigrostriatal (marigold) to dorsal striatum, tuberoinfundibular (plum) to the pituitary. Mesolimbic overactivity drives positive symptoms; mesocortical underactivity underlies negative and cognitive symptoms; blocking nigrostriatal D2 gives extrapyramidal side effects; blocking tuberoinfundibular D2 raises prolactin. Benefit and harm are the same drug read on different pathways.

2.1 Synthesis: tyrosine to dopamine, and why tyrosine hydroxylase is the pace-setter

Dopamine sits in the middle of the catecholamine synthetic chain, sharing its first two steps with noradrenaline and adrenaline (Kaplan & Sadock 2024). Bloodborne **tyrosine**, from dietary protein and from phenylalanine, crosses into the brain on the large neutral amino acid transporter and is taken into catecholamine neurons by a high-affinity amino acid transporter.

Step 1: Tyrosine to L-DOPA

In the cytosol, **tyrosine hydroxylase (TH)** hydroxylates tyrosine to L-DOPA (dihydroxyphenylalanine). This is the **rate-limiting step**: it sets the pace of the whole pathway and is the point most open to physiological regulation (end-product inhibition, autoreceptor feedback) and pharmacological attack. TH requires the cofactor *tetrahydrobiopterin (BH4)*, whose own synthesis depends on GTP-cyclohydrolase-1. The competitive TH inhibitor *alpha-methyltyrosine (metyrosine)* depletes catecholamines and is used in phaeochromocytoma.

Step 2: L-DOPA to dopamine

Cytosolic **aromatic amino acid decarboxylase (AADC)**, also called DOPA decarboxylase, decarboxylates L-DOPA to dopamine so avidly that brain L-DOPA levels stay very low. Because exogenous L-DOPA needs only AADC and bypasses the rate-limiting TH step, it is the mainstay of Parkinson disease treatment, restoring depleted striatal dopamine.

Onward (in other neurons only)

In noradrenergic neurons a further vesicular enzyme, *dopamine-beta-hydroxylase (DBH)*, converts dopamine to noradrenaline; adrenaline neurons add *PNMT*. Dopamine neurons lack DBH, which is precisely why they stop at dopamine.

Storage. Newly made dopamine is pumped from cytosol into synaptic vesicles by the **vesicular monoamine transporter (VMAT-2)**, which both concentrates the transmitter for release and shields it from mitochondrial MAO. *Reserpine* irreversibly inhibits VMAT and depletes stores; *tetrabenazine and valbenazine/deutetrabenazine* reversibly inhibit VMAT-2 and are used for chorea and tardive dyskinesia. Amphetamine-class drugs reverse VMAT and the membrane transporter, flooding the synapse.

CLINICAL ANCHOR

The carbidopa/benserazide logic falls straight out of this pathway. Given alone, L-DOPA is decarboxylated to dopamine in the periphery (by AADC in gut and vessels), causing nausea and hypotension and wasting most of the dose. A peripheral AADC inhibitor that cannot cross the blood-brain barrier (carbidopa, benserazide) blocks that peripheral conversion, so more L-DOPA reaches the brain and peripheral side effects fall. Peripheral dopamine also drives emesis via the area postrema, which lies outside the blood-brain barrier, the reason D2 antagonists such as metoclopramide and domperidone are antiemetics.

2.2 Metabolism: MAO, COMT and the HVA read-out

Dopamine is cleared first by reuptake and then by enzymatic degradation through two enzymes acting in either order (Kaplan & Sadock 2024). After release, most dopamine is recaptured by the **dopamine transporter (DAT)** on the presynaptic membrane, the target blocked by *cocaine, methylphenidate and amphetamine*. Degradation then proceeds through:

Monoamine oxidase (MAO)

A mitochondrial (chiefly intraneuronal) enzyme. The **MAO-B** isoform preferentially metabolises dopamine in human brain; its inhibitors (*selegiline, rasagiline, safinamide*) are used in Parkinson disease. MAO oxidatively deaminates dopamine to the intermediate DOPAC.

Catechol-O-methyltransferase (COMT)

A largely extraneuronal, methylating enzyme important in the **prefrontal cortex**, where DAT expression is sparse, so COMT (not reuptake) is the dominant terminator of dopamine action. COMT inhibitors (*tolcapone, entacapone, opicapone*) prolong L-DOPA action. The *COMT Val158Met* polymorphism (Met = lower enzyme activity, higher prefrontal dopamine) is a recurrent exam link to prefrontal cognition and schizophrenia risk.

Homovanillic acid (HVA)

The final, sequential product of MAO and COMT acting together. **HVA** is the principal end-metabolite of dopamine and, in CSF or plasma, is used as an index of central dopaminergic turnover.

PEARL

Fix the end-metabolites by transmitter: dopamine to **HVA**; noradrenaline to **MHPG** (3-methoxy-4-hydroxyphenylglycol); serotonin to **5-HIAA**. The shared dopamine/noradrenaline intermediate DOPAC and the vanilla-family naming (HVA is homovanillic) are common distractors. COMT dominating in the cortex while DAT dominates in the striatum is the single most useful regional contrast on this subtopic.

2.3 Receptors: two families, opposite signs

All five dopamine receptors are G-protein-coupled and sort into two families defined by their effect on adenylate cyclase and cyclic AMP. The D1-like family is stimulatory, the D2-like family inhibitory, and holding that polarity straight explains most of the pharmacology.

FAMILY	MEMBERS	G-PROTEIN / CYCLASE	LOCATION AND CLINICAL NOTE
D1-like	D1, D5	**Gs: stimulate adenylate cyclase, raise cAMP**	D1 densest in striatum and cortex; postsynaptic only; excitatory drive on the direct striatal pathway
D2-like	D2, D3, D4	**Gi/Go: inhibit adenylate cyclase, lower cAMP**	Pre- and postsynaptic; the antipsychotic target; D2 also mediates autoreceptor feedback

The two dopamine receptor families. The discriminator to memorise is the second-messenger sign: D1-like couples to Gs and raises cAMP, D2-like couples to Gi and lowers it.

Within-family detail. D2 is the receptor whose occupancy tracks antipsychotic efficacy and extrapyramidal risk; it exists as short (presynaptic autoreceptor) and long (postsynaptic) isoforms. **D3** concentrates in limbic regions (nucleus accumbens) and is a target of interest for negative symptoms and addiction; *cariprazine* is a D3-preferring D2/D3 partial agonist. **D4** is enriched in cortex and limbic areas, has been linked (weakly and inconsistently) to ADHD and novelty-seeking through the *DRD4 7-repeat* allele, and is notable as a receptor at which *clozapine* has relatively high affinity. Antipsychotic clinical potency correlates tightly with D2 (not D1) affinity, the pharmacological cornerstone of the dopamine hypothesis.

COMMON TRAP

Do not equate "D2 antagonism" with "antipsychotics only". The same D2 blockade that reduces psychosis also produces the antiemetic effect (area postrema), the extrapyramidal effect (nigrostriatal), and hyperprolactinaemia (tuberoinfundibular). Conversely, D2 *agonism* underlies dopamine-agonist treatment of Parkinson disease and prolactinoma. The receptor is neutral; the pathway decides whether an action is therapeutic or an adverse effect.

2.4 The four dopamine pathways as a map

Four projection systems carry the clinical weight of the topic. Two originate in the VTA (mesolimbic, mesocortical), one in the SNc (nigrostriatal), and one in the hypothalamic arcuate

nucleus (tuberoinfundibular). Each maps to one core function and one signature consequence of altered dopamine.

PATHWAY	ORIGIN TO TARGET	NORMAL FUNCTION	CLINICAL CORRELATE
Mesolimbic	VTA to nucleus accumbens / ventral striatum	Reward, motivation, salience	**Hyperactivity to positive symptoms; D2 blockade treats them**
Mesocortical	VTA to prefrontal cortex (DLPFC, VMPFC)	Executive function, affect	**Hypoactivity to negative and cognitive symptoms**
Nigrostriatal	SNc to dorsal striatum (caudate, putamen)	Motor planning, purposeful movement	**Loss to parkinsonism; D2 blockade to EPS and tardive dyskinesia**
Tuberoinfundibular	Arcuate/periventricular hypothalamus to median eminence	Tonic inhibition of prolactin	**D2 blockade to hyperprolactinaemia**

The four dopamine pathways with their signature correlates. The nigrostriatal system holds roughly 80% of brain dopamine, which is why its blockade dominates the motor side-effect profile.

Anatomical anchors. The mesolimbic and mesocortical pathways together form the **mesocorticolimbic system**. The nigrostriatal tract holds about 80% of the brain's dopamine and projects from the SNc to the caudate and putamen. The tuberoinfundibular pathway releases dopamine into the hypophyseal portal circulation to *tonically restrain* prolactin, so anything that lowers dopamine (D2 antagonist, stalk lesion) disinhibits prolactin. Two further minor tracts occasionally appear in vivas: the *hypothalamospinal (diencephalospinal) tract*, implicated in restless legs syndrome, and the *incertohypothalamic pathway* from the zona incerta.

MNEMONIC

"Limbic Lights up, Cortex Cools, Nigra Numbs, Tubero Talks (prolactin)"

Meso**limbic** is hyperactive in psychosis (lights up, positive symptoms). Meso**cortical** is hypoactive (cools, negative/cognitive symptoms). **Nigro**striatal blockade numbs movement (EPS, parkinsonism). **Tubero**infundibular blockade lets prolactin talk (hyperprolactinaemia). Same D2 antagonist, four different pathways, four different outcomes.

HOLD THIS

The receptor is neutral; the pathway decides whether a D2 action is therapeutic or an adverse effect. One D2 blockade reads out as antipsychotic (mesolimbic), EPS (nigrostriatal), antiemesis (area postrema) and hyperprolactinaemia (tuberoinfundibular).

2.5 The dopamine hypothesis of schizophrenia: three versions

The dopamine hypothesis is the most examined single theory in the syllabus, and the modern answer requires you to trace its evolution across three versions rather than reciting only the original (Howes & Kapur 2009).

Version I: the receptor hypothesis (1960s to 1970s)

Built on two pharmacological pillars: antipsychotic clinical potency correlates with **D2 receptor affinity**, and dopamine-releasing drugs (amphetamine, L-DOPA) can induce or worsen psychosis. The claim was a global *hyperdopaminergic* state. Its weakness: it could not explain negative and cognitive symptoms, nor the delay and incompleteness of antipsychotic response.

Version II: the regional / two-pathway hypothesis

Reframed the illness as *hyperactivity of the mesolimbic pathway* (driving positive symptoms) coupled with *hypoactivity of the mesocortical pathway* (driving negative and cognitive symptoms), the frontal hypodopaminergia possibly disinhibiting subcortical dopamine. This is Stahl's working model and reconciles the symptom domains.

Version III: the final common pathway (Howes & Kapur 2009)

The current consensus. Multiple risk factors (genes, obstetric events, drugs, psychosocial stress) converge on a single node: **presynaptic striatal dopamine dysregulation**, that is, increased dopamine synthesis and release capacity, demonstrated on molecular imaging. The lesion is presynaptic, not primarily at the receptor, and it is *associational* (linked to the psychosis, not the diagnostic label). It integrates the glutamatergic (NMDA hypofunction) account, where cortical disinhibition drives the subcortical dopamine excess.

Aberrant salience. The phenomenological bridge, from Kapur 2003, is that a dysregulated hyperdopaminergic state at the "brain" level produces *aberrant assignment of salience* to neutral internal and external stimuli at the "mind" level. Delusions are then a top-down cognitive effort to explain experiences that feel abnormally significant, and hallucinations are the direct experience of aberrant salience of internal representations. Antipsychotics do not erase symptoms but *dampen the salience*, allowing gradual re-learning (extinction-like); stopping them lets the dysregulation and salience return, the model's account of relapse.

> **CLINICAL ANCHOR**
>
> Version III explains three clinical observations at once: why molecular imaging shows elevated striatal dopamine synthesis capacity even in the prodrome, why D2 blockade helps positive symptoms but leaves negative and cognitive symptoms largely untouched (the lesion is upstream and presynaptic), and why roughly a third of patients whose psychosis is *not* dopaminergic (glutamate-driven) respond poorly to D2 antagonists and may need clozapine.

TRAP "Atypical" is a clinical outcome (lower EPS at effective doses), not a single receptor property; do not force one mechanism (5-HT2A block, fast D2 dissociation, D2 partial agonism) onto every atypical.

2.6 Stahl's antipsychotic logic: one blockade, four consequences

The pathway map converts directly into pharmacology. A pure D2 antagonist does not selectively find the mesolimbic pathway; it blocks D2 everywhere, so every pathway contributes a predictable effect (Stahl 2021).

- **Mesolimbic.** D2 blockade here is the intended action: reduced positive symptoms. This is the therapeutic target.

- **Mesocortical.** This pathway is already hypodopaminergic; adding D2 blockade risks worsening negative and cognitive symptoms (secondary negative symptoms, neuroleptic-induced deficit syndrome).
- **Nigrostriatal.** D2 blockade produces acute **extrapyramidal symptoms** (dystonia, parkinsonism, akathisia) and, with chronic blockade and receptor upregulation, **tardive dyskinesia**. High-potency first-generation agents (haloperidol) are the worst offenders.
- **Tuberoinfundibular.** D2 blockade disinhibits prolactin, causing hyperprolactinaemia (galactorrhoea, amenorrhoea, sexual dysfunction, reduced bone density). Risperidone, paliperidone and amisulpride are the classic culprits.

The atypical solution. Second-generation agents soften this by adding **5-HT2A antagonism**: serotonin normally brakes dopamine release in the nigrostriatal and tuberoinfundibular pathways, so blocking 5-HT2A disinhibits dopamine selectively in those tracts, sparing motor function and prolactin while retaining mesolimbic D2 blockade. The *D2 partial agonists* (aripiprazole, brexpiprazole, cariprazine) go further, acting as functional antagonists where dopamine is high (mesolimbic) but as agonists where it is low (mesocortical, tuberoinfundibular), which is why aripiprazole is prolactin-sparing and low in EPS. The 2024 US approval of *xanomeline-trospium*, a muscarinic M1/M4 agonist, is the first antipsychotic to treat psychosis *without* direct D2 blockade, acting upstream on the cholinergic modulation of dopamine and so avoiding EPS and hyperprolactinaemia by design.

COMMON TRAP

"Atypical" is not a receptor property but a clinical outcome (lower EPS at effective doses). The mechanism claimed for it varies: 5-HT2A antagonism (risperidone, olanzapine), fast D2 dissociation (quetiapine, clozapine), or D2 partial agonism (aripiprazole). Amisulpride is atypical yet has no meaningful 5-HT2A action, working through preferential limbic D2/D3 blockade and presynaptic autoreceptor effects at low dose. Do not force one mechanism onto every atypical.

2.7 Reward, addiction and the wanting/liking distinction

The mesolimbic (VTA to nucleus accumbens) pathway is the reward pathway, but its role in addiction is more precise than "the pleasure chemical" (Berridge & Robinson 1998; Koob & Volkow 2010). Phasic dopamine firing encodes a **reward prediction error** (Schultz): dopamine neurons fire to unexpected reward, shift to the predictive cue once learning occurs, and dip below baseline when an expected reward is omitted. This is the neural substrate of reinforcement learning.

Wanting versus liking. The incentive-salience account separates *"wanting"* (incentive motivation, dopamine-dependent) from *"liking"* (hedonic pleasure, more opioid- and endocannabinoid-dependent). Addiction is a pathology of wanting: repeated drug use sensitises the mesolimbic system so that drug cues acquire excessive incentive salience (craving) even as the drug's hedonic impact wanes, explaining why craving outlives pleasure. All major drugs of abuse converge on raising accumbens dopamine (cocaine and amphetamine directly via DAT and VMAT; opioids,

nicotine, alcohol and cannabinoids by disinhibiting VTA neurons). ICD-11 codes these under disorders due to substance use; DSM-5-TR uses the substance use disorder construct.

PEARL

The prediction-error framework also explains a therapeutic paradox: dopamine agonists used for Parkinson disease and restless legs (pramipexole, ropinirole) can trigger *impulse control disorders* (pathological gambling, hypersexuality, compulsive shopping) by over-driving the intact mesolimbic reward circuit while treating the degenerated nigrostriatal one. Same drug, two pathways, opposite valence, the recurring lesson of this topic.

2.8 Neurological correlates: Parkinson, ADHD and restless legs

Beyond psychosis, three disorders anchor dopamine to clinical neurology and neurodevelopment.

Parkinson disease

Progressive degeneration of the **nigrostriatal** dopaminergic neurons of the SNc, with Lewy-body (alpha-synuclein) pathology, producing the classic bradykinesia, rigidity, resting tremor and postural instability once about 60 to 80% of nigral neurons are lost. Treatment restores dopamine (L-DOPA plus carbidopa, dopamine agonists, MAO-B and COMT inhibitors). The mirror-image relationship with antipsychotic-induced parkinsonism (too little nigrostriatal dopamine either way) is a favourite comparison. The toxin *MPTP*, a selective nigrostriatal poison, is the standard chemical model.

ADHD

Framed as hypofunction of dopamine (and noradrenaline) signalling in the **prefrontal cortex and striatum**, impairing attention, working memory and response inhibition (Arnsten & Rubia 2012; Volkow 2009). Stimulants (methylphenidate blocks DAT and NET; amphetamine additionally reverses them and VMAT) raise synaptic dopamine and noradrenaline and are first-line. ICD-11 codes it as attention deficit hyperactivity disorder; DSM-5-TR as ADHD. The *DRD4* and *DAT1 (SLC6A3)* genes are the most replicated candidate associations, though effect sizes are small.

Restless legs syndrome (RLS)

A sensorimotor disorder with an urge to move the legs, worse at rest and in the evening, relieved by movement. The dopaminergic contribution is thought to involve the *hypothalamospinal (A11) diencephalospinal* dopaminergic projection to the cord, compounded by CNS *iron deficiency* (iron is the TH cofactor for dopamine synthesis). Low-dose dopamine agonists and alpha-2-delta ligands (gabapentin enacarbil) are used, though agonists carry a risk of *augmentation* (symptom worsening and spread over time).

INDIA

In Indian practice the dopamine trade-offs surface daily: high-potency first-generation antipsychotics (haloperidol, trifluoperazine) remain widely used for cost reasons, so clinicians must actively watch for EPS, tardive dyskinesia and drug-induced parkinsonism, and for prolactin-related complaints that patients may not volunteer (menstrual change, galactorrhoea, sexual dysfunction). Restless legs is easy to miss and worth screening for in patients on iron-poor vegetarian diets and in pregnancy, where iron deficiency is prevalent; check ferritin before attributing nocturnal restlessness to akathisia or anxiety.

3 · Serotonin system and receptor subtypes

One transmitter, at least fourteen receptors, and almost every drug we prescribe. Serotonin (5-hydroxytryptamine, 5-HT) is the monoamine the paper returns to most, because the serotonergic receptor family is the widest of any neurotransmitter and because the entire first line of antidepressant, anxiolytic and anti-obsessional pharmacology is built on it. The examinable spine of the topic is a chain of cause and effect: a single pool of 5-HT, arising from a handful of brainstem nuclei, is read by a receptor set whose members do opposite things (excite or inhibit, on the cell of origin or on the target), and the clinical phenomena, from the SSRI response lag to serotonin syndrome to the psychedelic experience, fall out of *which* receptor is engaged, *where*, and *for how long*.

Hold three organising facts before the detail. First, synthesis is **rate-limited by tryptophan hydroxylase** and by substrate availability, which is why dietary and cofactor manipulations move central 5-HT. Second, the raphe nuclei project almost everywhere, so serotonin is a *modulator* of whole networks rather than a point-to-point signal. Third, the receptor families are defined by their signal transduction (Gi, Gq, or a ligand-gated channel), and that coupling predicts function: this is the single most rewarding table in the topic, and it is flagged below (Stahl 2021; Kaplan & Sadock 2024).

3.1 Synthesis: tryptophan to 5-HTP to 5-HT, and the rate-limiting step

The two-step pathway. Synthesis begins with the essential amino acid **tryptophan**, which crosses the blood-brain barrier by an active transporter it shares with the other large neutral amino acids, so its central availability depends on the plasma tryptophan-to-competitor ratio (the basis of acute tryptophan depletion experiments). Tryptophan is hydroxylated to **5-hydroxytryptophan (5-HTP)** by **tryptophan hydroxylase (TPH)**, the *rate-limiting enzyme*, which requires the cofactor tetrahydrobiopterin (BH4); 5-HTP is then decarboxylated to 5-HT by aromatic L-amino acid decarboxylase (the same DOPA decarboxylase of the catecholamine pathway), which uses pyridoxal-5-phosphate (vitamin B6) as coenzyme (Bamalan 2023).

Two isoforms of the rate-limiting enzyme. The distinction the exam wants is that **TPH2** is the neuronal, brain-specific isoform expressed in the raphe, whereas TPH1 is peripheral (enterochromaffin cells of the gut, pineal). This matters because polymorphisms in the TPH2 gene, not TPH1, are the ones linked to mood and suicidality, and because it explains why the vast peripheral serotonin pool (roughly 90% of body serotonin is gut-derived) is a separate compartment that peripheral drugs can target without central effect.

> **PEARL**
>
> Serotonin is the obligatory precursor of **melatonin**. In the pineal, 5-HT is N-acetylated then O-methylated to melatonin under noradrenergic (dark-driven) control, which is why the serotonergic and circadian systems are biochemically continuous and why agomelatine (an MT1/MT2 agonist that is also a 5-HT2C antagonist) sits at their junction.

3.2 Storage, release and reuptake: the SERT and VMAT2 machinery

Vesicular packaging and the reuptake transporter. Cytoplasmic 5-HT is loaded into synaptic vesicles by the vesicular monoamine transporter (VMAT2), released on depolarisation, and, critically, cleared from the synapse by the **serotonin transporter (SERT, SLC6A4)**, a sodium-coupled plasma-membrane pump. SERT is the molecular target of the SSRIs, the SNRIs, and clomipramine, and its promoter polymorphism (**5-HTTLPR**, short versus long allele) is the classic gene-by-environment candidate for depression vulnerability. Recaptured 5-HT is either repackaged into vesicles or degraded (Bamalan 2023).

> **COMMON TRAP**
>
> Do not conflate the enzyme (TPH, which *makes* serotonin, rate-limiting for synthesis) with the transporter (SERT, which *clears* it, the drug target). SSRIs act on SERT and change nothing about the synthetic rate acutely; the delayed clinical response is a receptor-adaptation story, not a synthesis story (see 3.9).

3.3 Metabolism: MAO-A, 5-HIAA, and what the CSF metabolite tells you

The degradative pathway. Intraneuronal and extraneuronal 5-HT is oxidatively deaminated by **monoamine oxidase**, principally the **MAO-A** isoform (5-HT and noradrenaline are preferential MAO-A substrates; MAO-B prefers phenylethylamine and, jointly with MAO-A, dopamine), to 5-hydroxyindoleacetaldehyde and then by aldehyde dehydrogenase to **5-hydroxyindoleacetic acid (5-HIAA)**, the terminal metabolite excreted in urine and measurable in CSF (Bamalan 2023).

Why 5-HIAA is examinable. Low CSF 5-HIAA is the most durable biological correlate in psychiatry of **impulsive aggression, violent suicide attempts and impulsivity** (the "low-serotonin, low-impulse-control" association of Asberg and others), and 24-hour urinary 5-HIAA is the screening test for **carcinoid syndrome**, where a serotonin-secreting neuroendocrine tumour drives flushing and diarrhoea, a peripheral picture that overlaps symptomatically with serotonin syndrome. MAO-A knockout and the Brunner syndrome point mutation link the enzyme to aggression, closing the loop with the 5-HIAA data.

3.4 Raphe nuclei and the ascending projections (cross-reference the Functional Neuroanatomy & Neurophysiology notes)

The nuclei of origin. Serotonergic cell bodies are almost entirely confined to the midline **raphe nuclei** of the brainstem (Dahlgren and Fuxe's B1 to B9 groups). The rostral group, dominated by the **dorsal raphe and median raphe** of the midbrain and upper pons, supplies the ascending forebrain projection to cortex, striatum, limbic system, hippocampus and hypothalamus; the caudal group projects down the spinal cord to modulate pain (the descending analgesic system) and autonomic outflow. As with the locus coeruleus for noradrenaline, a very small number of neurons innervate the entire forebrain, which is the anatomical reason serotonin acts as a diffuse network modulator (see the Functional Neuroanatomy & Neurophysiology notes for the monoamine nuclei of origin and their projection architecture).

CLINICAL ANCHOR

The dorsal raphe carries the cell-body (somatodendritic) **5-HT1A autoreceptor** that gates the whole ascending system. When an SSRI first floods the synapse, these autoreceptors sense the excess and *shut the raphe down*, blunting the initial response; their desensitisation over two to four weeks is the leading mechanistic account of the therapeutic lag (Stahl 2021). Anatomy here directly predicts a clinical timeline.

3.5 The receptor map: seven families, three transduction logics

The organising principle is signal transduction. All 5-HT receptors are G-protein-coupled except one. The families sort into three functional classes, and knowing the class tells you the direction of the effect. The **5-HT1 family** couples to *Gi/Go*, inhibits adenylyl cyclase, lowers cAMP and opens potassium channels, so it is *inhibitory / hyperpolarising*. The **5-HT2 family** couples to *Gq*, activates phospholipase C and the IP3/DAG cascade, so it is *excitatory / depolarising*. The **5-HT3 receptor** is the odd one out, a *ligand-gated cation channel* (ionotropic, fast, like a nicotinic receptor), and it is excitatory by direct depolarisation. The remaining families, **5-HT4, 5-HT6 and 5-HT7**, couple to *Gs*, raising cAMP (excitatory), and 5-HT5 couples to Gi (Stahl 2021; Kaplan & Sadock 2024). Fix that scaffold and every subtype below hangs off it.

Autoreceptor

A receptor on the serotonergic neuron itself that senses its own transmitter and inhibits further firing or release. Somatodendritic autoreceptors (5-HT1A, on the raphe cell body) reduce firing rate; terminal autoreceptors (5-HT1B/1D, on the axon terminal) reduce release per impulse.

Heteroreceptor

The same receptor subtype sitting postsynaptically on a *non*-serotonergic neuron, where it mediates the network effect rather than feedback. 5-HT1A is thus an autoreceptor on the raphe and a heteroreceptor (postsynaptic, largely inhibitory) on cortical and hippocampal pyramidal cells.

3.6 5-HT1 family: 1A (auto- and heteroreceptor), 1B/1D (terminal autoreceptor and the triptan target)

5-HT1A. The most examined subtype. As a somatodendritic **autoreceptor** in the raphe it brakes firing; as a postsynaptic **heteroreceptor** in hippocampus and cortex it is the target that mediates anxiolysis and antidepressant effect. **Buspirone** and **gepirone** are 5-HT1A partial agonists used in anxiety; several second-generation antipsychotics (aripiprazole, ziprasidone, lurasidone) and the multimodal agent vortioxetine engage 5-HT1A partial agonism, and this partial agonism *increases prefrontal dopamine release*, part of why these agents spare or improve cognition and negative symptoms (Kaplan & Sadock 2024).

5-HT1B and 5-HT1D. These are the **terminal autoreceptors** that dampen serotonin release per impulse, and they are also the pharmacological target of the **triptans** (sumatriptan and congeners), 5-HT1B/1D agonists that abort migraine by cranial vasoconstriction and by suppressing trigeminal CGRP release. The exam pairing is that their cardiac and coronary expression is the reason triptans carry a coronary-vasospasm caution, and that provoking OCD symptoms with the mixed agonist meta-chlorophenylpiperazine (mCPP) implicates this and the 5-HT2C subtype in obsessional pathology.

3.7 5-HT2 family: 2A (the antipsychotic and hallucinogen hub) and 2C

5-HT2A. The pivotal cortical excitatory receptor and arguably the single most clinically loaded subtype. Its antagonism defines the **atypical (second-generation) antipsychotics**: the high 5-HT2A-to-D2 affinity ratio (Meltzer's index) is the classical pharmacological signature of atypicality and underlies the lower liability for extrapyramidal side effects, because 5-HT2A blockade disinhibits nigrostriatal dopamine. 5-HT2A antagonism also mediates the improvement of certain negative and cognitive features and, peripherally, is exploited by the hypnotics (low-dose trazodone, the 5-HT2A antagonist pimavanserin for Parkinson psychosis). Critically, 5-HT2A is the receptor at which the **classical hallucinogens** act (see 3.11).

5-HT2C. A Gq-coupled receptor prominent in the choroid plexus, hypothalamus and mesolimbic circuitry, central to appetite and mood. Its *agonism* suppresses appetite (the mechanism of the former anorectic lorcaserin) and its *antagonism* disinhibits dopamine and noradrenaline (part of the action of mirtazapine and agomelatine, and a contributor to the weight gain of some antipsychotics and to fluoxetine's activating profile via a weak 2C effect). It is also a major site of RNA editing, an examinable molecular-biology detail.

MNEMONIC

"1 is Inhibitory / auto, 2 is Excitatory / cortical, 3 is a Channel"

The three high-yield families in one line. 5-HT**1** = Gi, **i**nhibitory, the autoreceptor family (1A brakes the raphe, 1B/1D brake the terminal, triptan target). 5-HT**2** = Gq, **e**xcitatory, cortical (2A = antipsychotic and hallucinogen hub, 2C = appetite and mood). 5-HT**3** = the only ionotropic **c**hannel (nausea and the vagal gut, ondansetron target). Everything else (4, 6, 7) is Gs and cAMP-raising.

HOLD THIS

The SSRI therapeutic lag is a somatodendritic 5-HT1A autoreceptor-desensitisation story, not a synthesis story. SERT block is immediate; raphe firing recovers only as the autoreceptor desensitises over two to four weeks.

3.8 5-HT3 (ionotropic) and 5-HT4 to 5-HT7: the remaining families

5-HT3

The sole **ligand-gated cation channel** in the family, fast and excitatory, expressed on vagal afferents, the area postrema (chemoreceptor trigger zone) and the enteric nervous system. It mediates nausea and vomiting: **ondansetron** and the "-setron" antiemetics are 5-HT3 antagonists, and 5-HT3 antagonism is why several serotonergic drugs cause nausea early and why mirtazapine (a 5-HT3 blocker) is anti-nauseant and appetite-stimulating.

5-HT4

Gs-coupled, prokinetic in the gut (target of prucalopride for constipation) and implicated in cognition and hippocampal function; a candidate antidepressant mechanism under study.

5-HT5

Gi-coupled, least characterised; possible roles in circadian rhythm and cognition, low examinable yield beyond naming it.

5-HT6

Gs-coupled, almost exclusively central, dense in striatum and cortex; a cognition and antipsychotic-related target (many antipsychotics and antidepressants have appreciable 5-HT6 affinity).

5-HT7

Gs-coupled, involved in circadian entrainment, thermoregulation, sleep and mood; antagonism is part of the profiles of vortioxetine, lurasidone and several atypicals and is a putative antidepressant contributor.

3.9 Functional roles across systems: mood, anxiety, sleep, appetite, sexual function, impulsivity

Because the raphe projects everywhere, serotonin touches nearly every behavioural axis, and the paper likes the receptor-to-function mapping. **Mood and anxiety** run largely through postsynaptic 5-HT1A and modulation of 2A/2C. **Sleep** is dual: serotonin promotes wakefulness and suppresses REM at the raphe, yet is the melatonin precursor, and 5-HT2A antagonism (trazodone, low-dose quetiapine) deepens slow-wave sleep. **Appetite** is 5-HT2C-driven (agonism reduces intake). **Sexual function** is inhibited by serotonin, chiefly via 5-HT2A/2C, which is the receptor basis of SSRI-induced sexual dysfunction and, conversely, why 5-HT2 antagonists (mirtazapine, the 5-HT1A agonism of buspirone or vortioxetine) can rescue it. **Impulsivity and aggression** track inversely with serotonergic tone, the behavioural correlate of the low-CSF-5-HIAA finding (3.3). Serotonin also has substantial peripheral roles (platelet aggregation, gut motility, vascular tone, respiratory drive) that surface in serotonin syndrome and carcinoid.

> **CLINICAL ANCHOR**
>
> SSRI-emergent sexual dysfunction (delayed ejaculation, anorgasmia, reduced libido) is a 5-HT2-mediated, dose-related, and frequently persistent adverse effect that drives non-adherence. Naming the receptor (5-HT2A/2C) lets you reason about the switch: to an agent that antagonises 2A/2C (mirtazapine) or agonises 1A (vortioxetine, adjunct buspirone), rather than simply lowering the dose.

3.10 Clinical: depression, OCD, and the SSRI / 5-HT2A adaptation story

Depression and the monoamine account. Reduced serotonergic transmission is central to the classical monoamine hypothesis of depression, evidenced by the efficacy of SERT and MAO-A inhibitors, by symptom relapse on acute tryptophan depletion in remitted patients, and by low CSF 5-HIAA in a suicidal subgroup. The account is acknowledged as incomplete (the transmitter change is immediate but the response is delayed), which reframes it as a **receptor-adaptation and neuroplasticity** model: chronic SERT blockade desensitises the somatodendritic 5-HT1A autoreceptor, restoring raphe firing, and downstream downregulates postsynaptic 5-HT2A receptors, with BDNF-mediated plasticity as the final common path (Stahl 2021).

OCD. The serotonergic specificity of obsessive-compulsive disorder (ICD-11 6B20; DSM-5-TR obsessive-compulsive disorder) is a guaranteed exam point: only the serotonergic antidepressants (SSRIs and clomipramine) are effective, noradrenergic-selective agents such as desipramine are not, and the effective dose is typically higher and the latency longer than in depression. Symptom

provocation by the mixed serotonergic agonist mCPP implicates 5-HT2C and 5-HT1B/1D subtypes in the pathophysiology.

INDIA

SSRIs (fluoxetine, sertraline, escitalopram) are on the WHO and Indian essential medicines lists and are the pragmatic first line for depression, anxiety and OCD in Indian practice given cost and tolerability. Clomipramine remains widely used and affordable for OCD; the higher target dose and longer trial (10 to 12 weeks) must be counselled explicitly to sustain adherence.

3.11 Clinical: serotonin syndrome and hallucinogens at 5-HT2A

Serotonin syndrome (serotonin toxicity). An excess-serotonin state, usually from a serotonergic drug combination (classically an SSRI or SNRI with an MAOI, tramadol, linezolid, or triptans, or an overdose), evolving over hours. The Hunter triad the exam wants is **neuromuscular excitation** (spontaneous and inducible clonus, ocular clonus, hyperreflexia, tremor, rigidity, with a lower-limb predominance), **autonomic instability** (hyperthermia, diaphoresis, tachycardia, mydriasis, hyperactive bowel sounds and diarrhoea), and **altered mental state** (agitation, delirium). Management is withdrawal of the offending agents, supportive cooling and benzodiazepines, and the 5-HT2A antagonist **cyproheptadine** in severe cases (Bamalan 2023).

Hallucinogens at 5-HT2A. The classical serotonergic psychedelics (**LSD, psilocybin, DMT, mescaline**) are *agonists at the cortical 5-HT2A receptor*, and 5-HT2A agonism is both necessary and sufficient for the hallucinogenic effect (it is abolished by 5-HT2A antagonists such as ketanserin). The same receptor that atypical antipsychotics *block* is the one hallucinogens *activate*, a symmetry the paper likes. This has re-entered the syllabus with the 2020s trials of psilocybin-assisted therapy for treatment-resistant depression, and it separates the classical psychedelics mechanistically from the NMDA-antagonist dissociatives (ketamine and esketamine) and the entactogens (MDMA, a serotonin releaser).

RULE **5-HT2A is the one receptor atypical antipsychotics block and classical hallucinogens activate.** Same subtype, opposite direction; 5-HT2A agonism is necessary and sufficient for the psychedelic effect.

COMMON TRAP

Serotonin syndrome versus neuroleptic malignant syndrome. Both give hyperthermia and altered mental state, but serotonin syndrome is *hyperkinetic* (clonus, hyperreflexia, rapid onset over hours, offending serotonergic drug) whereas NMS is *hypokinetic* (lead-pipe rigidity without clonus, bradyreflexia, slower onset over days, a dopamine antagonist or dopaminergic withdrawal). Clonus, especially ocular and lower-limb, is the discriminator.

3.12 Serotonin-dopamine interaction: the reciprocal brake

Serotonin holds a tonic brake on dopamine, and releasing that brake at selected receptors is the engine of modern psychopharmacology. Serotonin, acting principally through **5-HT2A** receptors on dopaminergic circuits, inhibits dopamine release along the nigrostriatal, mesolimbic,

mesocortical and tuberoinfundibular pathways. This single fact explains the atypical antipsychotic advantage: by blocking 5-HT2A, these agents *disinhibit* dopamine specifically in the nigrostriatal pathway (reducing extrapyramidal side effects) and the tuberoinfundibular pathway (limiting hyperprolactinaemia), while their D2 blockade still delivers antipsychotic effect in the mesolimbic system. **5-HT1A** partial agonism adds a complementary pro-dopaminergic push in prefrontal cortex, improving cognition and negative symptoms (Kaplan & Sadock 2024; Stahl 2021). The pharmacological psychosis models (LSD and other 5-HT2A agonists as psychotomimetics) sit on the same axis.

3.13 The receptor-family reference table

The consolidating summary. Read the transduction column first: it predicts the direction of effect, and every drug and function in the last two columns follows from it.

FAMILY	SUBTYPES	TRANSDUCTION / EFFECT	KEY LOCATIONS	FUNCTION & DRUG RELEVANCE
5-HT1	1A, 1B, 1D, 1E, 1F	**Gi/Go, inhibitory (lowers cAMP)**	Raphe (1A soma), axon terminals (1B/1D), cranial vessels	1A auto- and heteroreceptor (buspirone, SSRI-lag); 1B/1D terminal autoreceptor and triptan target
5-HT2	2A, 2B, 2C	**Gq, excitatory (PLC, IP3/DAG)**	Cortex (2A), choroid plexus/hypothalamus (2C), heart valves (2B)	2A = atypical antipsychotic + hallucinogen hub, sexual dysfunction; 2C = appetite, mood; 2B = valvulopathy (fenfluramine)
5-HT3	3A to 3E	**Ligand-gated cation channel, fast excitatory**	Area postrema, vagal afferents, gut	Nausea and emesis; ondansetron ("-setron") antagonists; mirtazapine blockade
5-HT4	single	Gs, excitatory (raises cAMP)	Gut, hippocampus	Prokinetic (prucalopride); cognition; candidate antidepressant target
5-HT5	5A, 5B	Gi, inhibitory	CNS, least characterised	Possible circadian and cognitive roles; low yield
5-HT6	single	Gs, excitatory	Striatum, cortex (CNS-only)	Cognition target; affinity of many antipsychotics and antidepressants
5-HT7	single	Gs, excitatory	Hypothalamus, thalamus, limbic	Circadian, thermoregulation, sleep, mood; antagonism in vortioxetine, lurasidone

Serotonin receptor families by transduction logic: Gi families are inhibitory, Gq (5-HT2) and Gs (4, 6, 7) families are excitatory, and 5-HT3 alone is an ionotropic channel; the coupling predicts the clinical role.

4 · Noradrenergic system

Norepinephrine (NE, noradrenaline) is the catecholamine that tunes the brain's signal-to-noise ratio: it decides how vigilant, aroused and reactive the organism is at any given moment. First isolated by **Ulf von Euler** in the 1940s, it sits one enzymatic step downstream of dopamine and is the workhorse of the ascending arousal and stress-response systems. For Paper I you are

expected to build the full picture: the synthetic cascade and its rate-limiting step, the metabolite you measure clinically (MHPG), the anatomy of the locus coeruleus and its diffuse projections, the adrenoceptor family with its autoreceptor logic, and how all of this maps onto depression, anxiety, PTSD and ADHD together with the drugs that exploit each node.

The examiner's favourite framing is that NE is a **gain-control** transmitter. Unlike a fast point-to-point transmitter, the locus coeruleus fires tonically to set baseline arousal and phasically to flag behaviourally salient stimuli, so noradrenergic tone shapes attention, working memory and threat-detection through an inverted-U dose-response. Too little gives inattention and low arousal; too much gives anxiety, hypervigilance and, at the prefrontal cortex, cognitive collapse. Keep that curve in mind, because every clinical and pharmacological point below hangs off it.

4.1 Synthesis: the catecholamine cascade to noradrenaline

Pathway. NE synthesis is the tail end of the shared catecholamine pathway. Dietary **tyrosine** (or phenylalanine, converted to tyrosine by phenylalanine hydroxylase) crosses the blood-brain barrier and is hydroxylated to **L-DOPA** by **tyrosine hydroxylase**, the *rate-limiting* enzyme of the entire catecholamine pathway and the classic single-mark answer. L-DOPA is decarboxylated to **dopamine** by aromatic L-amino acid decarboxylase (DOPA decarboxylase). In noradrenergic neurons dopamine is transported into synaptic vesicles by the **vesicular monoamine transporter (VMAT2)**, and it is *inside the vesicle* that **dopamine beta-hydroxylase (DBH)** hydroxylates dopamine to norepinephrine (Stahl 2021). DBH is a copper-containing, vitamin-C-dependent enzyme and is the enzyme that defines a cell as noradrenergic.

Exam hook. Two features distinguish this cascade from the dopaminergic one: DBH is the noradrenergic-defining enzyme, and it acts *within the vesicle* rather than in the cytosol, which is why VMAT2 loading precedes the final synthetic step. Tyrosine hydroxylase remains rate-limiting for the whole family.

Tyrosine hydroxylase (TH)

Rate-limiting enzyme; converts tyrosine to L-DOPA; requires tetrahydrobiopterin cofactor.

DOPA decarboxylase (AADC)

Converts L-DOPA to dopamine; pyridoxal-phosphate dependent; not rate-limiting.

Dopamine beta-hydroxylase (DBH)

Vesicular, copper- and ascorbate-dependent; converts dopamine to norepinephrine; noradrenergic-defining.

PNMT

Phenylethanolamine-N-methyltransferase; methylates norepinephrine to epinephrine (adrenaline); needs cortisol induction.

4.2 Epinephrine as a central transmitter: PNMT and the C1-C3 adrenergic neurons

Beyond its familiar role as an adrenal-medullary hormone, **epinephrine (adrenaline)** is also a genuine CNS transmitter in a small dedicated population of neurons. In these cells the enzyme **phenylethanolamine-N-methyltransferase (PNMT)** methylates norepinephrine to epinephrine, using S-adenosylmethionine as the methyl donor. Centrally, PNMT-expressing

adrenergic neurons are clustered in the **C1, C2 and C3 adrenergic cell groups of the rostral ventrolateral and dorsomedial medulla**, and they project to the hypothalamus, the locus coeruleus and other brainstem autonomic nuclei (Kaplan and Sadock 2024). Their central role is minor compared with NE but real: they contribute to central cardiovascular control (baroreflex, blood-pressure and sympathetic set-point) and to neuroendocrine stress reactivity. PNMT is glucocorticoid-inducible, which links adrenaline synthesis mechanistically to the HPA axis and the stress response.

PEARL

Adrenaline in the brain is a medullary phenomenon. If a stem asks where central epinephrine comes from, the answer is the PNMT-positive C1-C3 adrenergic neurons of the medulla, not the locus coeruleus (which is noradrenergic). PNMT needs cortisol to be induced, which is why the adrenal medulla, bathed in cortisol-rich portal blood, is the great epinephrine factory and why chronic stress up-regulates adrenaline synthesis.

TRAP Central adrenaline is not made in the locus coeruleus. It comes from the PNMT-positive C1-C3 medullary neurons; the locus coeruleus is noradrenergic.

4.3 Metabolism: MAO, COMT and the MHPG and VMA end-products

NE is cleared from the synapse chiefly by **reuptake** through the **norepinephrine transporter (NET)**, a sodium- and chloride-dependent presynaptic transporter that is the target of most noradrenergic antidepressants. Recaptured or leaked NE is then degraded by two enzymes: **monoamine oxidase (MAO)**, located on the outer mitochondrial membrane and predominantly intraneuronal, and **catechol-O-methyltransferase (COMT)**, largely extraneuronal and glial. The order in which these two act determines the end-product.

The metabolite that matters. In the *central nervous system* the principal metabolite of NE is **3-methoxy-4-hydroxyphenylglycol (MHPG)**, the answer examiners want for a central NE marker; in the *periphery* complete oxidation in the liver yields **vanillylmandelic acid (VMA)**, the urinary metabolite screened for in phaeochromocytoma. Historically, urinary MHPG was studied as a biomarker to subtype depression and to predict differential response to noradrenergic versus serotonergic antidepressants, though its clinical utility never held up. The MAO isoenzyme distinction is high-yield: **MAO-A** preferentially deaminates NE and serotonin and is the isoform relevant to antidepressant MAOIs, whereas **MAO-B** favours phenylethylamine and is the selegiline target in Parkinson disease.

FEATURE	MHPG	VMA
Compartment	**Chiefly central (CNS) NE**	Peripheral / whole-body NE and adrenaline
Final site of formation	Brain, then some hepatic conversion	**Liver (complete oxidation)**
Enzymes	MAO then COMT, glycol branch (aldehyde reductase)	MAO then COMT, acid branch (aldehyde dehydrogenase)
Clinical use	Research marker of central NE turnover (depression subtyping)	**Urinary screen for phaeochromocytoma and neuroblastoma**

MHPG versus VMA is the classic discriminator: think MHPG for brain norepinephrine turnover and VMA for the phaeochromocytoma urine screen. The branch point is whether the intermediate aldehyde is reduced to a glycol (MHPG) or oxidised to an acid (VMA).

4.4 The locus coeruleus and its projections

Anatomy. The **locus coeruleus (LC)**, the A6 cell group, is a small pigmented (neuromelanin-rich, hence "blue spot") nucleus in the **dorsorostral pons** in the floor of the fourth ventricle, and it is the source of most of the CNS's norepinephrine (cross-referenced with the the Functional Neuroanatomy & Neurophysiology notes brainstem nuclei topic). Despite housing only a few thousand neurons per side, its axons ramify to nearly the entire neuraxis. Two ascending bundles carry the output: the **dorsal noradrenergic bundle** from the LC innervates the neocortex, hippocampus, thalamus and cerebellum, while the **ventral noradrenergic bundle** from LC and lateral tegmental groups supplies the hypothalamus, amygdala and midbrain. The LC also sends descending projections to the spinal cord dorsal horn, part of the endogenous analgesia system and the rationale for noradrenergic action in neuropathic pain.

Firing physiology. LC neurons show two modes. *Tonic* baseline firing sets global arousal and follows the sleep-wake cycle, being fastest in waking, slower in non-REM sleep and virtually silent in REM sleep (making the LC one of the REM-off cells). *Phasic* bursts fire to salient or novel stimuli, transiently boosting cortical gain to favour the current behaviour. The Aston-Jones and Cohen adaptive-gain model ties tonic-phasic balance to the exploitation-versus-exploration trade-off, and the inverted-U relationship between LC output and prefrontal performance underlies why both too little and too much NE impair attention.

4.5 Adrenoceptors: the alpha-1, alpha-2 and beta family

All adrenoceptors are **G-protein-coupled receptors**, and the whole family is examinable by second-messenger coupling, location and function. NE binds them with different affinities: **alpha-2 has the highest affinity, alpha-1 intermediate, beta the lowest**, which matters physiologically because low-level tonic release preferentially engages the inhibitory alpha-2 autoreceptor.

Alpha-1 (a1A, a1B, a1D)

Postsynaptic; Gq to phospholipase C, raising IP3 and DAG and intracellular calcium; excitatory. Mediates arousal and, peripherally, smooth-muscle contraction and vasoconstriction. Prazosin is the antagonist used for PTSD nightmares.

Alpha-2 (a2A, a2B, a2C)

Both pre- and postsynaptic; Gi/o, lowering cAMP; inhibitory. The presynaptic a2 is the **autoreceptor** that shuts off further NE release (negative feedback). Postsynaptic prefrontal a2A mediates working-memory enhancement (the guanfacine target).

Beta-1

Gs, raising cAMP and activating PKA; excitatory. Cortical and cardiac; role in memory consolidation and cardiac chronotropy.

Beta-2

Gs (and some Gi); glial and vascular; bronchodilation and vasodilation peripherally.

Beta-3

Adipose tissue; lipolysis and thermogenesis; minimal direct CNS role.

Autoreceptor logic. The presynaptic **alpha-2 autoreceptor** is the pivot of noradrenergic pharmacology. Agonists such as clonidine and guanfacine stimulate it, suppressing NE release (antiadrenergic, useful in ADHD, withdrawal states and hypertension), whereas antagonists such as **yohimbine** and idazoxan block it, increasing NE release, which is exploited both as a research challenge and, in mirtazapine's case, therapeutically (Kaplan and Sadock 2024). Mirtazapine blocks alpha-2 autoreceptors and heteroreceptors, disinhibiting both NE and serotonin release.

COMMON TRAP

Do not confuse the two directions at the alpha-2 receptor. Clonidine and guanfacine are alpha-2 *agonists* that *lower* NE release (antiadrenergic); yohimbine and idazoxan are alpha-2 *antagonists* that *raise* NE release (proadrenergic). A common error is to assume that agonising a receptor always increases the transmitter's effect; at a presynaptic autoreceptor, agonism suppresses release.

4.6 Functions: arousal, attention, stress and vigilance

The noradrenergic system's core CNS jobs are **arousal and wakefulness**, **selective attention and vigilance**, **stress reactivity** and the enhancement of **emotionally salient memory**. Through cortical gain modulation the LC sharpens signal detection and biases attention toward salient stimuli; through beta-adrenergic action in the basolateral amygdala it strengthens the consolidation of emotionally arousing memories, the substrate of flashbulb and traumatic memory (a mechanism directly relevant to PTSD). Peripherally, NE and adrenaline drive the classic *fight-or-flight* response: pupillary dilatation, tachycardia, bronchodilation, vasoconstriction, increased renin release and inhibited gut peristalsis, alongside metabolic mobilisation through glycogenolysis, gluconeogenesis and lipolysis.

MNEMONIC

"A-VATS": Arousal, Vigilance, Attention, Threat-response, Stress-memory

The five central jobs of norepinephrine map onto the LC's gain-control role: it keeps you Aroused and awake, sustains Vigilance, focuses Attention on salient input, mounts the Threat (fight-or-flight) response, and stamps in emotionally Stressful memories via the amygdala. All five are versions of one idea: turning up the gain on what matters right now.

HOLD THIS

At a presynaptic alpha-2 autoreceptor, agonism suppresses noradrenaline release. Clonidine and guanfacine (agonists) lower NE; yohimbine (antagonist) raises it and reliably provokes panic.

4.7 Clinical correlations and pharmacology

Depression. The **monoamine hypothesis** posits a relative deficiency of NE and serotonin. Noradrenergic drugs exploit this at several nodes: **SNRIs** (venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran) block both NET and the serotonin transporter, with NET inhibition becoming prominent at higher doses; the selective NET inhibitor **reboxetine** and the noradrenergic-and-dopaminergic **bupropion** act more purely on the catecholamine side; **tricyclics** such as desipramine and nortriptyline are strongly noradrenergic; **mirtazapine** works presynaptically by alpha-2 blockade; and non-selective **MAOIs** raise NE by blocking its degradation (Stahl 2021). Paradoxically, some data show *increased* tyrosine hydroxylase and urinary NE in depression, so the monoamine story is best taught as a downstream, receptor-adaptive model rather than a simple deficiency.

Anxiety and PTSD. Noradrenergic overactivity underlies the hyperarousal of anxiety disorders. The **yohimbine challenge** (an alpha-2 antagonist that floods the synapse with NE) reliably provokes panic and flashbacks in patients with panic disorder and PTSD, historic evidence for LC hyperexcitability in these conditions (Kaplan and Sadock 2024). This is the rationale for the alpha-1 antagonist **prazosin** in PTSD-related nightmares and for beta-blockers (propranolol) in the somatic symptoms of performance anxiety. PTSD (ICD-11 6B40; DSM-5-TR post-traumatic stress disorder) and panic disorder (ICD-11 6B01; DSM-5-TR panic disorder) are the disorders to name here.

ADHD. Prefrontal noradrenergic (and dopaminergic) hypofunction is central to ADHD (ICD-11 6A05; DSM-5-TR attention-deficit/hyperactivity disorder). Optimal prefrontal function needs a moderate level of NE acting on postsynaptic **alpha-2A** receptors, and the treatments follow this directly: the selective NET inhibitor **atomoxetine** raises synaptic NE and dopamine in the prefrontal cortex, while the alpha-2A agonists **guanfacine** and **clonidine** (extended-release) directly stimulate the postsynaptic receptor to strengthen prefrontal network connectivity (Stahl 2021). Stimulants also raise catecholamines by blocking and reversing their transporters.

AGENT / CLASS	NORADRENERGIC MECHANISM	MAIN INDICATION
SNRIs (venlafaxine, duloxetine)	NET plus SERT blockade	Depression, anxiety, neuropathic pain
Atomoxetine	**Selective NET inhibitor (non-stimulant)**	ADHD
Reboxetine	Selective NET inhibitor	Depression (limited availability)
Guanfacine, clonidine	**Alpha-2A agonist (postsynaptic; presynaptic autoreceptor)**	ADHD, tics, withdrawal, hypertension
Prazosin	**Alpha-1 antagonist**	PTSD nightmares

AGENT / CLASS	NORADRENERGIC MECHANISM	MAIN INDICATION
Propranolol	Beta-adrenergic antagonist	Performance anxiety, akathisia, tremor
Mirtazapine	Alpha-2 auto/heteroreceptor antagonist	Depression (noradrenergic and serotonergic disinhibition)
MAOIs	Block MAO-mediated NE degradation	Refractory / atypical depression
Yohimbine	**Alpha-2 antagonist (raises NE): panic challenge, not a treatment**	Research challenge; historic ED use

The noradrenergic pharmacopoeia sorted by node: reuptake blockers raise synaptic NE, alpha-2 agonists calm the system, alpha-1 and beta antagonists block downstream effects, and yohimbine is the provocation agent that maps NE overactivity onto panic and PTSD.

INDIA

In Indian practice, atomoxetine is the non-stimulant most readily prescribed for ADHD given that stimulant methylphenidate is a Schedule X / controlled substance with tighter prescription rules; guanfacine and clonidine extended-release formulations are less consistently available, so plain clonidine is sometimes substituted. Prazosin for PTSD nightmares is inexpensive and widely stocked, making it a practical first choice where specialised agents are hard to source.

4.8 Noradrenergic degeneration in neurodegenerative disease

The LC is one of the earliest sites of pathology in **Alzheimer disease**, where neurofibrillary (hyperphosphorylated tau) tangles accumulate and LC neurons are lost, reducing NE's endogenous anti-inflammatory and neuroprotective actions on the cortex and hippocampus. In **Parkinson disease**, alpha-synuclein deposition and LC neuronal loss contribute to the non-motor features (cognitive slowing, mood and autonomic symptoms) that dopaminergic therapy does not address. For the exam, the take-home is that LC noradrenergic loss is an early, under-recognised contributor to the cognitive and affective burden of both diseases, and current anti-amyloid monoclonal antibodies target the amyloid arm only, leaving noradrenergic decline unaddressed.

5 · Glutamate and NMDA receptor subtypes (hypofunction model)

Glutamate is the brain's principal excitatory neurotransmitter, present at the vast majority of fast synapses, and it is the axis on which the modern neurochemistry of both psychosis and depression now turns. For decades psychiatry was dopamine-centric; the field's centre of gravity shifted once it became clear that the **NMDA receptor hypofunction** model explained things the dopamine hypothesis could not, above all the negative and cognitive symptoms of schizophrenia and the psychotomimetic profile of phencyclidine and ketamine (Stahl 2021). The same receptor then reappeared as the target of the first genuinely novel antidepressant mechanism in a generation.

Examiners love this topic because it braids together basic pharmacology (a ligand-gated channel with an unusual co-agonist requirement and a voltage-dependent magnesium block), a disease model (disinhibition of cortical circuits), a therapeutics story (ketamine, esketamine, memantine) and a neuroimmunology vignette (anti-NMDA-receptor encephalitis). **Learn it as one circuit, not four facts.** Every clinical entity below is a perturbation of the same receptor.

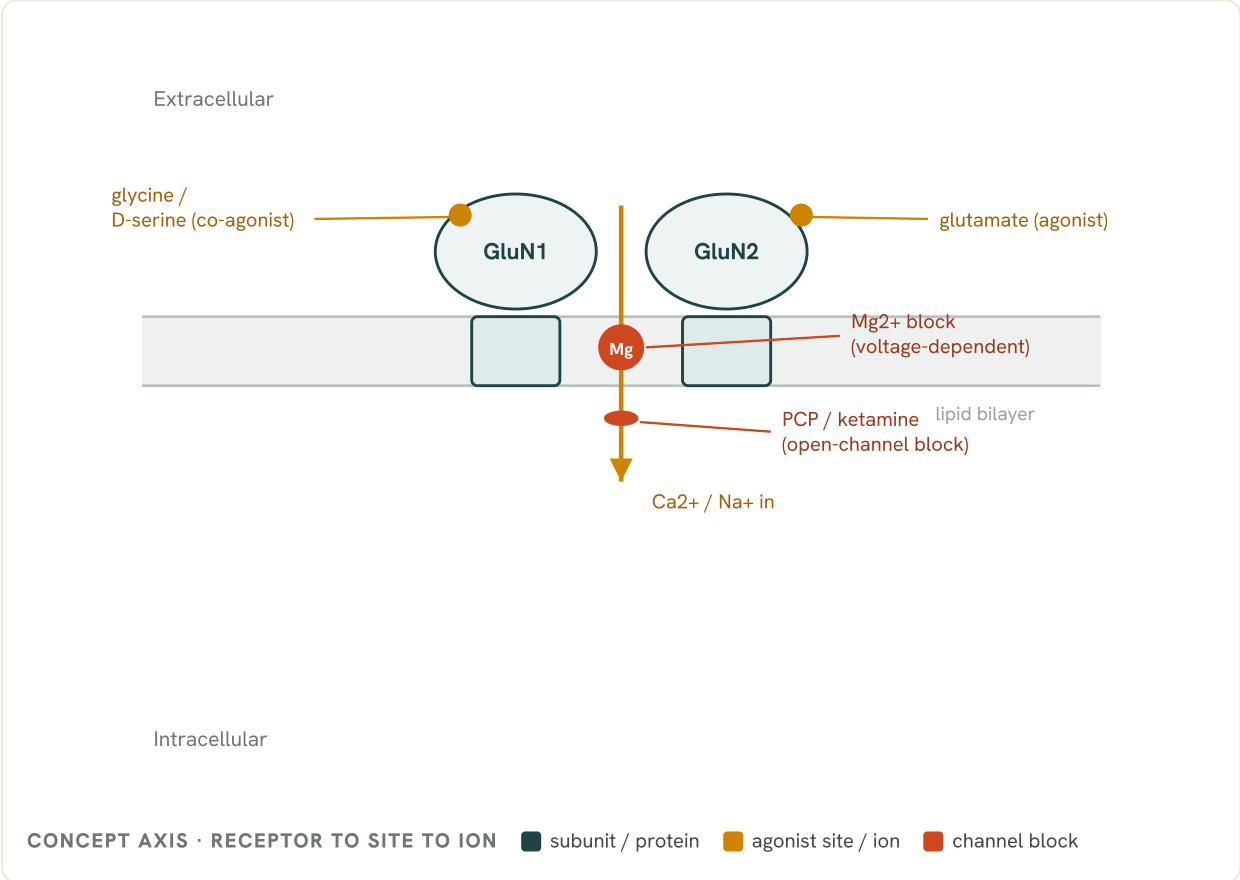


Fig 2.2 The NMDA receptor as a coincidence detector. Opening needs two things at once: the agonist glutamate at GluN2 and the co-agonist glycine or D-serine at GluN1, plus depolarisation to expel the voltage-dependent Mg2+ block from the pore. Only then do Ca2+ and Na+ flow in. Ketamine and PCP are open-channel blockers acting inside the pore; NMDA hypofunction on GABA interneurons is the disinhibition model of psychosis.

5.1 The glutamate-glutamine cycle and the EAAT reuptake system

Synthesis and packaging. Unlike monoamines there is no single dedicated synthetic enzyme with an obvious rate-limiting step; glutamate is made largely from glutamine by the neuronal enzyme *glutaminase*, and also arises from the Krebs-cycle intermediate alpha-ketoglutarate by transamination (Stahl 2021). It is then concentrated into synaptic vesicles by vesicular glutamate transporters (**vGluT**) ready for release.

Clearance is by uptake, not enzymatic breakdown. This is the single most examinable contrast with acetylcholine. After release, glutamate is not degraded in the cleft; it is removed by **excitatory amino acid transporters (EAAT1 to EAAT5)**, members of the SLC1 solute-carrier family, sited predominantly on surrounding *glia* (Stahl 2021). Rapid glial uptake keeps synaptic glutamate low and is what protects the synapse from the excitotoxicity described in 5.4.

The cycle closes in glia. Inside the astrocyte, glutamate is converted to the inert, non-neuroactive amino acid *glutamine* by **glutamine synthetase**. Glutamine is exported back to the

neuron, where glutaminase reconverts it to glutamate, and the loop begins again. This **glutamate-glutamine shuttle** is why glia are not passive scaffolding but active partners in excitatory transmission, and why glutamine is the peak that magnetic resonance spectroscopy often reports alongside glutamate as the combined "Glx" signal.

5.2 Ionotropic receptors: NMDA, AMPA and kainate

Glutamate acts on two receptor superfamilies. The **ionotropic** receptors are ligand-gated ion channels assembled from four subunits (a tetramer, in contrast to the pentameric nicotinic and GABA-A channels), and there are three families named for their selective agonists (Stahl 2021).

AMPA receptor

The workhorse of fast excitatory transmission. Opening lets sodium in to depolarise the postsynaptic membrane over milliseconds. Trafficking of AMPA receptors into the synapse is a molecular substrate of *long-term potentiation* and is central to the ketamine antidepressant story (5.6).

Kainate receptor

A less prominent ionotropic receptor, modulating both postsynaptic depolarisation and, presynaptically, transmitter release. Lower yield for exams than NMDA and AMPA, but name it.

NMDA receptor

The star of the topic. A calcium-permeable channel with three defining peculiarities: an obligatory co-agonist, a voltage-dependent magnesium block, and a role as a molecular coincidence detector. Detailed in 5.3.

NMDA receptors are heteromers built from an obligatory **GluN1** subunit (older nomenclature NR1) paired with **GluN2** subunits (NR2A to NR2D) and sometimes GluN3 (Stahl 2021). The GluN2 composition sets the channel's kinetics and pharmacology: GluN2B-rich receptors, for instance, are the target of the selective antagonist ifenprodil, and subunit switching over development is one substrate of the neurodevelopmental hypofunction idea.

5.3 The NMDA receptor: co-agonist, magnesium block and coincidence detection

The co-agonist requirement. The NMDA receptor is unique among fast receptors in that glutamate alone cannot open it. A second, obligatory **co-agonist** must occupy a separate glycine-binding site on the GluN1 subunit. That co-agonist is either *glycine* or *D-serine*, the latter an unusual D-amino acid manufactured in glia by **serine racemase** from L-serine (Stahl 2021). D-serine has high affinity for the glycine site and is now regarded as the principal endogenous co-agonist at many forebrain synapses. This co-agonist dependence is a druggable node: glycine, D-serine and D-cycloserine (a partial agonist at the glycine site) have all been trialled as augmentation strategies to enhance NMDA function in schizophrenia.

The magnesium block. At resting membrane potential the channel pore is physically plugged by an extracellular **magnesium ion**. Even with glutamate and co-agonist bound, no current flows until the membrane is depolarised enough (by neighbouring AMPA-receptor activity) to expel the Mg^{2+} plug in a voltage-dependent manner (Stahl 2021).

Coincidence detection. Because opening requires both chemical binding (glutamate plus co-agonist) and electrical depolarisation (to relieve the Mg block) at the same moment, the NMDA

receptor functions as a molecular **coincidence detector.** Only when presynaptic release and postsynaptic activity coincide does calcium flood in to trigger the intracellular cascades of synaptic plasticity. This is the cellular logic of Hebbian learning and the reason the NMDA receptor sits at the heart of memory and of the plasticity theories of both schizophrenia and depression.

RULE **The NMDA receptor is a coincidence detector: it needs glutamate, a glycine-site co-agonist and depolarisation to expel the magnesium plug, all at once.** Ketamine and PCP block a fourth thing entirely, sitting inside the open pore.

PEARL

Three keys open the NMDA channel and all three must turn together: glutamate at its site, glycine or D-serine at the co-agonist site, and depolarisation to remove the magnesium plug. Dissociative anaesthetics (ketamine, PCP) block a fourth thing entirely: they sit deep inside the open channel at the PCP or dizocilpine site. This is why they are *uncompetitive, open-channel* blockers rather than competitive antagonists at the glutamate site.

5.4 Metabotropic glutamate receptors (mGluR groups I to III)

The second superfamily is the **metabotropic** glutamate receptors, G-protein-coupled receptors that act slowly through second messengers rather than by gating an ion channel. There are at least eight subtypes sorted into three groups by sequence, signalling and pharmacology (Stahl 2021).

GROUP	MEMBERS	LOCATION AND SIGNALLING	NET EFFECT ON GLUTAMATE TONE
Group I	mGluR1, mGluR5	Mainly postsynaptic; couple to Gq to raise intracellular calcium	**Excitatory: facilitate and strengthen glutamate responses**
Group II	mGluR2, mGluR3	Presynaptic autoreceptors; couple to Gi to lower cyclic AMP	**Inhibitory: reduce glutamate release (autoreceptor brake)**
Group III	mGluR4, mGluR6, mGluR7, mGluR8	Predominantly presynaptic autoreceptors; Gi-coupled	Inhibitory: reduce glutamate release

The three mGluR groups. The exam discriminator: Group I is postsynaptic and excitatory, whereas Groups II and III are presynaptic autoreceptors that dampen release. mGluR6 sits atypically in the retina.

The presynaptic Group II and III autoreceptors are of therapeutic interest precisely because agonists that stimulate them *reduce* excess glutamate release; Group II (mGluR2/3) agonists were investigated as non-dopaminergic antipsychotics on exactly this logic, though pivotal efficacy proved inconsistent (Stahl 2021).

5.5 Excitotoxicity: when a good transmitter turns lethal

The very calcium permeability that makes the NMDA receptor useful for learning makes it dangerous when glutamate signalling runs unchecked. **Excitotoxicity** is neuronal death driven

by excessive glutamate-mediated calcium influx: sustained NMDA-receptor activation raises cytosolic calcium (and zinc) to concentrations that activate proteases, lipases, nitric oxide synthase and free-radical cascades, culminating in cell death.

This is the final common pathway of calcium-mediated injury in **stroke, traumatic brain injury, epilepsy and hypoglycaemia**, and it also contributes to the slower neurodegeneration of Huntington disease and Alzheimer disease. It is the theoretical rationale for the neuroprotective aspiration of NMDA antagonists, and it explains the apparent paradox that both too little NMDA signalling (the hypofunction of 5.7) and too much (excitotoxicity) are pathological. The therapeutic window is narrow, which is why a partial, gentle channel blocker such as memantine (5.8) succeeded clinically where high-affinity blockers failed.

5.6 The NMDA hypofunction hypothesis of schizophrenia

The pharmacological cornerstone is simple and reproducible: **phencyclidine (PCP) and ketamine**, both NMDA open-channel blockers, produce in healthy volunteers a syndrome that mimics schizophrenia more fully than any dopaminergic drug does, reproducing not just positive symptoms but the negative symptoms, cognitive impairment and thought disorder that amphetamine psychosis leaves untouched (Stahl 2021). If blocking NMDA receptors makes a healthy brain schizophrenia-like, then a hypofunctioning NMDA receptor may be intrinsic to the illness.

The disinhibition circuit. The elegance of the model lies in where the lesion sits. NMDA receptors are hypofunctional not on the principal glutamate neurons themselves but on inhibitory **GABAergic interneurons** in the prefrontal cortex, in particular the fast-spiking parvalbumin-expressing interneurons that normally restrain cortical glutamate output. If those interneurons are under-driven, they fail to inhibit; the cortical glutamate projection neurons are thereby *disinhibited* and fire excessively (Stahl 2021).

Downstream dopamine. This cortical disinhibition then propagates to the classical dopamine circuits: excess glutamatergic drive to the ventral tegmental area produces *mesolimbic hyperdopaminergia* (positive symptoms) while a separate deficient drive leaves the *mesocortical* dopamine projection hypoactive (negative and cognitive symptoms). In this way the NMDA hypofunction model does not replace the dopamine hypothesis; it sits upstream of it and generates it, unifying positive and negative symptoms under one initiating abnormality.

CLINICAL ANCHOR

The ketamine and PCP models are why glutamatergic agents are pursued in schizophrenia, and why a clinician seeing a young patient with an acute schizophrenia-like psychosis after recreational ketamine or PCP use is watching the hypofunction model unfold in real time. The 2024 arrival of the muscarinic agent xanomeline-trospium (a genuinely non-dopaminergic antipsychotic acting on cholinergic rather than glutamatergic targets) shows the field is finally moving beyond D2 blockade, though direct NMDA-enhancing strategies (glycine, D-serine, bitopertin, glycine-transporter inhibitors) have so far disappointed in pivotal trials.

5.7 Ketamine and esketamine as antidepressants: paradoxical plasticity

Here the same receptor block that models psychosis produces, at sub-anaesthetic doses, a rapid and robust antidepressant effect, often within hours, in patients with treatment-resistant depression (Molero et al. 2018). Reconciling this with the hypofunction model is the intellectual heart of the topic.

The disinhibition-to-glutamate-surge mechanism. Low-dose ketamine preferentially blocks NMDA receptors on the same GABAergic interneurons, transiently disinhibiting cortical glutamate neurons and producing a brief *glutamate surge*. That surge activates **AMPA receptors**, whose downstream signalling releases **BDNF** and activates the **mTOR** pathway (mammalian target of rapamycin), driving a rapid burst of synaptogenesis and dendritic-spine formation in the prefrontal cortex. The antidepressant effect is thus not the NMDA block per se but the AMPA-BDNF-mTOR synaptic remodelling it triggers, restoring the synaptic connectivity that chronic stress and depression erode (cross-reference the neurotrophins topic for the BDNF-TrkB cascade).

The pharmaceutical translation. **Esketamine**, the S-enantiomer, delivered as an intranasal spray, gained US regulatory approval in 2019 for treatment-resistant depression and subsequently for major depressive disorder with acute suicidal ideation or behaviour, always used alongside an oral antidepressant and administered under supervision because of the dissociation, sedation and blood-pressure rise, with a mandatory post-dose monitoring period. Racemic intravenous ketamine remains widely used off-label (Molero et al. 2018).

> **COMMON TRAP**
>
> Do not say ketamine treats depression "by blocking NMDA receptors" and leave it there: that would make every NMDA antagonist an antidepressant, which is false. The mechanism is the *downstream* AMPA-BDNF-mTOR synaptogenic burst produced by transient disinhibition. Also do not confuse the enantiomers: *es*ketamine is the approved intranasal S-enantiomer; *arketamine* (the R-enantiomer) is investigational. And do not overlook the abuse-liability and bladder-toxicity (ketamine cystitis) that shadow chronic use.

5.8 Memantine and the therapeutic uses of channel blockade

Memantine is the clinical proof that NMDA antagonism can be beneficial rather than psychotomimetic, and the difference lies in the kinetics. It is a *low-affinity, uncompetitive, open-channel blocker* that enters the pore only after the receptor is activated and, crucially, leaves it quickly (fast off-rate, "low-trapping"). This lets it dampen the pathological, tonic, low-level over-activation that drives excitotoxicity while sparing the sharp, phasic, high-amplitude signalling needed for normal synaptic transmission and learning.

Memantine is approved for **moderate-to-severe Alzheimer disease**, where it is neither a cure nor disease-modifying but offers symptomatic benefit and is often combined with a cholinesterase inhibitor. It is used off-label in Huntington disease, where excitotoxicity contributes to striatal degeneration. The contrast with ketamine and PCP (high-affinity, deeply trapping blockers that produce dissociation and psychosis) is the exam-favourite discriminator

and a clean lesson in how binding kinetics, not just the target, determine a drug's clinical face (Stahl 2021).

MNEMONIC

MEMANTINE = "MEMory, MEek block"

MEMory names its indication (moderate-to-severe Alzheimer disease); a **ME**ek, low-affinity, fast-off block is why it is tolerated where the greedy, deeply-trapping block of PCP and ketamine causes dissociation and psychosis. Same target, opposite clinical personality.

HOLD THIS

NMDA hypofunction on GABAergic interneurons disinhibits glutamate; that one lesion is both the schizophrenia model and the ketamine antidepressant. The antidepressant effect is the downstream AMPA-BDNF-mTOR burst, not the NMDA block itself.

5.9 Anti-NMDA-receptor encephalitis: the receptor as an antigen

The final clinical face is neuroimmunological and a high-yield can-not-miss for psychiatry, because it presents to psychiatrists first. **Anti-NMDA-receptor encephalitis** is an autoimmune encephalitis in which IgG autoantibodies target the *GluN1 (NR1) subunit* of the NMDA receptor, causing receptor internalisation and a functional, antibody-mediated NMDA hypofunction (Dalmau et al.).

The classic evolution. A young woman (though any age and sex occurs) develops a prodrome, then a *psychiatric phase* of anxiety, agitation, delusions, hallucinations and disorganised behaviour that is readily mistaken for a primary psychotic or affective illness, followed by seizures, movement disorder (orofacial dyskinesias are characteristic), autonomic instability and a declining level of consciousness. The diagnosis rests on detecting anti-NMDA-receptor (anti-GluN1) antibodies, ideally in *cerebrospinal fluid*. A substantial proportion, especially young women, harbour an underlying **ovarian teratoma** providing the ectopic neural antigen, so tumour search is mandatory.

Treatment is tumour removal where present plus immunotherapy (corticosteroids, intravenous immunoglobulin, plasma exchange, and second-line rituximab or cyclophosphamide), and recovery, though often slow, is possible. In ICD-11 this is coded under autoimmune encephalitis rather than as a primary mental disorder, and any young patient with new psychosis plus seizures, dyskinesias, autonomic lability or a fluctuating conscious level should trigger a request for anti-NMDA-receptor antibodies before the presentation is filed as schizophrenia.

INDIA

In Indian psychiatric practice, where a young woman with acute-onset psychosis, catatonia or unexplained seizures may present first to psychiatry, anti-NMDA-receptor encephalitis is an important organic mimic to keep on the differential, particularly when there are neurological soft signs, autonomic instability or catatonia poorly responsive to usual treatment. CSF antibody testing and pelvic imaging for teratoma are the decisive steps; missing it means treating a reversible autoimmune illness as if it were a lifelong psychiatric disorder. This entity is the strongest single argument for a low threshold to investigate atypical first-episode psychosis organically.

6 · GABA receptor subtypes and pharmacology

The brake on the brain. Gamma-aminobutyric acid (**GABA**) is the principal fast inhibitory neurotransmitter of the mature CNS; nearly half of all central synapses carry a GABA receptor of some kind. Almost every drug that sedates, calms anxiety, aborts a seizure, or covers alcohol withdrawal converges on GABAergic signalling, which is why this receptor family is the single most examined target in basic psychopharmacology. The recurring exam distinction is **ionotropic GABA-A** (a ligand-gated chloride channel giving fast, millisecond inhibition) versus **metabotropic GABA-B** (a G-protein-coupled receptor giving slow, sustained inhibition), and the map of allosteric sites layered onto the GABA-A pentamer.

For the exam, three threads recur: the synthesis-and-metabolism loop (GAD, GABA-transaminase, the pyridoxine link), the allosteric-site architecture of GABA-A (benzodiazepine, barbiturate, neurosteroid, anaesthetic, alcohol, Z-drug, picrotoxin sites and the flumazenil antagonist), and the newest clinical translation, neurosteroid antidepressants brexanolone and zuranolone (Kaplan & Sadock 2024; Stahl 2021).

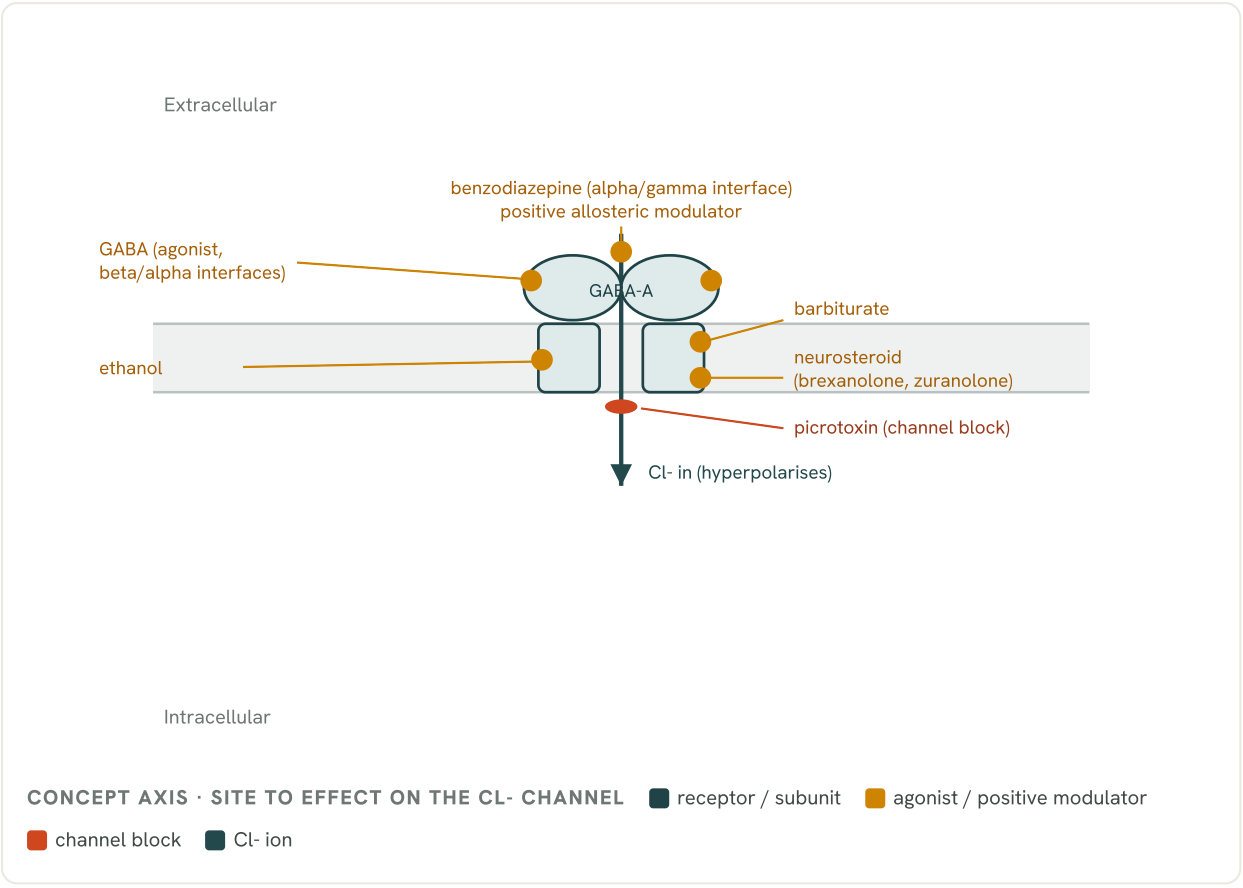


Fig 2.3 The GABA-A receptor is one chloride channel with many doors. GABA itself opens it at the beta/alpha subunit interfaces; benzodiazepines bind the separate alpha/gamma site and increase the frequency of opening (flumazenil blocks this site); barbiturates increase the duration of opening; neurosteroids (allopregnanolone, and the drugs brexanolone and zuranolone) and ethanol are further positive modulators; picrotoxin blocks the pore. All converge on more chloride entry and inhibition.

6.1 Synthesis: glutamate to GABA via GAD

The excitatory-inhibitory pivot. GABA is synthesised in a single decarboxylation step from the excitatory transmitter glutamate by **glutamic acid decarboxylase (GAD)**, the rate-limiting enzyme, which requires **pyridoxal-5-phosphate** (the active cofactor of pyridoxine, vitamin B6). Two isoforms exist, GAD65 (membrane-associated, activity-dependent vesicular pool) and GAD67 (cytosolic, tonic pool). Newly formed GABA is loaded into synaptic vesicles by the vesicular inhibitory amino-acid transporter (VIAAT/VGAT) and released by calcium-dependent exocytosis. Because a single enzyme converts a stimulant into a depressant transmitter, GAD is a mechanistic bottleneck: anything that impairs pyridoxal-phosphate synthesis collapses GABA production and unmasks seizures (StatPearls 2026; Companion to Psychiatric Studies).

6.2 Termination: reuptake and the GABA-transaminase shunt

Recycled into the Krebs cycle. Synaptic GABA is cleared by GABA transporters (GAT-1 to GAT-3) on neurons and astrocytes, then degraded by **GABA-transaminase (GABA-T)**, a mitochondrial enzyme, into **succinic semialdehyde**. Succinic semialdehyde dehydrogenase (SSADH) then oxidises this to succinic acid, which feeds the citric-acid cycle. The transamination is coupled: GABA-T simultaneously converts alpha-ketoglutarate to glutamate, regenerating the precursor and closing the "GABA shunt". This metabolic loop is the substrate for several

anticonvulsants (vigabatrin irreversibly inhibits GABA-T; valproate partially inhibits it) and for a set of rare inborn errors of GABA metabolism (StatPearls 2026).

COMMON TRAP

SSADH deficiency, not GABA-T deficiency, is the commonest inherited disorder of GABA metabolism (and the most prevalent neurotransmitter metabolic disease). Blocked SSA oxidation diverts succinic semialdehyde to **gamma-hydroxybutyrate (GHB)**, so both GABA and GHB rise in serum and urine; the MRI clue is increased globus pallidus signal, with language delay, hypotonia and seizures (StatPearls 2026).

6.3 GABA-A: the pentameric chloride channel

Fast phasic inhibition. The GABA-A receptor is a **pentamer** assembled from a menu of subunits (six alpha, three beta, three gamma, plus delta, epsilon, theta, pi and rho); the most common synaptic isoform is 2 alpha, 2 beta, 1 gamma, typically 2 alpha-1, 2 beta-2, 1 gamma-2. The two orthosteric GABA-binding sites sit at the **beta-alpha interfaces**. Agonist binding opens the intrinsic chloride channel; in the mature neuron the electrochemical gradient drives Cl into the cell, producing **hyperpolarisation** and reduced excitability. GABA-A mediates fast, millisecond-scale synaptic (phasic) inhibition and is concentrated in limbic structures and retina (StatPearls 2026; Kaplan & Sadock 2024).

PEARL

In the fetal and early postnatal brain GABA is **excitatory**, not inhibitory: high intracellular chloride (low KCC2 expression) means channel opening drives Cl out and depolarises the cell. GABA is the first active transmitter in the developing brain and drives progenitor proliferation and migration; the switch to inhibition follows KCC2 maturation (StatPearls 2026).

6.4 Allosteric sites on GABA-A: the modulator map

One channel, many doors. Layered onto the GABA orthosteric site are distinct allosteric sites, each a drug target. A **positive allosteric modulator (PAM)** has no effect without GABA present; it only amplifies GABA's action, which is why these agents have a ceiling and are far safer in overdose than direct agonists. The pharmacologically load-bearing distinction is **benzodiazepines increase the frequency of channel opening** whereas **barbiturates increase the duration of opening** (and, at high dose, open the channel directly, losing the ceiling and becoming lethal) (StatPearls 2026; Stahl 2021).

Benzodiazepine (omega) site

At the alpha-gamma interface; requires a gamma-2 subunit and an alpha-1/2/3/5 subunit. Increases opening frequency. Diazepam, lorazepam, alprazolam, clonazepam.

Z-drug site

Same benzodiazepine pocket but selective for alpha-1-containing receptors (the "omega-1" sedative-hypnotic subtype). Zolpidem, zopiclone, zaleplon; sedative-hypnotic with lower anxiolytic/anticonvulsant profile.

Barbiturate site

Distinct from the benzodiazepine site; prolongs opening duration and directly gates at high dose. Phenobarbital, thiopental.

Neurosteroid site

Transmembrane site distinct from both; potentiates synaptic and extrasynaptic (delta-containing) receptors. Allopregnanolone, brexanolone, zuranolone.

Anaesthetic / alcohol sites

Propofol, etomidate and volatile anaesthetics are GABA-A PAMs; ethanol potentiates GABA-A (notably extrasynaptic delta subtypes) alongside NMDA antagonism.

Picrotoxin / convulsant site

In the channel pore; a non-competitive antagonist (channel blocker), pro-convulsant. Bicuculline is the competitive orthosteric antagonist.

> **CLINICAL ANCHOR**
>
> **Flumazenil** is a competitive antagonist at the benzodiazepine site: it reverses benzodiazepine and Z-drug sedation but does not touch the barbiturate, alcohol or neurosteroid sites, so it is useless in pure barbiturate or ethanol overdose. In benzodiazepine-dependent patients it can precipitate withdrawal seizures, so it is used cautiously and is not a routine reversal agent (StatPearls 2026).

6.5 Subunit selectivity maps to clinical effect

Why one benzodiazepine site gives many effects. The alpha subunit at the benzodiazepine pocket dictates the pharmacological signature: alpha-1 mediates sedation, amnesia and anticonvulsant action (and is the Z-drug target); alpha-2 and alpha-3 mediate anxiolysis and muscle relaxation; alpha-5 (hippocampal) is linked to memory and cognition. This subunit logic is the rationale behind subtype-selective drug design, including the goal of an anxiolytic without sedation, and explains why zolpidem is hypnotic but weakly anxiolytic (Kaplan & Sadock 2024). Note the neurosteroids bind subunits (including alpha-4 and alpha-6) that benzodiazepines do not, a clue to their distinct spectrum.

- **alpha-1** - sedation, amnesia, anticonvulsant action; the Z-drug (zolpidem) target.
- **alpha-2 / alpha-3** - anxiolysis and muscle relaxation.
- **alpha-5** - hippocampal, memory and cognition.

6.6 GABA-B: the metabotropic receptor and baclofen

Slow, sustained inhibition. The **GABA-B receptor** is a G-protein-coupled (Gi/Go) obligate heterodimer of B1 (B1a/B1b) and B2 subunits. It signals through a second-messenger cascade rather than an intrinsic channel. Presynaptically, it reduces adenylyl cyclase activity and inhibits voltage-gated calcium channels, cutting neurotransmitter release (autoreceptor and heteroreceptor). Postsynaptically, it opens inward-rectifying (GIRK) potassium channels, letting K out and producing a slow hyperpolarising IPSP. **Baclofen** is the prototype GABA-B agonist, licensed as a muscle relaxant for spasticity and used off-label (unlicensed) in alcohol dependence with mixed evidence; gamma-hydroxybutyrate is also a GABA-B agonist (StatPearls 2026; Maudsley Prescribing Guidelines).

FEATURE	GABA-A	GABA-B
Receptor class	**Ionotropic, ligand-gated Cl channel**	**Metabotropic, Gi/Go-coupled**
Structure	Pentamer (e.g. 2 alpha, 2 beta, 1 gamma)	Obligate heterodimer (B1 + B2)
Ion / effector	Cl influx, direct	**K efflux (GIRK) + Ca channel inhibition**
Speed	**Fast (milliseconds), phasic**	**Slow (100s of ms), sustained**
Agonist	Muscimol; GABA	**Baclofen; GHB**
Antagonist	Bicuculline (competitive), picrotoxin (channel)	Saclofen, phaclofen
Key drugs	Benzodiazepines, barbiturates, Z-drugs, neurosteroids, propofol	Baclofen (spasticity)

Core discriminators between the two principal GABA receptor families; the third type, GABA-C, is a rho-subunit-only pentameric Cl channel of the retina.

TRAP Gabapentin and pregabalin are not GABAergic despite the name: they block the alpha-2-delta calcium-channel subunit and cut glutamate release.

6.7 Tonic versus phasic inhibition

Two modes of GABA-A signalling. **Phasic inhibition** is the classic fast IPSP: vesicular GABA hits synaptic GABA-A receptors (gamma-2-containing) transiently. **Tonic inhibition** is a persistent background chloride conductance mediated by high-affinity **extrasynaptic GABA-A receptors**, characteristically **delta-subunit**-containing (alpha-4-beta-delta, alpha-6-beta-delta), activated by low ambient GABA that spills out of the synapse. Tonic inhibition sets the neuron's gain and excitability threshold. It is clinically pivotal because **neurosteroids and ethanol preferentially potentiate extrasynaptic delta-containing receptors**, and this tonic pool is the proposed substrate of the neurosteroid antidepressants (Kaplan & Sadock 2024).

6.8 Clinical translation I: anxiety, epilepsy, alcohol withdrawal

The GABAergic workhorses. Benzodiazepines are PAMs used short-term for panic disorder, generalised anxiety disorder and insomnia, as abortive therapy for status epilepticus (lorazepam, diazepam, midazolam), and as first-line cover for **alcohol withdrawal**, where they prevent withdrawal seizures and delirium tremens (chlordiazepoxide, diazepam, or lorazepam in hepatic impairment). The mechanistic rationale in withdrawal is that chronic alcohol downregulates GABA-A and upregulates glutamatergic tone; abrupt cessation leaves an unopposed excitatory state that a GABA-A PAM restores. The 2020 FDA boxed warning covers dependence, life-threatening withdrawal seizures on abrupt cessation, and respiratory-depressant synergy with opioids (StatPearls 2026; Maudsley Prescribing Guidelines).

COMMON TRAP

Not every "GABA analog" acts on GABA transmission. **Gabapentin and pregabalin**, despite the name, do not bind GABA receptors; they inhibit the alpha-2-delta subunit of voltage-gated calcium channels and reduce glutamate release. **Isoniazid** (and hydrazine, and false-morel gyromitrin) deplete pyridoxal phosphate, shut down GAD, and cause benzodiazepine-refractory seizures treated with high-dose **pyridoxine** (StatPearls 2026).

6.9 Clinical translation II: neurosteroid antidepressants

Brexanolone and zuranolone. **Allopregnanolone** (3-alpha,5-alpha-tetrahydroprogesterone), a metabolite of progesterone, is an endogenous neurosteroid PAM of synaptic and extrasynaptic GABA-A receptors. Its levels fall sharply after delivery, the proposed trigger for postpartum mood collapse. **Brexanolone** (Zulresso), an IV allopregnanolone formulation, is FDA-approved for postpartum depression, given as a 60-hour infusion under monitoring for sedation and loss of consciousness. **Zuranolone** (SAGE-217, Zurzuvae) is the orally available analog, a 14-day bedtime course approved for postpartum depression (its trials in major depressive disorder more broadly were mixed) (Kaplan & Sadock 2024; Practical Psychopharmacology). Both are restricted to the postpartum window (up to one year), cause psychomotor impairment (no driving), and preclude breastfeeding during treatment. These are the first mechanistically GABAergic antidepressants, contrasting the delayed monoamine reuptake inhibitors with a rapid, days-scale response.

INDIA

Brexanolone and zuranolone are not routinely available in Indian practice, so postpartum depression management here remains SSRI-led (sertraline preferred in lactation for high protein binding and short half-life) with psychotherapy. For alcohol withdrawal in Indian ICUs, benzodiazepine-based regimens (chlordiazepoxide, diazepam) remain the mainstay, consistent with observed practice patterns (Gopaldas et al. 2023).

6.10 ICD-11 mapping and diagnostic anchors

Where these drugs land nosologically. The disorders driving GABAergic prescribing map to ICD-11 as: alcohol withdrawal within disorders due to use of alcohol (cross-mapped to DSM-5-TR alcohol withdrawal); anxiety and fear-related disorders including generalised anxiety disorder and panic disorder (DSM-5-TR anxiety disorders); depressive disorders including a peripartum-onset specifier (the target for brexanolone and zuranolone; DSM-5-TR MDD with peripartum onset). Epilepsy is neurological rather than an ICD-11 mental-disorder category. Specific ICD-11 alphanumeric codes are omitted here where certainty is incomplete (see gaps).

MNEMONIC

"FRequency vs duRation: Benzos are FRequent, Barbs enduRe."

Benzodiazepines increase the **fr**equency of GABA-A chloride channel opening; barbiturates increase the du**r**ation. Barbiturates additionally open the channel directly at high dose, which is why they lack the benzodiazepine ceiling and are lethal in overdose.

HOLD THIS

Benzodiazepines raise frequency, barbiturates raise duration; barbiturates also gate the channel directly at high dose, so they lose the ceiling and become lethal. This single contrast explains the benzodiazepine's wider therapeutic index.

7 · Cholinergic systems

Acetylcholine is the oldest neurotransmitter in psychiatry's story: it was the first chemical proven to carry a nerve signal (Loewi's 1921 vagusstoff experiment) and it remains the transmitter whose *loss* gave us the first rationally designed dementia drugs. For the exit exam the cholinergic system pays back in four distinct currencies, and a strong answer keeps them separate: the **molecular pharmacology** (synthesis by ChAT, breakdown by AChE, and the split between nicotinic ion channels and five muscarinic G-protein-coupled receptors), the **central anatomy** (two forebrain and two brainstem source nuclei with named projection targets), the **physiology** (memory, cortical arousal, and the generation of REM sleep), and the **clinical translation** (the cholinergic hypothesis of Alzheimer disease and cholinesterase inhibitors, anticholinergic burden and delirium in the elderly, the smoking-schizophrenia link, and the 2024 arrival of muscarinic agonism as an antipsychotic principle with xanomeline-trospium).

Why it recurs. Cholinergic pharmacology is the through-line that connects a neurochemistry viva, a geriatric-psychiatry station, and a psychopharmacology question in a single sitting. The same M1 receptor that anticholinergics block to treat drug-induced parkinsonism is the receptor whose blockade causes the memory clouding of anticholinergic delirium; the same muscarinic system that xanomeline stimulates to quiet psychosis is the one whose peripheral M2/M3 activation trospium is added to suppress. Understanding the wiring once lets you reason your way through all of these rather than memorising each in isolation.

7.1 Synthesis, storage, release and inactivation

Synthesis. Acetylcholine (**ACh**) is an ester of acetic acid and choline, assembled in the axon terminal by **choline acetyltransferase** (ChAT, older abbreviation CAT), which transfers an acetyl group from mitochondrial acetyl-coenzyme A onto choline. Choline is the limiting substrate: it comes from the diet (egg yolk, liver, legumes) and from hepatic synthesis, crosses the blood-brain barrier, and is scavenged back into the terminal by a **high-affinity, sodium-dependent choline transporter** whose uptake is the true rate-limiting step in ACh production (Sam and Bordoni 2023). ChAT is manufactured in the soma and shipped down the axon; because it is uniquely present in cholinergic neurons, **ChAT immunostaining is the definitive**

marker of a cholinergic cell, and its reduction in Alzheimer cortex is the biochemical cornerstone of the cholinergic hypothesis.

Storage and release. New ACh is pumped into synaptic vesicles by the **vesicular acetylcholine transporter** (VAChT), which exchanges one cytoplasmic ACh for one vesicular proton using the gradient built by a vesicular H-ATPase. Arrival of an action potential opens voltage-gated calcium channels; calcium triggers SNARE-mediated vesicle fusion (synaptobrevin as the v-SNARE, SNAP-25 and syntaxin-1 as t-SNAREs, synaptotagmin as the calcium sensor), releasing ACh into the cleft (Sam and Bordoni 2023). Two classic toxins bracket this step and are examiner favourites: **botulinum toxin cleaves SNARE proteins and blocks ACh release** (flaccid paralysis, exploited therapeutically for dystonia, spasticity and cosmesis), whereas **black widow (alpha-latrotoxin) venom forces massive ACh release** and exhausts the terminal.

Inactivation. Unlike the monoamines, ACh is not reclaimed by reuptake of the intact transmitter; it is **hydrolysed in the cleft** into choline and acetate by **acetylcholinesterase** (AChE), a fixed, GPI-anchored or soluble enzyme, with the liberated choline recaptured for resynthesis. AChE is extraordinarily fast, which makes cholinergic transmission crisp and short-lived; a second enzyme, **butyrylcholinesterase** (BuChE, pseudocholinesterase, made mainly in liver and glia), also degrades ACh and becomes relatively more important as AChE-bearing neurons are lost in advancing dementia. This two-enzyme architecture is the direct rationale for the cholinesterase inhibitors in subtopic 7.6.

PEARL

ACh is the transmitter defined by its enzyme, not its transporter. Serotonin, dopamine and noradrenaline are terminated by reuptake (hence SSRIs and reuptake inhibitors); acetylcholine is terminated by *enzymatic hydrolysis* in the cleft. That single difference explains why the drug class that boosts ACh is a group of *esterase inhibitors*, not reuptake inhibitors, and why organophosphate and nerve-agent poisoning (irreversible AChE inhibition) produces a cholinergic crisis.

7.2 Nicotinic receptors: the ionotropic arm

Nicotinic acetylcholine receptors (nAChRs) are **ligand-gated cation channels**, members of the pentameric Cys-loop superfamily alongside GABA-A, glycine and 5-HT3 receptors. Five subunits ring a central pore; binding of two ACh molecules opens the channel to sodium, potassium and calcium, depolarising the cell and driving fast excitatory transmission (Companion to Psychiatric Studies). Two broad classes matter. The **muscle type** (N1, subunit stoichiometry 2-alpha, beta, delta, gamma or epsilon) sits at the neuromuscular junction and is the receptor destroyed by autoantibodies in **myasthenia gravis**. The **neuronal type** (N2) is built from alpha and beta subunits and populates autonomic ganglia, the adrenal medulla and the brain, concentrated in the ventral tegmental area, nucleus accumbens, hippocampus, prefrontal cortex and amygdala (Sam and Bordoni 2023).

Two subtypes carry the psychiatry. The **alpha-4-beta-2** nAChR is the high-affinity target for nicotine and the site of the reinforcing, dependence-producing dopamine surge in the

mesolimbic system; it is the target of the smoking-cessation partial agonist *varenicline* (Stahl 2021). The homomeric **alpha-7** nAChR is highly calcium-permeable, enriched in hippocampus and cortex, and implicated in sensory gating and cognition, making it a repeatedly pursued (and repeatedly disappointing) drug target for the cognitive deficits of schizophrenia. A defining feature of nAChRs is **desensitisation**: with prolonged agonist exposure the channel enters a non-conducting but agonist-bound state. Because AChE normally clears ACh within milliseconds the receptor rarely desensitises to its own transmitter, but **nicotine is not a substrate for AChE**, so it lingers, desensitises and then inactivates the receptor over the course of a single cigarette, which explains the characteristic dosing rhythm of smoking (Stahl 2021).

7.3 Muscarinic receptors: the five metabotropic subtypes

Muscarinic acetylcholine receptors (mAChRs) are **seven-transmembrane G-protein-coupled receptors**, subtypes M1 through M5, all five expressed in the CNS. They divide cleanly by their coupling, and this coupling is the single most examinable fact about them. The **odd-numbered receptors (M1, M3, M5)** couple to **Gq**, activating phospholipase C to generate IP3 and diacylglycerol, raising intracellular calcium and activating protein kinase C: broadly *excitatory/stimulatory*. The **even-numbered receptors (M2, M4)** couple to **Gi/Go**, inhibiting adenylyl cyclase and lowering cAMP (M2 also opens potassium channels): broadly *inhibitory* (Sam and Bordoni 2023).

SUBTYPE	G-PROTEIN / SECOND MESSENGER	NET EFFECT	KEY LOCATIONS (EXAM-RELEVANT)
M1	**Gq → PLC, IP3/DAG ↑Ca**	Excitatory	Cortex, hippocampus, striatum, gastric/salivary glands; cognition and memory
M2	**Gi → ↓cAMP, ↑K**	Inhibitory (autoreceptor)	Heart (bradycardia), CNS presynaptic autoreceptor limiting ACh release
M3	**Gq → PLC, IP3/DAG ↑Ca**	Excitatory	Smooth muscle (bronchi, bladder, gut), exocrine glands; pupillary constriction
M4	**Gi → ↓cAMP**	Inhibitory	Striatum (dopamine modulation), hippocampus; antipsychotic-relevant
M5	Gq → PLC	Excitatory	Substantia nigra/VTA (dopamine neurons), cerebral vasculature; least understood

The odd/even coupling rule: M1, M3, M5 are Gq-coupled and excitatory; M2 and M4 are Gi-coupled and inhibitory. Peripherally, M2 is the cardiac (vagal bradycardia) receptor and M3 the smooth-muscle/glandular receptor, which is why non-selective antimuscarinics produce the dry-mouth, blurred-vision, tachycardia, constipation and urinary-retention picture.

COMMON TRAP

Do not label all muscarinic receptors "inhibitory" because the parasympathetic system is often taught as the calming counterpart to sympathetic drive. At the receptor level M1, M3 and M5 are **excitatory** Gq signals; the parasympathetic *slowing* of the heart is a special case mediated by M2 opening potassium channels. Marrying the odd/even numbering to the Gq/Gi split (odd = Gq = excitatory, even = Gi = inhibitory) is the reliable way to avoid the error.

HOLD THIS

Muscarinic odd numbers are Gq and excitatory (M1, M3, M5); even numbers are Gi and inhibitory (M2, M4). Vagal cardiac slowing is the M2-opens-potassium special case, not proof that all muscarinic receptors inhibit.

7.4 Central cholinergic projection systems (cross-reference the Functional Neuroanatomy & Neurophysiology notes)

Central ACh arises from two source regions, one in the basal forebrain and one in the brainstem, giving **four named nuclei** whose projection targets are high-yield (these overlay the ascending arousal/reticular systems mapped on the Functional Neuroanatomy & Neurophysiology notes). Learn them as two pairs.

Nucleus basalis of Meynert (Ch4)

The large-celled (magnocellular) basal forebrain nucleus that supplies the **diffuse cholinergic innervation of the entire neocortex and the amygdala**. Its degeneration is the anatomical lesion of the Alzheimer cholinergic deficit; there is a documented correlation between the depth of amnesia and the extent of nucleus basalis damage (Tasman Psychiatry).

Medial septal nucleus and diagonal band (Ch1-Ch2)

The **septohippocampal** projection, running through the fornix to the hippocampus (and to entorhinal cortex). Medial-septal cholinergic neurons **pace the hippocampal theta rhythm** that is essential for encoding new declarative memory; their loss produces the forgetfulness of hippocampal ACh depletion (Companion to Psychiatric Studies).

Pedunculopontine tegmental nucleus (PPT/PPN)

Part of the mesopontine (brainstem) cholinergic group projecting rostrally to the **thalamus, basal forebrain and basal ganglia**; a component of the ascending reticular activating system that drives cortical arousal and, with the LDT, gates REM sleep.

Laterodorsal tegmental nucleus (LDT)

The second mesopontine nucleus, closely allied with the PPT; together the **PPT/LDT** constitute the "REM-on" cholinergic generator of the brainstem (subtopic 7.5).

A separate, purely local cholinergic population, the **striatal cholinergic interneurons (tonically active neurons)**, does not project but sets the dopamine-acetylcholine balance within the striatum that underlies extrapyramidal side effects and their anticholinergic treatment (subtopic 7.7).

7.5 Functions: memory, cortical arousal and REM sleep

Memory and attention. Cortical and hippocampal ACh is permissive for **encoding new information and for attention**, not for retrieving old memories. The pharmacological proof is scopolamine, a centrally acting antimuscarinic that reproducibly **impairs the learning of new material** while leaving established memory intact (Sam and Bordoni 2023); this "scopolamine model of amnesia" is the mirror image of the therapeutic logic behind cholinesterase inhibitors. Basal-forebrain ACh also sharpens signal-to-noise in sensory cortex, supporting selective attention.

Cortical arousal. The brainstem (PPT/LDT) and basal-forebrain cholinergic systems are core components of the **ascending reticular activating system**. Cholinergic tone **desynchronises the cortical EEG**, shifting it from the slow high-voltage rhythms of drowsiness to the fast low-voltage activity of wakefulness and REM, which is why anticholinergic drugs sedate and cloud consciousness.

REM sleep. ACh is the pro-REM transmitter. The **reciprocal-interaction (McCarley-Hobson) model** frames REM as the output of "REM-on" cholinergic PPT/LDT neurons switched off by "REM-off" aminergic (noradrenergic locus coeruleus, serotonergic raphe) neurons; REM occurs when cholinergic activity is high and aminergic activity is low. This maps directly onto two exam points: cholinergic REM facilitation explains the **REM rebound and vivid dreaming seen with cholinesterase inhibitors**, and the reduced REM latency of depression is read as a relative cholinergic-aminergic imbalance.

MNEMONIC

"ACh WAKES you to LEARN and to DREAM"

Acetylcholine drives cortical arousal (WAKES: EEG desynchronisation), consolidation of new memory (LEARN: hippocampal theta and encoding), and REM sleep (DREAM: PPT/LDT REM-on neurons). Block it (scopolamine, atropine, deliriant plants) and you get the opposite triad: sedation, amnesia for new events, and a confusional, dream-like delirium.

TRAP Acetylcholine is not cleared by reuptake. It is hydrolysed in the cleft, which is why the drugs that raise it are esterase inhibitors, not reuptake inhibitors.

7.6 The cholinergic hypothesis of Alzheimer disease and cholinesterase inhibitors

The hypothesis. The **cholinergic hypothesis** holds that the cognitive decline of Alzheimer disease reflects **progressive loss of basal-forebrain cholinergic neurons** (the nucleus basalis of Meynert), with fallen cortical ChAT and ACh (Maudsley Prescribing Guidelines). It was the first mechanistic account to yield a drug class, but it is now understood as one strand rather than the whole story: the deficits are not confined to ACh, and cholinergic replacement is symptomatic, not disease-modifying. Contemporary texts (Stahl 2021) accordingly de-emphasise it relative to the amyloid and tau pathways while retaining it as the basis of current symptomatic therapy.

Cholinesterase inhibitors (ChEIs). These raise synaptic ACh by blocking its hydrolysis; three are licensed for mild-to-moderate (and, in guidance, severe) Alzheimer dementia and give **modest symptomatic benefit** without altering the underlying course.

DRUG	ENZYME SELECTIVITY	EXTRA MECHANISM	NOTES
Donepezil	**Selective reversible AChE-I**	None	Once daily; best tolerated of the three; 23 mg formulation for moderate-severe AD
Rivastigmine	**AChE + BuChE (pseudo-irreversible)**	Dual esterase inhibition	Oral or transdermal patch (better GI tolerability); also licensed in Parkinson disease dementia
Galantamine	Selective reversible AChE-I	**Allosteric nicotinic receptor potentiation**	Additional nicotinic modulation; more peripheral adverse-effect profile

The three ChEIs differ mechanistically (donepezil pure selective AChE inhibition, rivastigmine dual AChE plus BuChE, galantamine AChE inhibition plus allosteric nicotinic potentiation) but head-to-head trials show broadly similar efficacy; choice is driven by tolerability and formulation (Maudsley Prescribing Guidelines).

Adverse effects and combination. The predictable price of raised ACh is **cholinergic excess**: nausea, vomiting, diarrhoea, anorexia and weight loss, bradycardia and syncope (caution in sick sinus syndrome and conduction block), muscle cramps, and vivid dreams; slow titration reduces these. For **moderate-to-severe AD**, NICE and other guidelines recommend an AChE-I *plus* the NMDA-receptor antagonist **memantine** rather than an AChE-I alone, a combination supported by network meta-analysis and Cochrane review (Maudsley Prescribing Guidelines). Newer disease-modifying anti-amyloid monoclonal antibodies (for example lecanemab, donanemab) act on a different pathway and do not displace symptomatic ChEI therapy.

CLINICAL ANCHOR

ChEIs are also first-line for the cognitive symptoms of **dementia with Lewy bodies** and Parkinson disease dementia, where the cholinergic deficit is often even more marked than in Alzheimer disease and the response can be striking; rivastigmine is specifically licensed for Parkinson disease dementia. Conversely, in **myasthenia gravis** the same principle is applied peripherally: the reversible AChE inhibitor *pyridostigmine* raises ACh at the neuromuscular junction to overcome antibody-mediated loss of N1 receptors.

7.7 Anticholinergic burden, delirium and the dopamine-acetylcholine balance

The striatal balance. Within the nigrostriatal system dopamine and ACh sit in **reciprocal opposition**: dopamine at D2 receptors normally suppresses striatal cholinergic interneurons, so *blocking* D2 receptors with an antipsychotic releases ACh and produces the rigidity and bradykinesia of drug-induced parkinsonism (Stahl 2021). Adding an **antimuscarinic (M1-blocking) anticholinergic**, trihexyphenidyl, benztropine or procyclidine, restores the balance

and relieves parkinsonism and acute dystonia (intramuscular anticholinergic is near-uniformly effective within about 20 minutes for acute dystonia). Akathisia, by contrast, responds poorly to anticholinergics and is better treated with a beta-blocker or benzodiazepine.

The cost of blockade. The same central M1 blockade that treats extrapyramidal symptoms carries a cognitive price: **constipation, dry mouth, blurred vision, urinary retention, drowsiness and, critically, memory and attention impairment**, the pharmacological counterpart of the scopolamine amnesia model (Stahl 2021). The concept of **anticholinergic burden** captures the additive antimuscarinic load of a patient's whole regimen, since many non-psychiatric drugs (oxybutynin, some antihistamines, tricyclics, low-potency antipsychotics) carry hidden anticholinergic activity.

CLINICAL ANCHOR

Anticholinergic delirium should always be considered in an agitated or confused older adult (Tasman Psychiatry). Central antimuscarinic toxicity produces the classic picture: agitation and visual hallucinations, disorientation and fluctuating consciousness, with peripheral signs of "mad as a hatter, hot as a hare, dry as a bone, red as a beet, blind as a bat" (delirium, hyperthermia, anhidrosis, flushing, mydriasis). High cumulative anticholinergic burden is an independent, and modifiable, risk factor for both delirium and longer-term cognitive decline in the elderly, which is why deprescribing antimuscarinics is a standard geriatric-psychiatry intervention.

INDIA

Antimuscarinic anti-parkinsonian drugs, especially **trihexyphenidyl**, are widely and often reflexively co-prescribed with first-generation antipsychotics such as haloperidol in Indian practice, and trihexyphenidyl carries a recognised potential for **misuse** (euphoriant and hallucinogenic at high dose). Good practice is to reserve it for established extrapyramidal symptoms rather than prophylaxis, review the need periodically, and stay alert to diversion, particularly given the high anticholinergic-burden risk in older and physically comorbid patients.

7.8 Smoking and schizophrenia; the alpha-7 and nicotinic story

Rates of cigarette smoking in schizophrenia are strikingly high (well above the general population), and the relationship is more than a lifestyle association. The leading explanation is a **self-medication / sensory-gating hypothesis**: nicotine, acting on **alpha-7 and alpha-4-beta-2 nicotinic receptors**, transiently improves the impaired auditory sensory gating (the P50 evoked-potential deficit) and some attentional and working-memory deficits characteristic of schizophrenia, deficits linked to reduced alpha-7 nicotinic function and to the CHRNA7 gene. Nicotine also induces hepatic CYP1A2, so **smoking lowers plasma levels of clozapine and olanzapine** (both CYP1A2 substrates); abrupt smoking cessation can raise levels sharply and precipitate toxicity, a frequently examined interaction. This nicotinic-cognitive link is the same rationale that drove alpha-7 agonist drug programmes for cognitive impairment in schizophrenia, which have so far largely failed to deliver a licensed agent.

COMMON TRAP

When a stabilised inpatient smoker on clozapine is admitted to a smoke-free ward, or stops smoking, expect clozapine levels to **rise** (loss of CYP1A2 induction), not fall. The mechanism is nicotine-independent (it is the polycyclic aromatic hydrocarbons in tobacco smoke, not the nicotine, that induce CYP1A2), so nicotine-replacement therapy does *not* maintain the induction. Anticipate a dose reduction and monitor levels.

7.9 Muscarinic agonism as an antipsychotic: xanomeline-trospium (2024)

The most important recent development in cholinergic psychopharmacology is the arrival of a **muscarinic mechanism of antipsychotic action**, the first genuinely new antipsychotic principle in decades and one that does not rely on direct dopamine D2 blockade. **Xanomeline** is a central agonist selective for the **M1 and M4** muscarinic receptors. Via M4 it *indirectly* reduces dopamine cell firing in the ventral tegmental area (theoretically damping positive psychotic symptoms), and via M1 it raises prefrontal dopamine and acetylcholine (theoretically aiding negative, cognitive and affective symptoms), achieving antipsychotic effect without touching the D2 receptor and therefore **without the extrapyramidal, prolactin and metabolic liabilities of dopamine blockers** (Stahl 2021).

Xanomeline alone was historically limited by peripheral cholinergic side effects from M2 and M3 stimulation (nausea, vomiting, sweating, salivation, GI upset). The solution is the **co-formulation with trospium**, a peripherally restricted antimuscarinic that **does not cross the blood-brain barrier** and so blocks the offending peripheral M2/M3 receptors while sparing the central M1/M4 agonism that carries the therapeutic effect (Stahl 2021). This combination, developed as **KarXT** (xanomeline-trospium, brand name Cobenfy), gained **US FDA approval for schizophrenia in adults in September 2024**, establishing the muscarinic system as a validated antipsychotic target and vindicating a line of research that began with xanomeline trials in Alzheimer disease decades earlier.

PEARL

KarXT is the clean worked example of exploiting the blood-brain barrier for selectivity. **Xanomeline works centrally (M1/M4 agonism → antipsychotic); trospium works only peripherally (M2/M3 antagonism → blocks cholinergic side effects) because it cannot enter the brain.** Contrast this with the older strategy in Parkinson disease, where a peripheral decarboxylase inhibitor (carbidopa) is added to levodopa for the analogous reason: keep the therapeutic action central and the unwanted action peripheral.

8 · Neuropeptides (substance P, CRF, oxytocin and others)

Neuropeptides are the second, slower transmitter language of the brain. Where the classical small-molecule transmitters (glutamate, GABA, the monoamines, acetylcholine) are packaged in small clear vesicles and act in milliseconds at the synaptic cleft, neuropeptides are chains of amino acids, stored in large dense-core vesicles, released more diffusely (from the axon, from dendrites, sometimes far from any synapse) and act over seconds to minutes through **G-protein-**

coupled receptors. They almost never work alone: most are *co-transmitters* released alongside a monoamine or amino acid, and they tune the gain of that faster circuit rather than carrying the primary message. For the examiner this topic is a checklist of "who does what, which receptor, and which drug story went with it," and the single most reliable trap is the one built into the whole field: peptide biology is beautiful in rodents and has repeatedly disappointed in humans.

This fragment covers the co-transmission principle, then substance P, CRF, the oxytocin-vasopressin pair, the endogenous opioid peptides (a Paper-1 must-have), and the shorter roster of NPY, CCK, galanin and orexin, closing on why translation has been so hard. It cross-references the the Functional Neuroanatomy & Neurophysiology notes stress circuit and the HPA axis topic of this same day, since CRF is the molecular hinge of both.

8.1 The co-transmission principle

One neuron, more than one transmitter. Dale's original one-neuron-one-transmitter rule was overturned once immunohistochemistry showed peptides sitting inside the same neurons as classical transmitters. The organising fact is **co-localisation**: neuropeptide Y coexists with noradrenaline in the locus coeruleus and with GABA and somatostatin elsewhere; galanin coexists with noradrenaline in the locus coeruleus and with serotonin in the dorsal raphe; substance P co-exists with serotonin in raphe neurons (Tasman 2013). The peptide is generally released only at higher firing frequencies than the fast transmitter, so it acts as a *state-dependent modulator*, engaged when the circuit is driven hard, as in stress.

Storage and release

Peptides are made as large precursors in the cell body, cleaved and packaged into **large dense-core vesicles**, then released by calcium-triggered exocytosis. Release is *not* confined to the synapse or axon terminal: it occurs along the axon and from dendrites, giving diffuse, paracrine-like signalling.

Precursor economy

A single gene product often yields several active peptides. Pro-opiomelanocortin (POMC) is the exemplar: differential cleavage gives beta-endorphin, ACTH and the melanocyte-stimulating hormones from one precursor, tissue-specifically.

Receptors

Almost all neuropeptide receptors are *metabotropic*, seven-transmembrane GPCRs (the same superfamily as monoamine receptors), which is why peptide actions are slow and modulatory rather than fast and ionotropic.

Inactivation

There is no reuptake transporter for peptides; they are terminated by extracellular *peptidases*. This is a practical drug-design problem, since peptides are also degraded in the gut and cross the blood-brain barrier poorly.

PEARL

The "no reuptake, degraded by peptidases, poor blood-brain-barrier penetration" triad explains two recurring facts: why most peptide-based drugs are given intranasally (oxytocin, NPY) to reach the brain, and why the successful drugs in this space are small-molecule *receptor* ligands (antagonists at NK1, CRF1, orexin receptors) rather than the peptides themselves.

8.2 Substance P and the NK1 receptor: the aprepitant story

The tachykinin of pain, stress and emesis. Substance P is an 11-amino-acid **undecapeptide** of the tachykinin family, discovered in the 1930s and among the most studied of all neuropeptides. It signals mainly through the **neurokinin-1 (NK1) receptor**, a GPCR densely expressed in limbic regions (amygdala, hypothalamus, periaqueductal grey) that govern the stress and fear response; the family also includes NK2 (largely peripheral smooth muscle) and NK3 (central) receptors. Substance P is a classic pain neurotransmitter in the dorsal horn, and its central injection is anxiogenic in the elevated-plus-maze.

The psychiatric signal. Depressed and PTSD patients show elevated CSF substance P (Tasman 2013), which made NK1 antagonism an attractive antidepressant strategy. The landmark result was **MK-869 (later aprepitant)**: an early trial reported it superior to placebo and comparable to paroxetine in moderate-to-severe major depression (Kramer 1998). This was the great hope of the peptide era.

The disappointment, and the pivot. Subsequent adequately powered phase-III trials of aprepitant in major depression *failed* to separate from placebo, and the antidepressant programme was abandoned. The molecule was not wasted: NK1 antagonism is a powerful antiemetic, and **aprepitant was approved (as Emend) for chemotherapy-induced and post-operative nausea and vomiting**, the durable clinical legacy of the substance P story. This is the template for the whole topic: rodent-validated, human-disappointing on the primary psychiatric endpoint, salvaged by an adjacent indication.

TRAP When a neuropeptide antagonist is linked to emesis rather than mood, think substance P / NK1 and aprepitant: it failed as an antidepressant but succeeded as an antiemetic.

CLINICAL ANCHOR

When a question links a neuropeptide antagonist to *emesis* rather than mood, think substance P / NK1 and aprepitant. Its antiemetic use, especially with highly emetogenic chemotherapy, is the fact most likely to be tested, and it is the counterexample to the claim that peptide drugs "never made it."

8.3 CRF/CRH: the master driver of the stress axis

The peptide that starts the cascade. Corticotropin-releasing factor (CRF, also CRH) is the apical hypothalamic peptide of the stress response. Parvocellular neurons of the **paraventricular nucleus (PVN)** synthesise CRF and release it into the hypophyseal portal system to drive pituitary ACTH, and thence adrenal cortisol; this is the **HPA axis** covered in detail in the HPA

topic of these notes, and CRF is the same molecule that opens the the Functional Neuroanatomy & Neurophysiology notes stress circuit. Vasopressin, co-secreted from the PVN, is a permissive co-secretagogue that potentiates CRF-driven ACTH release (Kaplan & Sadock 2024).

Central versus endocrine CRF. Beyond the neuroendocrine axis, CRF acts as a genuine *extrahypothalamic neurotransmitter*, notably in the amygdala and the bed nucleus of the stria terminalis, where it mediates the behavioural and emotional (rather than hormonal) components of stress, anxiety and fear. Two receptors matter: **CRF1**, the anxiogenic, pro-stress receptor, and **CRF2**, with a more complex, sometimes counter-regulatory role. CRF1-knockout mice show decreased anxiety and a blunted stress response (Smith 1998).

The translational failure. Hyperactivity of the CRF system is a robust correlate of chronic stress and depression, and CRF1 antagonists looked like a rational antidepressant/anxiolytic class. An open-label CRF1-antagonist trial hinted at antidepressant activity, but controlled trials of CRF1 antagonists in depression and anxiety did not deliver convincing efficacy (Paez-Pereda 2011), and the class stalled, another rodent-to-human disappointment. Vasopressin V1b antagonism was pursued in parallel for the same axis; the V1b antagonist SSR149415 was discontinued in 2008 for lack of clinical efficacy.

> **CLINICAL ANCHOR**
>
> CRF hyperdrive is the biochemical bridge between early-life adversity, chronic stress and depression. Elevated CSF CRF and non-suppression on the dexamethasone suppression test both index this overactivity and both tend to normalise with clinical recovery, one of the more reliable state markers linking the HPA topic to affective illness.

8.4 Oxytocin and vasopressin: bonding, trust and the social brain

A nine-amino-acid pair from the same nuclei. Oxytocin and arginine vasopressin (AVP) are structurally near-identical **nonapeptides** (9 amino acids, differing at two positions) synthesised in the **paraventricular and supraoptic nuclei** of the hypothalamus and released both peripherally via the posterior pituitary and centrally within the brain (Kaplan & Sadock 2024). Peripherally, oxytocin drives uterine contraction and milk let-down; centrally, it is the prosocial, stress-buffering peptide.

Oxytocin: prosocial and anxiolytic

Anxiogenic and stressful stimuli trigger central oxytocin release, which *dampens* the HPA axis and reduces anxiety. Intranasal oxytocin in healthy men reduces amygdala reactivity to fearful faces, lowers anxiety and improves emotion recognition and social memory. Oxytocin exerts inhibitory effects on the HPA axis and facilitates extinction of social fear (Kaplan & Sadock 2024).

Vasopressin: arousal and aggression

AVP acts through **V1a** (anxiety, social recognition, aggression) and **V1b** (HPA-axis modulation, co-driving ACTH). V1a-knockout mice are less anxious; V1a-overexpressing mice are more anxious (Kaplan & Sadock 2024). Oxytocin and vasopressin are functional opposites in the central amygdala, exciting distinct neuronal populations.

Autism and trust. Oxytocin is the peptide most tied to social cognition. Reduced CSF oxytocin is reported after early-life stress, and oxytocin-receptor gene polymorphisms and reduced OXTR methylation associate with social anxiety and with heightened cortisol and amygdala reactivity. Intranasal oxytocin has been trialled in autism spectrum disorder to improve social reciprocity, and in social anxiety disorder as an augment to exposure therapy, with modest and inconsistent benefit. Note a recurring *sex difference*: several oxytocin effects seen in men are not reproduced in women.

COMMON TRAP

Do not overstate the "trust hormone" and "autism cure" claims. Intranasal oxytocin's effects in human trials are small, context- and sex-dependent, and large controlled trials in autism have been largely negative for core social deficits. In an exam, the safe statement is that oxytocin modulates social cognition, amygdala reactivity and HPA-axis tone, not that it is an established treatment.

8.5 Endogenous opioid peptides: three families, three receptors

The brain's own morphine system. This subtopic is a Paper-1 must-have. The **endogenous opioid** system is a neuropeptide system with three families of peptides, each derived from its own precursor, acting on three classical opioid receptors (Oxford Handbook of DBT 2018). The mnemonic pairing of family to receptor is high-yield.

Endorphins (from POMC)

Beta-**endorphin** is cleaved from pro-opiomelanocortin, the same precursor that yields ACTH and MSH, so endorphin release is intrinsically coupled to HPA-axis activation. Beta-endorphin is the highest-affinity endogenous agonist at the **mu (μ)** receptor, the receptor of reward, euphoria and analgesia.

Enkephalins (from proenkephalin)

Enkephalins (met- and leu-enkephalin) are short pentapeptides preferring the **delta (δ)** receptor (with mu activity too). They are widely distributed in pain-modulating and limbic circuits; alcohol releases enkephalins in the nucleus accumbens, part of alcohol's rewarding action (Stahl, Substance Use).

Dynorphins (from prodynorphin)

Dynorphins are the endogenous agonists of the **kappa (κ)** receptor. Kappa signalling is the dark mirror of mu: rather than euphoria it produces *dysphoria*, aversion and stress-like states, and dynorphin in the central amygdala disinhibits somatostatin neurons to generate anxiety (Kaplan & Sadock 2024).

PEPTIDE FAMILY	PRECURSOR	PREFERRED RECEPTOR	SIGNATURE EFFECT
Beta-endorphin	POMC (proopiomelanocortin)	Mu (μ)	**Reward, euphoria, analgesia; HPA-linked**
Enkephalins (met-, leu-)	Proenkephalin	Delta (δ)	Analgesia, mood, limbic reward
Dynorphins	Prodynorphin	**Kappa (κ)**	**Dysphoria, aversion, stress**

The three endogenous opioid families mapped to precursor, receptor and effect. The discriminator is the kappa/dynorphin axis, which drives dysphoria rather than reward.

Reward, analgesia and stress in one system. The mu system underlies opioid analgesia and the euphoric "high" of exogenous opioids and is a core node of the brain reward circuit; descending endogenous-opioid projections to the periaqueductal grey and dorsal horn gate nociceptive input, which is the endogenous analgesia mimicked by exogenous opioids (Stahl 2021). The kappa/dynorphin system, by contrast, mediates the aversive, dysphoric side of stress and has become a target for anti-anhedonic and anti-addiction agents (kappa antagonists). Clinically, this circuitry underpins naltrexone (a mu antagonist) in alcohol and opioid use disorder, and the endogenous-opioid dysregulation hypothesis of non-suicidal self-injury, where tissue damage releases beta-endorphin against a low baseline tone (Oxford Handbook of DBT 2018).

MNEMONIC

END-en-DYN → μ-δ-κ; Kappa = Krummy

ENDorphin to **mu** (μ), **EN**kephalin to **delta** (δ), **DYN**orphin to **kappa** (κ), read in that order. And "**Kappa is Krummy**": kappa/dynorphin produces dysphoria and aversion, the opposite of the mu/endorphin high.

HOLD THIS

Endorphin-mu, enkephalin-delta, dynorphin-kappa; the kappa/dynorphin arm produces dysphoria, the mirror of the mu high. That aversive kappa axis is the anti-anhedonia and anti-addiction target.

CLINICAL ANCHOR

Two agents make this concrete. **Naltrexone** and **naloxone** are non-selective opioid antagonists (mainly mu) used in opioid overdose (naloxone) and in alcohol and opioid use disorder (naltrexone), where they blunt endogenous-opioid-mediated reward. Kappa-directed compounds are an active 2020s research front for treatment-resistant depression and anhedonia.

8.6 The shorter roster: NPY, CCK, galanin and orexin

Four more peptides with clean exam handles. Each has one or two facts examiners favour; the table fixes the discriminators and the prose gives the mechanism.

Neuropeptide Y (NPY)

A 36-amino-acid peptide, one of the most abundant and conserved in the brain, concentrated in locus coeruleus, hypothalamus and amygdala. It is the endogenous **anxiolytic and stress-resilience** peptide: Y1-receptor activation is anxiolytic and antidepressant, Y2 activation is anxiogenic (Kaplan & Sadock 2024). Intranasal NPY has shown early promise in PTSD and depression.

Cholecystokinin (CCK)

A gut-brain peptide whose brain form (CCK-8) sits in cortex, hippocampus and amygdala. Its exam identity is **panicogenesis**: the CCK-2 (CCK-B) agonists *CCK-4* (tetrapeptide) and pentagastrin reliably provoke panic attacks in humans and are used as a laboratory panic-challenge model. CCK-2 antagonists were trialled as anti-panic drugs and failed to beat placebo (Kaplan & Sadock 2024).

Galanin

A 29-to-30-amino-acid peptide co-expressed with noradrenaline in the locus coeruleus and with serotonin in the dorsal raphe, acting as an inhibitory neuromodulator through GalR1-3. GalR1 activation is anxiolytic; galanin buffers mood and anxiety, particularly under high noradrenergic (high-stress) drive.

Orexin / hypocretin

Two peptides, orexin-A (33 aa) and orexin-B (28 aa), from a single prepro-orexin precursor, made by a small set of **lateral hypothalamic** neurons that project across the neuroaxis. They act at OX1R and OX2R to promote **wakefulness and arousal**, feeding, and reward (via the ventral tegmental area). Loss of orexin neurons causes **narcolepsy with cataplexy (type 1)**, marked by very low CSF orexin-A.

PEPTIDE	HEADLINE RECEPTOR/SUBTYPE	EXAM-FAVOURITE ASSOCIATION
NPY	Y1 (anxiolytic), Y2 (anxiogenic)	**Endogenous anxiolytic and resilience peptide**
CCK	CCK-2 / CCK-B	**CCK-4 and pentagastrin provoke panic**
Galanin	GalR1-3 (GalR1 anxiolytic)	Co-transmitter in locus coeruleus, buffers stress
Orexin / hypocretin	OX1R, OX2R	**Deficiency causes narcolepsy; target of DORAs**

The four supporting peptides with their receptors and the single association examiners test. Orexin is the one that yielded an approved drug class.

Orexin is the peptide success story. Where substance P and CRF antagonism failed, the orexin system delivered a marketed class by working *with* the biology rather than against a disease correlate. Because orexin drives wakefulness, **orexin-receptor antagonists** promote sleep. The **dual orexin receptor antagonists (DORAs)**, suvorexant, lemborexant and daridorexant, block both OX1R and OX2R and are licensed for insomnia, a mechanism-based hypnotic class that avoids the GABA-A dependence profile of the benzodiazepines and Z-drugs. Orexin biology also explains why the same lateral-hypothalamic neurons couple arousal, appetite and reward, and why the system is being probed in addiction and mood.

INDIA

The DORAs (suvorexant, lemborexant, daridorexant) remain expensive and not yet widely stocked in most Indian pharmacies, so benzodiazepines, Z-drugs and low-dose sedating antidepressants still dominate insomnia prescribing here. Knowing the orexin mechanism matters more for exams and for counselling than for day-to-day availability, but the class is worth flagging to patients asking about non-benzodiazepine options. CSF orexin-A assay for suspected narcolepsy type 1 is available only at a few tertiary centres.

8.7 Translation and its disappointments

Why the peptide era over-promised. The through-line of this topic is a translational gap. Neuropeptide manipulation produces clean, replicable effects on anxiety- and depression-like behaviour in rodents, yet the human drug programmes have mostly failed on their primary psychiatric endpoints: NK1 (substance P) antagonists in depression, CRF1 antagonists in

depression and anxiety, vasopressin V1b antagonists in anxiety, and CCK-2 antagonists in panic all separated poorly or not at all from placebo in controlled trials (Kaplan & Sadock 2024).

Several reasons recur and are worth stating in a viva. First, **redundancy**: peptide systems overlap and compensate, so blocking one rarely collapses the behaviour. Second, **pharmacokinetics**: peptides degrade fast, cross the blood-brain barrier poorly and lack reuptake handles, forcing reliance on small-molecule ligands or intranasal delivery. Third, a **biomarker-versus-target confusion**: an elevated peptide (CSF substance P, CSF CRF) can be a downstream correlate of illness rather than a causal, druggable node. The instructive contrast is orexin: the DORAs succeeded because they targeted a *physiological function* (arousal) with a clear behavioural readout (sleep), not a disease-correlated peptide level. That is the lesson the field carries into the 2020s as kappa-opioid and oxytocin programmes continue.

COMMON TRAP

A tempting but wrong answer is that neuropeptide drugs "failed and the field is dead." The accurate framing: the *antidepressant/anxiolytic* peptide-antagonist programmes largely failed, but the same molecules succeeded in adjacent indications (aprepitant for emesis, DORAs for insomnia), and mechanism-first targets (orexin, kappa opioid) remain live. Say "disappointing for mood and anxiety, productive elsewhere," not "abandoned."

9 · Novel and gasotransmitters: endocannabinoids, nitric oxide, trace amines

Beyond the classical amine and amino-acid transmitters sits a class of unconventional messengers that break almost every rule the standard synapse taught you. They are not pre-packaged into vesicles, several are not proteins or even discrete molecules but dissolved gases, several travel *backward* across the cleft, and several act inside the target cell rather than on a surface receptor. For the exit exam this cluster is high-yield precisely because it is a favourite viva probe: the examiner uses it to test whether a candidate genuinely understands what defines a neurotransmitter, or has merely memorised a list. A strong answer keeps three families straight: the lipid **endocannabinoids** (anandamide and 2-AG), the **gasotransmitters** (nitric oxide, carbon monoxide, hydrogen sulfide), and the **trace amines** acting through TAAR1, with a footnote on purinergic signalling.

Why it recurs. Each family carries a piece of live clinical currency. Endocannabinoids explain both the appeal of cannabis and the cautionary collapse of the anti-obesity drug rimonabant; nitric oxide is the worked example of a gas that carries signal and the mechanism behind the phosphodiesterase-5 inhibitors; and TAAR1 agonism is the most talked-about non-dopaminergic antipsychotic principle of the decade, embodied by ulotaront. Learn the shared theme, on-demand synthesis and unconventional signalling, and each drug story becomes deducible rather than memorised (Kaplan and Sadock 2024, Stahl 2021).

9.1 Endocannabinoids: the on-demand lipid messengers

The ligands. The two principal **endocannabinoids** are **anandamide** (N-arachidonoylethanolamine, named from the Sanskrit *ananda*, bliss) and **2-AG** (2-

arachidonoylglycerol). Both are lipids built from the omega-6 fatty acid arachidonic acid, which is also the precursor of prostaglandins and leukotrienes (Kaplan and Sadock 2024). Anandamide was the first isolated, by Mechoulam and colleagues in 1992, after the CB1 receptor had already been cloned in the late 1980s and the field reasoned that an endogenous ligand must exist. Minor endocannabinoids (noladin ether, virodhamine, N-arachidonoyldopamine) exist but are not exam-critical.

Synthesised on demand, not stored. The single most examinable structural fact is that endocannabinoids are **not pre-packaged in synaptic vesicles**; they are manufactured from membrane phospholipid precursors at the moment of need, exactly as the gasotransmitters are. Neuronal depolarisation raises intracellular calcium, which activates the synthetic enzymes (NAPE-PLD for anandamide, diacylglycerol lipase for 2-AG), and the freshly made lipid diffuses out of the cell (Kaplan and Sadock 2024). Because they are highly lipophilic they cross membranes freely rather than being released by classical exocytosis.

Inactivation. Anandamide is degraded postsynaptically by **fatty acid amide hydrolase** (FAAH) into arachidonic acid and ethanolamine; 2-AG is broken down mainly presynaptically by monoacylglycerol lipase (MAGL). FAAH inhibition raises endocannabinoid tone and has been pursued as an anxiolytic strategy, the endocannabinoid analogue of the MAO inhibitor logic for monoamines (Kaplan and Sadock 2024).

9.2 Cannabinoid receptors: CB1 versus CB2

Two G-protein-coupled receptors carry endocannabinoid signalling, and their contrast is a reliable one-line question.

CB1

The dominant **central nervous system** cannabinoid receptor, possibly the most abundant GPCR in the brain, densest in basal ganglia, cerebellum, hippocampus, hypothalamus, anterior cingulate and frontal cortex. It sits **presynaptically** on axons and nerve termini, couples through Gi/Go to inhibit adenylyl cyclase, opens potassium channels and blocks N-type calcium channels, thereby *suppressing neurotransmitter release*. CB1 mediates the psychoactive "high" of THC and the appetite, mood, memory and reward effects of the system (Kaplan and Sadock 2024).

CB2

Predominantly expressed on **immune cells** (white blood cells, microglia), with only small amounts in brain. It carries the immunomodulatory and neuroinflammatory arm of endocannabinoid signalling and is not responsible for the central psychoactive effects.

Of the ligands, anandamide is relatively CB1-selective, whereas 2-AG does not strongly discriminate between CB1 and CB2 (Kaplan and Sadock 2024).

9.3 Retrograde signalling and DSI/DSE

Backward across the cleft. Endocannabinoids are the textbook example of a **retrograde messenger**. Classical transmission runs presynaptic to postsynaptic; endocannabinoids run the other way. A presynaptic dopamine or glutamate neuron fires and depolarises the postsynaptic cell; the resulting postsynaptic calcium rise triggers on-demand endocannabinoid synthesis; the

lipid then diffuses **back** across the synapse to activate presynaptic CB1 receptors, which dampen further transmitter release (Kaplan and Sadock 2024). This gives the postsynaptic neuron a way to turn down its own inputs, a form of short-term synaptic plasticity.

DSI and DSE. When the suppressed presynaptic terminal is *inhibitory* (GABAergic), the phenomenon is called **depolarisation-induced suppression of inhibition** (DSI); when it is *excitatory* (glutamatergic), it is depolarisation-induced suppression of excitation (DSE). CB1 antagonists and CB1 knockout abolish hippocampal DSI, which is the experimental proof that endocannabinoids are the retrograde mediator. Endocannabinoids are also implicated in long-term depression (LTD) and other plasticity (Kaplan and Sadock 2024).

PEARL

Two of these novel messengers are **retrograde**, and it is worth pairing them: endocannabinoids diffuse from postsynaptic to presynaptic to *suppress transmitter release*, while nitric oxide diffuses from postsynaptic to presynaptic to *strengthen* transmission in LTP. Same direction of travel, opposite functional sign, and both are made on demand rather than stored, which is the unifying theme of the whole topic.

9.4 Physiological roles: appetite, anxiety, memory and reward

Appetite. CB1 activation in the hypothalamus and limbic circuitry **stimulates appetite**, the neural basis of the cannabis "munchies" and the reason CB1 blockade was pursued for weight loss (subtopic 9.5). **Anxiety and mood.** Endocannabinoid tone is broadly **anxiolytic**: CB1-deficient animals are more anxious in novel or stressful settings, and anandamide and 2-AG rise in the amygdala during aversive learning (Kaplan and Sadock 2024). The system is implicated in the **extinction of aversive memory**, the ability to stop fearing a cue once it no longer predicts harm; CB1 knockouts fail to extinguish conditioned fear, which frames the endocannabinoid system as a candidate target in PTSD and phobias.

Memory. The dense hippocampal CB1 expression underlies the short-term memory impairment that accompanies acute cannabis intoxication. **Reward.** Cannabinoids increase dopamine release in the nucleus accumbens, and this reward-relevant surge requires mu-opioid receptors, linking the endocannabinoid and opioid systems in addiction (Kaplan and Sadock 2024).

9.5 Clinical translation: cannabis and the rimonabant cautionary tale

Cannabis. Exogenous THC is a CB1 agonist; it drives the euphoria, appetite stimulation, memory disruption and, at high or vulnerable exposure, the association with psychosis that make the endocannabinoid system clinically central. **Rimonabant.** The mirror-image experiment was **rimonabant** (Acomplia), a CB1 inverse agonist developed as an anti-obesity and smoking-cessation drug. It did produce weight loss, but blocking a tonically anxiolytic, mood-supporting system exacted a psychiatric price. In a 2007 meta-analysis (Christensen et al.), patients on rimonabant had roughly a **2.5-fold higher risk of discontinuing for depression and a threefold higher risk of discontinuing for anxiety**, and these effects appeared even though people with a history of mood or anxiety disorders had been excluded from the trials (Kaplan and Sadock

2024). Reports of increased suicidal ideation followed, the drug was withdrawn, and rimonabant became the standing cautionary tale that pharmacologically silencing endocannabinoid signalling can precipitate depression, anxiety and suicidality.

CLINICAL ANCHOR

The rimonabant story is the clean exam illustration of the endocannabinoid system's tonic role in emotional regulation: a drug that worked exactly as designed for metabolism unmasked depression and suicidality by removing a background anxiolytic tone. A converging human finding is that postmortem prefrontal cortex from people who died by suicide shows **increased CB1 receptor density**, consistent with a dysregulated endocannabinoid system in mood pathology (Kaplan and Sadock 2024).

CLASSIC TRAP Rimonabant "worked exactly as designed" for weight loss, yet blocking a tonically anxiolytic system unmasked depression, anxiety and suicidality, and it was withdrawn.

9.6 Nitric oxide: the gaseous retrograde messenger of LTP

An atypical transmitter on every count. **Nitric oxide** (NO, written with a dot to mark it as a free radical) was, in the early 1990s, the first gas ascribed a neurotransmitter role, and it violates the classical definition comprehensively: it is **not stored in vesicles**, it is synthesised on demand, it **diffuses freely across membranes** rather than being exocytosed, it has **no cell-surface receptor**, and it has no reuptake, being limited instead by a half-life of a few seconds (Kaplan and Sadock 2024).

Synthesis downstream of the NMDA receptor. NO is made by **nitric oxide synthase** from the amino acid arginine (yielding citrulline as byproduct), using NADPH and oxygen. The brain-predominant isoform is **neuronal NOS (nNOS)**, first described by Bredt and Snyder; the other isoforms are endothelial (eNOS, vasodilatation) and inducible (iNOS, inflammation). Crucially, nNOS is activated by calcium via calmodulin, so NO is generated when **NMDA-receptor activation admits calcium** into the postsynaptic cell (Kaplan and Sadock 2024).

Retrograde messenger in LTP. This is the headline function. **Long-term potentiation**, the synaptic model of learning, is induced by postsynaptic NMDA-receptor calcium influx but maintained partly by presynaptic changes. NO made postsynaptically diffuses **backward** to the presynaptic terminal, where it activates soluble guanylyl cyclase, raising cyclic GMP, and enhances further transmitter release, closing the loop that strengthens the synapse (Stahl 2021, Kaplan and Sadock 2024). NO acts intracellularly, either through the cGMP pathway or by S-nitrosylation of cysteine residues on target proteins, not through a membrane receptor. Peripherally the same nNOS-cGMP axis mediates penile erection, which is why phosphodiesterase-5 inhibitors (sildenafil, tadalafil, vardenafil), by preserving cGMP, treat erectile dysfunction, a favourite peripheral tie-in.

9.7 Carbon monoxide and hydrogen sulfide: the other gasotransmitters

Nitric oxide is the prototype but not the only gas. Two further **gasotransmitter**s are recognised, sharing NO's defining features of on-demand synthesis, membrane-permeant diffusion and

receptor-independent intracellular action.

Carbon monoxide (CO)

Generated by heme oxygenase during heme breakdown; like NO it can stimulate guanylyl cyclase and cyclic GMP signalling, and the heme oxygenase pathway carries a neuroprotective role that appears impaired in Alzheimer disease (Kaplan and Sadock 2024).

Hydrogen sulfide (H2S)

The newest and once dismissed as merely a toxic, foul-smelling gas. It is generated by cystathionine beta-synthase (CBS), the brain-abundant enzyme, which like the other gas-generating enzymes is calcium/calmodulin-activated. H2S potentiates NMDA-receptor currents, modulates hippocampal LTP and has low-level neuroprotective effects (Kaplan and Sadock 2024).

MNEMONIC

"NO-CO-H2S: Not stored, no receptor, just diffuse"

The three gasotransmitters (nitric oxide, carbon monoxide, hydrogen sulfide) share the trio of exam-defining negatives: **N**ot vesicle-stored, **N**o classical surface receptor, and no reuptake; they are made on demand and act by diffusing into the target cell, typically converging on the guanylyl cyclase / cyclic GMP pathway. State those three negatives and you have answered the "why is X an atypical neurotransmitter" question for any of them.

HOLD THIS

A gasotransmitter is defined by three negatives: not vesicle-stored, no surface receptor, no reuptake. Made on demand, it diffuses into the cell and works on intracellular guanylyl cyclase.

9.8 Trace amines and TAAR1: the ulotaront story

What trace amines are. **Trace amines** are endogenous monoamines present at very low (trace) brain concentrations: the five principal ones are beta-phenylethylamine (PEA), p-tyramine, tryptamine, p-octopamine and p-synephrine (Stahl 2021). They form when the hydroxylase step is skipped during dopamine or serotonin synthesis, and they modulate the uptake and release of the classical monoamines. Their chief receptor is **TAAR1** (trace amine-associated receptor type 1), a GPCR expressed widely in monoaminergic centres, the ventral tegmental area, dorsal raphe and their projection fields, where it acts as a brake tuning dopaminergic and serotonergic tone (Stahl 2021).

Why it matters therapeutically. TAAR1 agonism is the most prominent recent attempt at a **non-D2 antipsychotic mechanism**. The lead compound is **ulotaront** (SEP-363856), a TAAR1 agonist that also has 5-HT1A agonist activity (with additional 5-HT1D and 5-HT7 binding), tested in schizophrenia (Stahl 2021, Maudsley 15th edition). Because it does not block dopamine D2 receptors, it promised antipsychotic effect without extrapyramidal side effects, hyperprolactinaemia or the metabolic burden of D2 antagonists, an attractive profile that placed it alongside the muscarinic agonist xanomeline as a genuinely novel mechanism.

COMMON TRAP

Do not overstate ulotaront's arrival. TAAR1 agonism is a mechanistically exciting, **investigational** principle, and the pivotal phase 3 schizophrenia programme for ulotaront reported negative results, tempering early enthusiasm. Contrast this with the muscarinic agonist principle, which *did* reach the clinic as xanomeline-trospium in 2024. The safe exam line is that TAAR1 agonism is a promising non-dopaminergic strategy exemplified by ulotaront (a TAAR1 and 5-HT1A agonist) whose clinical validation remains unproven, rather than a licensed treatment.

9.9 Purinergic signalling: adenosine, ATP and caffeine

A brief but examinable coda. **Purinergic signalling** uses purine messengers, ATP and its breakdown product adenosine, acting at purinergic receptors: the P1 **adenosine receptors** (A1, A2A, A2B, A3, all GPCRs) and the P2 receptors for ATP, split into ionotropic P2X channels and metabotropic P2Y GPCRs (Goodman and Gilman). A1 receptors couple to Gi (inhibitory), A2A to Gs (stimulatory), giving adenosine its broadly inhibitory, sleep-promoting and neuroprotective tone. The clinically indispensable one-liner is that **caffeine is a non-selective adenosine receptor antagonist, blocking A1 and A2A**; relieving adenosine's inhibitory brake is how caffeine produces arousal and wakefulness. The A2A receptor, densely expressed in striatum where it interacts with dopamine D2 signalling, is an active target of interest in Parkinson disease.

10 · Second messengers and signal transduction

Chemical neurotransmission does not stop at the receptor. When a first-messenger transmitter binds its target, the message is handed inward through a relay of intracellular molecules that Stahl memorably calls a molecular "pony express": a **first messenger** (the transmitter) generates a **second messenger** (a small intracellular signal such as cAMP or calcium), which activates a **third messenger** (a kinase or phosphatase), which modifies a **fourth messenger** (a phosphoprotein), ultimately reaching gene expression and structural change (Stahl 2021). The events at the membrane happen in under a second, but the downstream limb takes hours to days and can last the lifetime of the synapse. This time-lag is the single most examinable idea in the topic: it explains why antidepressants and antipsychotics have a therapeutic latency of two to three weeks despite occupying their receptors within hours, because the clinically relevant change is in gene transcription and plasticity, not receptor occupancy.

Why it recurs. Signal transduction is the connective tissue of the whole paper. It supplies the receptor pharmacology behind every transmitter section (the Gq/Gi split that defines muscarinic and adrenergic subtypes), the molecular target of lithium (inositol monophosphatase and GSK-3), the mechanism of antidepressant latency (CREB and BDNF), and the 2020s frontier of rational drug design (biased agonism, the muscarinic antipsychotics, PDE inhibitors). A candidate who can draw the cAMP and phosphoinositide cascades and place lithium, caffeine, and sildenafil on them can answer a dozen apparently separate questions from one diagram.

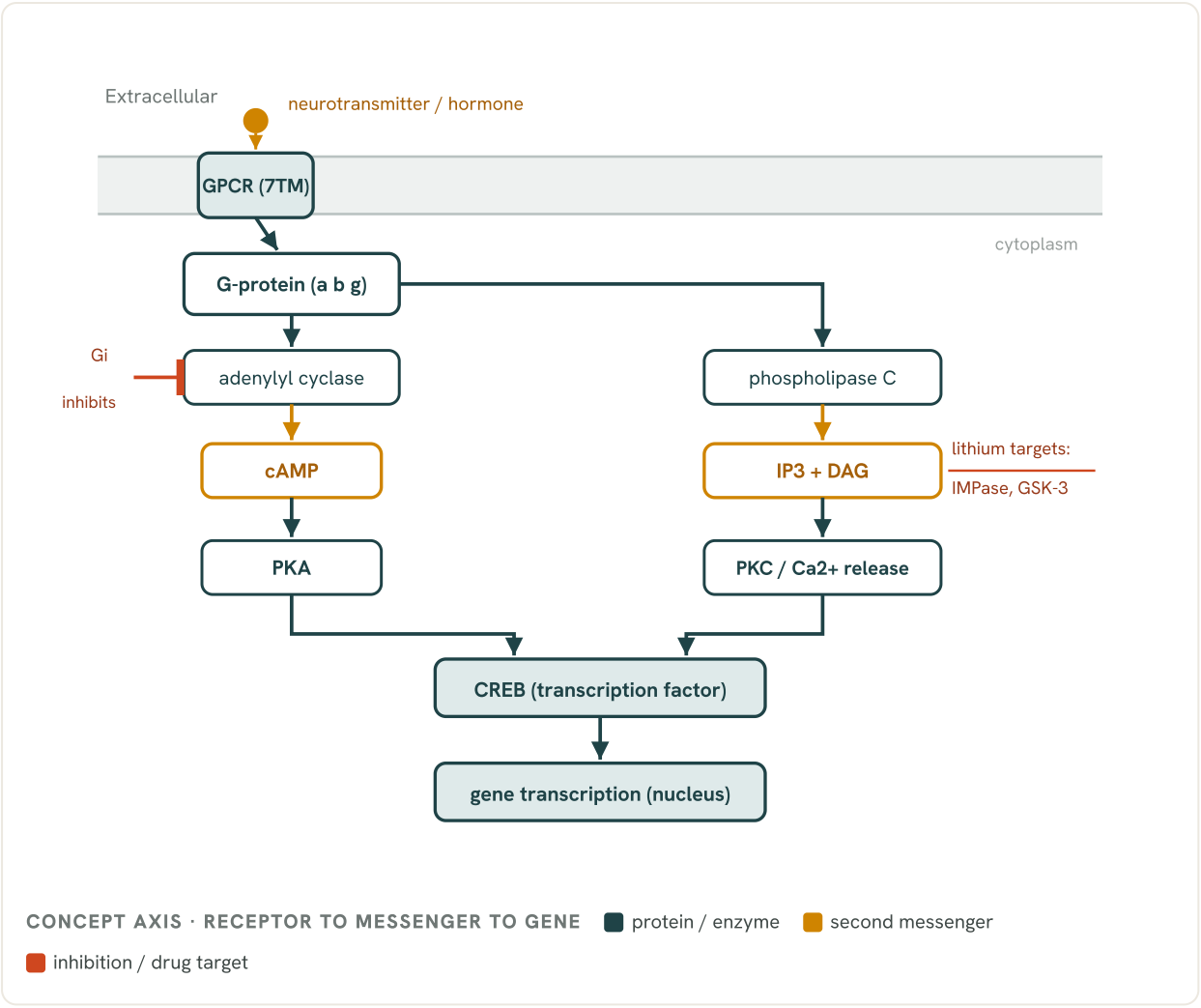


Fig 2.4 The two main G-protein-coupled cascades. Gs drives adenylyl cyclase to cAMP to PKA; Gq drives phospholipase C to IP3 and DAG, raising intracellular Ca2+ and activating PKC; Gi inhibits adenylyl cyclase. Both converge on CREB and gene transcription, the slow, plasticity-relevant layer that explains the delay in antidepressant action. Lithium acts here, inhibiting inositol monophosphatase and GSK-3.

10.1 The G-protein cycle: how a bound receptor becomes an intracellular signal

The switch. G-protein-coupled receptors (GPCRs) are the **seven-transmembrane superfamily** that carries most slow, modulatory neurotransmission. The transducer is a **heterotrimeric G protein** (alpha, beta, gamma subunits) sitting on the inner membrane leaflet. At rest the alpha subunit holds GDP. Agonist binding changes the receptor conformation so it can engage the G protein, catalysing exchange of **GDP for GTP** on the alpha subunit; the trimer then dissociates into a free GTP-bound alpha subunit and a beta-gamma dimer, both of which regulate downstream effectors (Kaplan and Sadock 2024). Signalling is self-terminating: the alpha subunit has **intrinsic GTPase activity** that hydrolyses GTP back to GDP and reassembles the inactive trimer.

Four alpha families, two main effectors. The particular alpha class a receptor couples to dictates which second messenger is made. The four neurotransmitter-relevant classes are **Gs**, **Gi**, **Gq**, and **G12/13**. Gs and Gi both act on the cAMP system (stimulating and inhibiting adenylate cyclase respectively); Gq drives the phosphoinositide system; G12/13 modulates Rho/Rac cytoskeletal signalling and is rarely examined (Kaplan and Sadock 2024). Crucially, a single receptor can

recruit more than one G protein and each active G protein can turn over many effector molecules, giving the **signal amplification** that lets a few occupied receptors produce a large intracellular response.

Turning it off. Two brakes are worth naming. **Regulators of G-protein signalling (RGS proteins)** are GTPase-activating proteins that accelerate alpha-subunit GTP hydrolysis and so shorten the signal; over 20 subtypes exist, and reduced striatal RGS9 (which restrains Gi-linked dopamine signalling) has been reported in schizophrenia postmortem brain, consistent with excess dopamine signalling (Kaplan and Sadock 2024). Separately, agonist-occupied receptors are phosphorylated by **G-protein-coupled receptor kinases (GRKs)**, which recruit arrestin to uncouple and internalise the receptor: the molecular basis of desensitisation, tolerance, and part of the delayed therapeutic response to psychotropics (subtopic 10.7).

PEARL

The G protein is a molecular timer, not a switch you flip. Its "on" duration equals the interval before the alpha subunit hydrolyses its own GTP. RGS proteins are the tuning knob that speeds this up; cholera toxin (locks Gs on) and pertussis toxin (locks Gi off) are the classic experimental probes that freeze the timer in one position and thereby prove which limb a receptor uses.

10.2 The cAMP / PKA pathway (Gs and Gi)

The cAMP system, discovered by Sutherland and Rall in the 1950s, is the **prototypical second-messenger cascade** (Kaplan and Sadock 2024). A Gs-coupled receptor activates the membrane enzyme **adenylate cyclase**, which converts ATP to **cyclic AMP (cAMP)**; a Gi-coupled receptor inhibits the same enzyme and lowers cAMP. The net cAMP level at a given synapse is therefore the arithmetic of its Gs- and Gi-coupled receptors, illustrated classically by noradrenaline *raising* cAMP through beta-adrenergic receptors and *lowering* it through alpha-2 receptors on the same cell.

cAMP's principal target is **protein kinase A (PKA)**, a tetramer of two regulatory and two catalytic subunits. At baseline the regulatory subunits inhibit the catalytic ones; when cAMP binds the regulatory subunits they release the catalytic subunits, which then **phosphorylate serine and threonine residues** on a broad range of substrates: ion channels (fast effects), transmitter-synthetic enzymes (slower effects), and, critically, transcription factors that alter gene expression (slowest effects). The signal is terminated by **phosphodiesterases (PDEs)**, which cleave cAMP to AMP (Kaplan and Sadock 2024).

CLINICAL ANCHOR

Three drugs sit directly on this pathway and recur in vivas. **Caffeine** nonselectively inhibits PDEs (and antagonises adenosine receptors), raising cAMP. **Rolipram**, a PDE4 inhibitor, showed antidepressant promise but was limited by nausea; **PDE10A inhibitors** have been pursued as antipsychotics. And **sildenafil** works on the parallel cGMP system by inhibiting the PDE5 isoform enriched in vascular smooth muscle. The unifying principle: block the phosphodiesterase, and you prolong the cyclic-nucleotide signal.

10.3 The phosphoinositide pathway (Gq): PLC, IP3, DAG, PKC and calcium

Many receptors do not touch cAMP at all; they couple through **Gq** to the phosphoinositide (PI) system, which parallels the cAMP system but branches into three signals (Kaplan and Sadock 2024). Gq activates **phospholipase C (PLC)**, which cleaves the membrane lipid **phosphatidylinositol bisphosphate (PIP2)** into two second messengers at once: **diacylglycerol (DAG)** and **inositol trisphosphate (IP3)**.

DAG

Hydrophobic, so it stays in the membrane and recruits **protein kinase C (PKC)** from the cytoplasm to the membrane, where PKC is activated and phosphorylates numerous substrates. Some PKC isoforms additionally require calcium.

IP3

Water-soluble, so it diffuses to the endoplasmic reticulum and binds the **IP3 receptor** (a ligand-gated calcium channel), releasing large stores of intracellular Ca2+.

Ca2+ (third arm)

Released calcium is itself a second messenger. It directly triggers vesicle release and opens calcium-activated channels, and it acts more slowly through **calmodulin**: four calcium ions bind calmodulin, and the complex activates **calcium/calmodulin-dependent kinase (CaMK)** and other targets, converging on gene transcription.

The odd-numbered muscarinic (M1, M3, M5) and alpha-1 adrenergic receptors are the exam-favourite Gq couplings; the pathway is terminated by lipases degrading DAG, calcium pumps clearing Ca2+, and inositol phosphatases recycling IP3 back to inositol, the step lithium blocks (subtopic 10.6).

MNEMONIC

"Q cuts PIP2 into a DIP"

Gq activates PLC to *cut* PIP2 into **D**AG (activates PKC) and **IP**3 (releases calcium). The odd muscarinic receptors (1, 3, 5) and alpha-1 use this line; the even muscarinics (2, 4), alpha-2, D2, and 5-HT1A use Gi to *lower* cAMP. Odd equals Gq equals excitatory; even equals Gi equals inhibitory.

10.4 Minor cascades: cGMP / nitric oxide and arachidonic acid

Two smaller lipophilic-signal systems round out the GPCR-linked repertoire and appear as single-mark discriminators. **cGMP and nitric oxide.** Unlike cAMP, **cyclic GMP** is made by guanylate cyclases that are **not directly activated by G proteins**; the cytoplasmic form is switched on by the gas **nitric oxide (NO)**, itself synthesised by NO synthase after activation by calcium-calmodulin (Kaplan and Sadock 2024). NO is small enough to diffuse across membranes and can act as a **retrograde messenger** back onto the presynaptic terminal, blurring the line between intracellular and intercellular signalling; cGMP then acts through protein kinase G (PKG). **Arachidonic acid.** Certain receptors activate **phospholipase A2**, which liberates arachidonic acid from membrane phospholipid; cyclooxygenase converts it to prostaglandins and thromboxanes, lipoxygenase to leukotrienes. These lipophilic metabolites can leave the neuron

and act on GPCRs elsewhere, and COX inhibition has been explored as adjunctive treatment in schizophrenia and depression via anti-inflammatory effects (Kaplan and Sadock 2024).

10.5 Receptor tyrosine kinases: the neurotrophin cascade

The GPCR pathways signal through diffusible small molecules; the fourth great cascade does not. **Receptor tyrosine kinases (RTKs)** are transmembrane receptors with a **tyrosine kinase enzyme built into their own intracellular tail**, and they carry the neurotrophic factors NGF and BDNF rather than classical transmitters (Kaplan and Sadock 2024). Neurotrophins bind the **Trk family** of RTKs (BDNF binds TrkB), which causes two receptors to **dimerise** and cross-phosphorylate each other on tyrosine residues, a process called **autophosphorylation**. The new phosphotyrosines become docking sites: the adaptor Grb2 (via its SH2 domain) binds and recruits the exchange factor SOS, which switches on the **small G protein Ras** (GTP for GDP). Active Ras drives the **MAPK cascade**, a conserved relay of kinases (Raf, then MEK, then ERK), and ERK activates ribosomal S6 kinase and transcription factors to change gene expression, synaptic plasticity, and neuronal survival.

Two contrasts with the GPCR pathways are high-yield. First, RTK signalling produces **no small-molecule second messenger**: the message passes as a chain of protein phosphorylations, not as cAMP or calcium. Second, the small G proteins (Ras, Rho, Ral) resemble the alpha subunit but are activated by separate GEFs rather than directly by the receptor, and are switched off by GAPs, the exact analogue of RGS proteins on heterotrimeric G proteins (Kaplan and Sadock 2024).

FEATURE	GPCR PATHWAYS	RECEPTOR TYROSINE KINASE PATHWAY
First messenger	Classical transmitters, hormones	**Neurotrophins (NGF, BDNF)**
Transducer	Heterotrimeric G protein (Gs/Gi/Gq)	**Small G protein (Ras), via Grb2-SOS**
Second messenger	cAMP, IP3/DAG, Ca2+	**None; a kinase cascade instead**
Core kinase relay	PKA, PKC, CaMK	Raf to MEK to ERK (MAPK)
Timescale, main role	Fast to slow modulation, transmission	Slow: growth, plasticity, survival

GPCR and RTK cascades converge on transcription (both can phosphorylate or induce CREB), but differ in transducer and in whether a small-molecule second messenger is generated; the RTK route is the molecular substrate of the neurotrophic hypothesis of mood disorders (subtopic 10.8).

10.6 Lithium's molecular targets: inositol monophosphatase and GSK-3

Lithium is the exam's favourite worked example of a psychotropic acting on second messengers rather than receptors, and it has **two mechanistically distinct targets. Inositol depletion.** Lithium inhibits **inositol monophosphatase (IMPase)**, the enzyme that dephosphorylates inositol monophosphate to free inositol needed to regenerate membrane PIP2. Blocking it depletes free inositol and runs down the phosphoinositide cycle, the **inositol depletion hypothesis** proposed by Berridge and colleagues (Berridge et al 1982); over time this downregulates specific PKC isoforms with downstream changes in transmitter release

(Companion to Psychiatric Studies). The hypothesis is almost certainly too simple as a whole-brain account but may hold in specific regions and cell types.

GSK-3 inhibition. Lithium is a potent inhibitor of **glycogen synthase kinase 3 (GSK-3, especially the beta isoform)** (Stambolic et al 1996). GSK-3 phosphorylates and modulates a wide set of substrates that link lithium to plasticity and neuroprotection: Wnt-pathway proteins and beta-catenin, microtubule-associated tau (whose hyperphosphorylation forms Alzheimer tangles), and the transcription factors AP-1 (jun) and CREB (Companion to Psychiatric Studies). Inhibiting GSK-3 is thought to underlie lithium's neuroprotective and possibly pro-cognitive effects; the Lithium Handbook links lithium's advantages (reduced suicide and dementia risk) to falling IP3, GSK-3-beta inhibition, and reduced telomere shortening (Nelson and Meyer 2023).

PEARL

The two lithium targets map onto the two great cascades. **IMPase inhibition acts on the Gq/phosphoinositide arm** (inositol depletion, PKC downregulation); **GSK-3 inhibition acts on the plasticity arm** shared with the neurotrophin/Wnt pathways. There is even a third thread: dopamine D2 receptors signal through a non-canonical **beta-arrestin-2 pathway** that *raises* GSK-3-beta activity to drive amphetamine-like hyperlocomotion, and lithium blunts this too, a molecular link between lithium and its antimanic action (Nelson and Meyer 2023).

RULE **Lithium acts inside the cell, not at a receptor.** IMPase inhibition (inositol depletion) hits the Gq/phosphoinositide arm; GSK-3 inhibition hits the plasticity arm shared with the neurotrophin pathways.

10.7 Desensitisation, arrestin, and biased agonism (functional selectivity)

The classical model, then its revision. The old teaching was that a given ligand is a full agonist, partial agonist, or antagonist and behaves the same across every pathway a receptor can access. This is now known to be incomplete. **Biased agonism** (also called **functional selectivity**) is the finding that a ligand can preferentially activate one downstream pathway while leaving another relatively untouched (Kaplan and Sadock 2024). The best-characterised split is between **canonical G-protein signalling and beta-arrestin signalling**: after GRK phosphorylation, arrestin not only desensitises and internalises the receptor but also acts as a scaffold for its own signalling, notably MAPK/ERK. A biased agonist can therefore favour the therapeutic limb and spare the limb that mediates side effects or tolerance.

Why it matters for drug design. The canonical example is the **mu-opioid receptor**: arrestin-knockout mice show less morphine tolerance, prompting development of G-protein-biased opioids (such as oliceridine) intended to keep analgesia while reducing respiratory depression, though whether the real-world benefit holds remains contested and dependence persists (Kaplan and Sadock 2024). Bias arises because different ligands stabilise different receptor conformations, and it can also be produced by receptor dimerisation or by signalling from intracellular membrane compartments (location bias). The concept now shapes rational psychiatric drug design and is a recurring viva prompt on the future of pharmacology.

COMMON TRAP

Do not equate biased agonism with partial agonism. A **partial agonist** produces a submaximal response through *all* pathways equally (lower efficacy everywhere). A **biased agonist** can be a full agonist at one pathway and near-silent at another (different pathways, not different ceilings). Aripiprazole is usually taught as a D2 partial agonist; a G-protein-biased opioid is a distinct idea about *which* pathway is engaged, not *how much*.

10.8 The molecular bridge to mood and plasticity: CREB and BDNF

All roads in this topic converge on the nucleus, and the shared endpoint is **CREB (cAMP response element-binding protein)**. PKA (from the cAMP arm), CaMK (from the calcium arm), and RSK (from the neurotrophin/MAPK arm) all phosphorylate CREB; once phosphorylated, CREB binds **cAMP response elements (CREs)** in target-gene promoters and drives transcription of genes for neuronal survival, plasticity, and long-term memory (Kaplan and Sadock 2024). This is where a receptor event on the millisecond scale becomes a lasting structural change.

The neurotrophic hypothesis of depression. The most examinable clinical translation is the CREB-BDNF link. Chronic stress lowers hippocampal **BDNF** and causes atrophy of CA3 neurons, mirroring the modest hippocampal volume loss seen on MRI in depression and PTSD (Kaplan and Sadock 2024). Serotonin and noradrenaline reuptake inhibitors **upregulate BDNF, CREB, and TrkB** in the hippocampus on a timescale of roughly ten to twenty days that matches their therapeutic latency, and CREB drives BDNF gene expression. This is the mechanistic answer to "why do antidepressants take weeks to work": receptor blockade is immediate, but the plasticity change (CREB activation to BDNF induction to synaptic and structural remodelling) unfolds over weeks. The picture is not uniform, exogenous BDNF in the mesolimbic dopamine circuit is *pro*-depressive rather than antidepressant, underscoring that BDNF's effect is region-specific (Kaplan and Sadock 2024).

CLINICAL ANCHOR

The rapid antidepressants exploit this cascade from a different entry point. Ketamine and esketamine block NMDA receptors to trigger a fast burst of glutamate, AMPA-receptor activation, and a surge of **BDNF-TrkB and downstream mTOR signalling** that drives rapid synaptogenesis, which is the leading account of antidepressant effect within hours rather than weeks. Whichever pathway is used, the therapeutic common denominator is convergence on neurotrophin-driven plasticity, the molecular bridge between transmitter, gene, and mood.

HOLD THIS

Antidepressant latency is a gene-transcription story: receptor occupancy is immediate, but the CREB-to-BDNF-to-plasticity change takes weeks. Lithium acts here too (IMPase, GSK-3), inside the cell, not at a receptor.

10.9 Exam integration: placing drugs and diseases on the cascade

The examiner reward for this topic is the ability to locate any agent or lesion on a single map. Positive-symptom antipsychotics act on Gi-coupled D2 receptors (lowering cAMP), and the newest antipsychotic principle, **xanomeline-trospium**, works through M1/M4 muscarinic GPCRs rather than direct D2 blockade. Mood stabilisers sit downstream: lithium on IMPase and GSK-3, and valproate also modulates GSK-3 and ERK-pathway signalling. Stimulant and caffeine effects run through cAMP/PDE. Antidepressant latency, ketamine's speed, and lithium's neuroprotection all resolve at the level of CREB, BDNF, and synaptic plasticity.

INDIA

Lithium remains a first-line and cost-effective mood stabiliser in Indian practice, and its second-messenger mechanism carries a practical message worth voicing in a viva: because lithium acts on intracellular enzymes with a narrow therapeutic index, **serum-level monitoring, thyroid and renal surveillance, and attention to dehydration and drug interactions (NSAIDs, thiazides, ACE inhibitors)** are integral to safe use in settings where laboratory access can be intermittent. The molecular story is not academic: it is why lithium is monitored the way it is.

11 · Neurodevelopment: migration, pruning, critical periods

The brain is built once, refined twice, and each stage is a separate window through which a disorder can enter. This topic is the developmental backbone of biological psychiatry, and the paper mines it in two directions at once: as a stepwise list of processes (neurulation to myelination) that must be named in order, and as a set of mechanisms whose failure produces named disorders. The examinable logic is temporal. A hit that lands in the first trimester (a migration failure) produces a different phenotype from one that lands in adolescence (a pruning failure), and the two-hit and neurodevelopmental hypotheses of schizophrenia are simply the formal statement that both windows matter. Fix the sequence and the timing, and the clinical associations, heterotopias, schizophrenia, autism, the effect of early sensory deprivation, all hang off it (Stahl 2021; Kaplan & Sadock 2024).

Hold three organising ideas before the detail. First, development is *overproduce then eliminate*: the brain makes a surplus of neurons, then of synapses, and sculpts the adult circuit by killing back the excess (apoptosis for cells, pruning for synapses). Second, the sculpting is **experience-dependent** and time-locked, so there are critical periods when input is not merely helpful but required. Third, the same molecule that guides construction (reelin) or performs the sculpting (complement, microglia) is where the pathology sits, which is why one topic connects fetal neuroanatomy to a 2016 genetics landmark (Sekar 2016).

11.1 The seven stages in order: the examinable sequence

Learn the sequence as an ordered list before anything else; the paper asks it as a bare recall item. Neurodevelopment proceeds through overlapping but ordered stages: **neurulation** (the neural plate folds into the neural tube by the end of the fourth gestational week, the source of the entire CNS); **proliferation / neurogenesis** (mitosis of neural progenitors in the periventricular

ventricular and subventricular zones, generating the roughly twenty billion neurons of the cortex, largely by mid-gestation); **migration** (young neurons travel from the germinal zones to their final positions, chiefly along radial glial guides); **differentiation** (the settled neuron acquires its transmitter identity, dendritic tree and axon); **synaptogenesis** (formation of synaptic contacts, exuberant and continuing after birth); **apoptosis** (programmed death of the surplus, roughly half of the neurons generated); and **myelination** (oligodendrocyte ensheathing of axons, beginning prenatally in sensorimotor tracts and continuing into the third and fourth decades in prefrontal cortex). Most neurogenesis, selection and migration are complete before birth; differentiation, synaptogenesis and myelination continue for years to decades (Stahl 2021).

MNEMONIC

"Nervous Programmers Make Dozens, Synapse Away, Myelinate" (N-P-M-D-S-A-M)

Neurulation, **P**roliferation, **M**igration, **D**ifferentiation, **S**ynaptogenesis, **A**poptosis, **M**yelination. The order is the answer to most single-line questions, and each transition is a candidate lesion: neural tube defects at N, microcephaly at P, heterotopias at M, schizophrenia-type pruning at the S/A boundary in adolescence.

11.2 Neurulation and proliferation: the neural tube and the germinal zones

Neurulation. The neural plate, an ectodermal thickening, invaginates and fuses dorsally to form the **neural tube**, which closes between roughly the ADHD & specific learning/communication disorders notes and the Perinatal/women's mental health & emergency psychiatry notes of gestation. The rostral tube swells into the three primary vesicles (prosencephalon, mesencephalon, rhombencephalon) that become forebrain, midbrain and hindbrain. Failure of anterior closure yields anencephaly; failure of posterior closure yields spina bifida, the disorders that folate supplementation and periconceptional folic acid target. The lumen of the tube persists as the ventricular system.

Proliferation. Neurons are not born where they live. Progenitors divide in the **ventricular zone (VZ)** lining the tube and the overlying **subventricular zone (SVZ)**; in the primate and human neocortex an additional **outer subventricular zone** populated by *outer radial glia* is the substrate of the expanded human cortex, a point the current literature stresses because human-evolved regulatory elements are enriched in these cells (Kaplan & Sadock 2024). Peak human cortical neurogenesis is largely a first-and-second-trimester event; a failure of proliferation gives microcephaly, an excess or failure to stop gives megalencephaly.

11.3 Migration: radial glia, the inside-out cortex, and tangential interneurons

Radial migration and the inside-out rule. Most excitatory (glutamatergic pyramidal) neurons migrate *radially* from the VZ to the cortical plate, climbing the fibre scaffold of **radial glial cells** that span from ventricle to pia. The cortex is laid down **inside-out**: the deepest layers (VI and V) are generated and settle first, and each later-born wave migrates *past* the existing neurons to occupy a progressively more superficial layer (IV, then III and II). This counter-intuitive ordering

is examinable and is the reason a defined stop signal is needed at the top of the stack, which is reelin (11.10) (New Oxford Textbook 2020).

Tangential migration of interneurons. The cortex has two cellular sources. The glutamatergic pyramidal cells arise from the dorsal VZ/SVZ and migrate radially; the inhibitory **GABAergic interneurons** (parvalbumin, somatostatin and calretinin classes) arise separately in the **ganglionic eminences** (medial, lateral and caudal) of the ventral forebrain and migrate *tangentially* across the cortex before turning into it. The medial ganglionic eminence supplies the parvalbumin basket and chandelier cells and the somatostatin Martinotti cells; the caudal eminence supplies calretinin and reelin-expressing types (New Oxford Textbook 2020). The interneuron origin matters because parvalbumin interneuron dysfunction is a leading account of the cortical circuit abnormality in schizophrenia and of the machinery that opens and closes critical periods (11.8).

CLINICAL ANCHOR

Neuronal migration disorders are the clinical face of this stage. Complete failure gives *lissencephaly* (smooth, agyric cortex, classically the LIS1 and doublecortin/DCX genes); arrest of a subset of neurons short of the cortex gives *subcortical band heterotopia* ("double cortex") or *periventricular nodular heterotopia*; over-migration and disorganisation gives *polymicrogyria*. These present with epilepsy and intellectual disability and are the concrete answer to "name a consequence of disordered neuronal migration." The same genes (LIS1, DCX, reelin/RELN) recur, tying the syndrome to the molecular stop-signal biology.

11.4 Differentiation and synaptogenesis: overproduction of connections

Differentiation. Once settled, the neuron elaborates its dendritic tree, extends an axon toward its target (guided by chemotropic cues such as netrins, semaphorins and ephrins), and adopts a neurotransmitter phenotype. This is where transmitter-identity genes and the growth-factor environment (BDNF, NT-3, NGF) act, and it continues throughout life at a reduced rate.

Synaptogenesis is deliberately excessive. The developing brain forms a large *surplus* of synapses. Synaptic density in the human cortex rises steeply after birth, overshoots the adult value by a wide margin, and peaks in early childhood (classic primate data from Bourgeois and Rakic in the visual cortex, and Huttenlocher's human counts, show a peak well above adult density before net decline). The developmental strategy is to build more connections than are needed and then let experience decide which survive, which sets up the pruning phase (11.5). Synaptogenesis is not uniform across the cortex: sensory areas peak and stabilise early, whereas **prefrontal cortex** peaks later and prunes latest, protracting its refinement into the third decade (Kaplan & Sadock 2024).

11.5 Apoptosis and synaptic pruning: two different sculpting knives

The exam repeatedly tests the distinction between killing cells and cutting connections; they are separate processes at separate scales. Apoptosis (programmed cell death) removes whole neurons, chiefly those that fail to secure enough target-derived trophic support (the neurotrophic hypothesis: neurons compete for a limited supply of factors such as NGF, and the losers die). On

the order of half of the neurons generated are eliminated this way, mostly perinatally. It is an active, gene-directed process (the caspase cascade, Bcl-2 family regulation), distinct from passive necrosis. **Synaptic pruning** removes connections, not cells: weakly active or redundant synapses are selectively eliminated while active ones are retained and strengthened, the structural correlate of "cells that fire together wire together." Pruning is *activity-dependent* and executed largely by **microglia** and the complement system (11.6), and it is the process that continues, region by region, from early childhood through adolescence (Faust 2021).

Apoptosis

Programmed death of a whole neuron via an intrinsic gene-directed cascade (caspases, Bcl-2/Bax balance), driven by loss of the competition for target-derived neurotrophic factor. Scale: the cell. Timing: predominantly prenatal and early postnatal.

Synaptic pruning

Selective activity-dependent elimination of individual synapses, sparing whole neurons, executed by microglial engulfment of complement-tagged synapses. Scale: the connection. Timing: childhood through adolescence, region-specific.

11.6 The mechanism of pruning: microglia, complement, and the "eat-me" tag

The immune system builds the brain. The molecular executioners of developmental pruning are borrowed from innate immunity. Astrocyte-derived and neuronal signals induce the classical complement proteins **C1q and C3** to be deposited on weak or supernumerary synapses; the C3 breakdown product iC3b acts as an "eat-me" opsonin recognised by **complement receptor 3 (CR3/CD11b)** on **microglia**, which then engulf and digest the tagged synapse (Stevens 2007; Schafer 2012). Complement is not the only route: the microglial fractalkine receptor CX3CR1, TREM2, class-I MHC and pentraxins also drive pruning, and complement-independent pruning occurs in some regions, so the exam-safe statement is that complement-microglial signalling is the *best-characterised* mechanism rather than the sole one (Faust 2021).

PEARL

This mechanism is why neuroinflammation and neurodevelopment are the same topic seen twice. The complement cascade that lyses bacteria in the periphery is repurposed in the CNS to tag synapses for microglial removal. It explains why maternal infection (11.13), which activates this system, is a neurodevelopmental risk factor, and why *C4*, a complement gene, is the strongest common-variant risk locus for schizophrenia (11.11).

11.7 The adolescent pruning peak and the maturational gradient

Adolescence is a second construction window, and its signature is net synaptic loss in the last cortex to mature. After the childhood synaptic peak, the cortex undergoes protracted net elimination that proceeds in a **back-to-front (posterior-to-anterior)** gradient: primary sensory and motor cortex prunes and stabilises first, association cortex later, and the **dorsolateral prefrontal cortex last**, with active synaptic reorganisation continuing well into the twenties (Petanjek's human counts; Gogtay's longitudinal grey-matter mapping). On MRI this reads as a rise in cortical grey-matter volume in late childhood followed by a decline through puberty,

mirrored by rising white-matter volume from ongoing myelination. The behavioural correlate is the maturational mismatch of adolescence: a limbic/reward system that matures early against a prefrontal control system that matures late, the standard account of adolescent risk-taking and of the window in which drugs of abuse and social stress bite hardest (Kaplan & Sadock 2024).

COMMON TRAP

Do not equate "adolescent grey-matter loss on MRI" with atrophy or degeneration. It is normal, programmed synaptic pruning and continued myelination (which shifts tissue from the grey to the white compartment), a maturational *gain* in efficiency, not a loss of function. The disease models (schizophrenia) invoke *excessive* or mistimed pruning against this normal backdrop, not pruning per se.

11.8 Critical versus sensitive periods: definitions and the machinery of closure

This distinction is a favourite discriminator. A **critical period** is a discrete, time-limited window during which specific experience is *necessary* to instigate a fundamental and largely irreversible change in a neural circuit; miss the window and the capacity is lost or permanently degraded. A **sensitive period** is a broader, softer window of heightened but not all-or-none plasticity, during which circuits are more malleable by experience but change remains possible outside it (Rice and Barone 2000; Knudsen 2004). The two are a spectrum rather than a dichotomy, but the exam wants the contrast: critical = discrete and necessary and closing; sensitive = graded and facilitatory.

RULE **Critical period = discrete, necessary, closing; sensitive period = graded, facilitatory, stays open.** Interneurons open the window and perineuronal nets shut it.

What opens and closes the window. The maturation of **parvalbumin-positive GABAergic interneurons** and the resulting inhibitory (GABA) tone triggers the *opening* of the visual critical period; the window is *closed* by structural brakes, chiefly the deposition of **perineuronal nets** (condensed chondroitin-sulphate extracellular matrix that encases parvalbumin cells) and myelin-associated inhibitors (Hensch 2005). Perineuronal net maturation temporally parallels the end of the critical period, degrading them (for example with chondroitinase) reopens plasticity, and their density is reduced in schizophrenia prefrontal cortex. This gives a clean molecular story: interneurons open the window, matrix nets shut it.

11.9 Critical periods in practice: the visual paradigm and its clinical parallels

The Hubel and Wiesel paradigm. The archetypal critical period is **ocular dominance** in visual cortex. Monocular deprivation in a kitten or monkey during the postnatal critical window causes the deprived eye to lose its cortical territory permanently; the identical deprivation in an adult does not (Wiesel and Hubel 1963; Hensch 2005). This is the physiological basis of the clinical parallels: **amblyopia** ("lazy eye") from childhood strabismus or unequal refraction must be treated within the visual critical period, and congenital cataract must be removed early or vision is permanently impaired. Other modalities have their own windows: first-language phonology

and the perceptual narrowing of infancy (Maurer and Werker), and the language-acquisition sensitivity that closes around puberty.

CLINICAL ANCHOR

The critical-period concept is the rationale for early intervention across child psychiatry: early cochlear implantation for congenital deafness, early enriched care for institutionally deprived children (the Romanian orphan / Bucharest Early Intervention findings, where duration of deprivation before foster placement predicted outcome), and early behavioural intervention in autism. The clinical maxim, treat the sensory or social deprivation before the window closes, is a direct application of this biology.

11.10 Reelin: the stop-signal glycoprotein and its psychiatric footprint

What reelin does. **Reelin (RELN)** is a large secreted extracellular-matrix glycoprotein, expressed during development by the **Cajal-Retzius cells** of the cortical marginal zone (the most superficial layer). It is the *stop signal* for radial migration: as each wave of migrating neurons approaches the top of the cortical plate, reelin halts it at the correct position, allowing the next wave to pass beneath and layer above the previous one, which is the mechanism of the inside-out cortex (11.3). Reelin signals through the ApoE receptor family (VLDLR and ApoER2) and the adaptor Dab1 (New Oxford Textbook 2020).

Why psychiatry cares. The *reeler* mouse (reelin-deficient) has an *inverted*, disorganised cortex, the direct demonstration that reelin controls lamination; homozygous human RELN mutation causes lissencephaly with cerebellar hypoplasia. Beyond the frank malformation, **reduced reelin expression** (with reduced GAD67, the GABA-synthesising enzyme) is one of the more replicated post-mortem molecular findings in *schizophrenia and bipolar disorder*, attributed partly to hypermethylation of the RELN promoter, an epigenetic link that connects a fetal patterning molecule to adult psychosis (Kaplan & Sadock 2024).

COMMON TRAP

Reelin is a migration stop signal made by Cajal-Retzius cells in the marginal zone, not a migration motor and not made by the migrating neuron itself. Contrast it with LIS1 and doublecortin (DCX), which are intrinsic to the migrating neuron's cytoskeletal machinery; loss of those *arrests* migration (lissencephaly, heterotopia), whereas loss of reelin *disorganises the layering* because the stop signal is gone.

11.11 The neurodevelopmental hypothesis of schizophrenia and the two-hit model

The core hypothesis. The neurodevelopmental model (Weinberger, Murray and Lewis) holds that schizophrenia originates in abnormal brain development beginning *in utero*, long before the illness declares itself, with the fixed lesion lying dormant until later maturational events unmask it. The classical evidence: an excess of obstetric complications and prenatal insults (famine, maternal influenza) in those who later develop schizophrenia; minor physical anomalies and premorbid neuromotor, cognitive and social deviations in childhood; and post-mortem findings of disturbed cortical cytoarchitecture and neuronal disarray without gliosis, implying a

developmental rather than degenerative origin (Tasman 2024). The absence of gliosis is the classic examinable point, it argues the lesion is fetal, not a later scarring injury.

Feinberg's pruning hypothesis and the adolescent second epoch. Feinberg (1982) proposed that schizophrenia reflects a *fault in programmed synaptic elimination during adolescence*, either too much pruning or pruning of the wrong synapses, explaining why an early lesion produces symptoms only at the adolescent pruning peak. This dovetails with the modern genetics: the **C4 (C4A) complement locus**, mapped by Sekar and colleagues (2016) from the MHC schizophrenia signal, is the strongest common-variant risk locus, higher C4A copy number predicts higher C4 expression, and C4 drives complement-mediated synaptic pruning, so the risk allele plausibly causes *excess* pruning during adolescence. Grey-matter loss, reduced dendritic spine density and perineuronal-net reduction in schizophrenia prefrontal cortex all fit an over-pruning account (Sekar 2016; Feinberg 1982).

MNEMONIC

"Two hits: the seed (in utero) and the trigger (adolescence)"

The **two-hit model** formalises the two epochs. **Hit one** is an early (genetic or prenatal) event that creates a latent vulnerability, a mis-wired circuit that is clinically silent. **Hit two** is a later stressor (adolescent synaptic pruning, cannabis, psychosocial stress, HPA-axis activation) acting on the primed substrate to precipitate psychosis. Neither hit alone suffices; the model explains both the fetal origin and the late-adolescent/early-adult onset in one frame.

11.12 Autism as a neurodevelopmental disorder: the opposite pruning imbalance

The mirror-image framing. Autism spectrum disorder (ICD-11 6A02; DSM-5-TR autism spectrum disorder) is neurodevelopmental with earlier onset and a partly opposite structural signature to schizophrenia. Whereas schizophrenia is associated with reduced spine density and grey-matter loss (over-pruning), autism is associated with *increased* dendritic spine density and early brain **overgrowth** (larger early brain volume, macrocephaly in a subset), consistent with *under-pruning* or deficient early synapse elimination (Kaplan & Sadock 2024). Post-mortem and imaging work reports defects of neurogenesis and neuronal migration, patchy cortical disorganisation, and altered developmental trajectories of the amygdala, hippocampus and cortex. Mechanistically, autism-associated genes converge on *synaptic* function and the excitatory-inhibitory balance (neurexins, neuroligins, SHANK, mTOR-pathway genes as in tuberous sclerosis and fragile X), reframing it as a "synaptopathy" of connectivity.

COMMON TRAP

The clean "schizophrenia = over-pruning, autism = under-pruning" contrast is a useful exam scaffold but a simplification: both are polygenic and heterogeneous, the complement/C4 story is present in only a subset of schizophrenia, and no complement locus reaches genome-wide significance in autism. State the contrast as a *heuristic about the direction of synaptic imbalance*, not as an established single mechanism for either disorder.

11.13 Maternal immune activation: the prenatal environmental hit

The epidemiology and the mechanism. **Maternal immune activation (MIA)** is the leading environmental limb of the neurodevelopmental hypothesis. Epidemiologically, maternal infection during pregnancy (influenza, and prenatal exposures indexed by the 1957 influenza pandemic and famine cohorts) and raised maternal inflammatory markers are associated with increased offspring risk of schizophrenia and autism. The mechanism, worked out in animal models, is that it is the *maternal inflammatory response*, not the pathogen itself, that harms the fetal brain: injecting the viral mimic **poly(I:C)** or the bacterial mimic LPS into pregnant rodents, in the absence of any live infection, produces offspring with behavioural and neuropathological abnormalities. The key mediator is the cytokine **interleukin-6 (IL-6)**: blocking maternal IL-6 prevents the offspring phenotype, and injecting IL-6 alone reproduces it (Kaplan & Sadock 2024).

Why it belongs here. MIA converges on the very machinery of 11.6. Maternal cytokines cross to the fetal compartment, activate fetal microglia and complement, and perturb neurogenesis, migration, interneuron development and synaptic patterning, providing a biologically continuous route from a first-trimester infection to an adult psychiatric phenotype and a mechanistic candidate for "hit one" of the two-hit model.

> **INDIA**
>
> The MIA and prenatal-insult data give a public-health frame that matters in the Indian setting: antenatal care, maternal nutrition (the famine-cohort and folate data), infection control and immunisation in pregnancy, and reduction of obstetric complications are primary-prevention levers for neurodevelopmental risk at the population level, upstream of any psychiatric treatment. The mechanism is a maternal-and-child-health argument, not only a neuroscience one.

11.14 Myelination: the last and longest process

Myelination outlasts every other stage and is the structural engine of protracted cognitive maturation. Oligodendrocytes wrap axons in myelin, raising conduction velocity and enabling fast, synchronised long-range communication. Myelination follows a strict caudal-to-rostral, posterior-to-anterior order: brainstem and sensorimotor tracts myelinate first (prenatally and in infancy), and **association and prefrontal white matter** last, continuing into the third and fourth decades. This is the white-matter counterpart of the back-to-front pruning gradient (11.7): the prefrontal cortex is the last to prune its grey matter and the last to myelinate its connections, which is the neural substrate usually invoked for the late maturation of executive control, judgement and impulse regulation. Diffusion-tensor imaging tracks this maturation as rising fractional anisotropy through adolescence, and disordered white-matter development is a candidate lesion in schizophrenia and in the demyelinating contribution to some neuropsychiatric presentations (Stahl 2021).

11.15 The consolidating table: stage, timing, mechanism, and the disorder of failure

The summary map. Read the timing column first: it predicts *which* disorder a hit at that stage produces, and the last column is the examinable clinical pairing.

STAGE	PEAK TIMING	KEY MECHANISM / MOLECULE	DISORDER OF FAILURE (DISCRIMINATOR)
Neurulation	Week 3 to 4	Neural tube closure; folate	**Anencephaly, spina bifida (neural tube defects)**
Proliferation	1st to 2nd trimester	VZ/SVZ mitosis; outer radial glia	**Microcephaly (too few) / megalencephaly (too many)**
Migration	2nd trimester	Radial glia; reelin stop signal; LIS1, DCX	**Lissencephaly, heterotopia, polymicrogyria**
Differentiation	Prenatal onward	Axon guidance (netrin, ephrin); BDNF	**Connectivity / dendritic anomalies**
Synaptogenesis	Birth to early childhood (overshoot)	Excess synapse formation; neurexin/neuroligin	**Autism: increased spine density (underpruning)**
Apoptosis	Perinatal	Caspases; neurotrophic competition (NGF)	**Failure gives dysregulated cell number**
Pruning	Childhood to adolescence (back-to-front)	Microglia, complement C1q/C3/C4, CR3	**Schizophrenia: overpruning (Feinberg; C4A)**
Myelination	Infancy to 3rd to 4th decade	Oligodendrocytes; posterior-to-anterior	**Late prefrontal maturation; white-matter disorders**

The neurodevelopmental timeline as a lesion map: the timing of an insult predicts its phenotype, from first-trimester migration disorders through the adolescent pruning peak that unmasks schizophrenia to the decades-long myelination that paces prefrontal maturation.

HOLD THIS

The timing of the insult predicts the phenotype. A migration failure (first trimester) gives heterotopia; an adolescent pruning failure gives schizophrenia. The two-hit model is just the statement that both windows matter: an in-utero seed and an adolescent trigger.

12 · Neurotrophins and BDNF

The neurotrophins are the growth-factor arm of neurochemistry, and they are the molecular hinge on which the modern **neurotrophic (neuroplasticity) hypothesis of depression** turns. Where the monoamine hypothesis explained why antidepressants raise synaptic serotonin in minutes, it could never explain why the clinical benefit takes weeks; the neurotrophic account fills exactly that gap, proposing that mood disorder is a disorder of stress-driven synaptic loss, and that antidepressants work slowly because they act by rebuilding synapses through **BDNF** rather than by flooding the cleft (Stahl 2021; Kaplan & Sadock 2024). This is why neurotrophins now appear in the same breath as glutamate, ketamine and mTOR.

Examiners return to this topic because it stitches together basic cell biology (a family of secreted growth factors and their two receptor systems), a disease model (stress lowers BDNF, treatments raise it), a pharmacogenetic vignette (the Val66Met polymorphism) and the mechanism of the

newest antidepressants (ketamine to AMPA to BDNF to mTOR). **Learn it as one causal chain, not a bag of facts.** Everything below is either an input to BDNF, a receptor for it, or a consequence of having too little of it.

12.1 The neurotrophin family: NGF, BDNF, NT-3 and NT-4/5

Four classic members, one shared logic. The neurotrophins are a family of small secreted polypeptide growth factors comprising **nerve growth factor (NGF)**, **brain-derived neurotrophic factor (BDNF)**, **neurotrophin-3 (NT-3)** and **neurotrophin-4/5 (NT-4)** (Kaplan & Sadock 2024). NGF was the first neurotrophic factor discovered, in the 1950s (Cohen, Levi-Montalcini); BDNF was isolated in the 1980s (Barde 1982), and NT-3 and NT-4 followed. They govern neuronal proliferation, differentiation, survival and, in the adult brain, synaptic plasticity.

Distribution matters clinically. NGF has a restricted distribution: in the periphery it supports sympathetic and nociceptive sensory neurons, and in the CNS it maintains the *basal forebrain cholinergic neurons* that project to the hippocampus and degenerate in Alzheimer disease. BDNF and NT-3 by contrast are the dominant CNS neurotrophins, highly expressed in cortex and hippocampus (Kaplan & Sadock 2024). BDNF specifically rises after stress, injury, neural stimulation and exercise, which is the fact that makes it the mood-relevant member of the family.

12.2 Synthesis, cleavage and the proBDNF story

All neurotrophins begin as precursors. Each is first made as a larger **proneurotrophin** that is then cleaved to release the mature, active protein (a stable non-covalent dimer of roughly 12 to 14 kDa). Cleavage of proBDNF can happen intracellularly (in the Golgi by *furin*, or in dense-core vesicles by proconvertases) or extracellularly (by *plasmin* or matrix metalloproteinases) (Kaplan & Sadock 2024).

The precursor is not inert: it is the biological opposite of mature BDNF. This is the high-yield twist. Mature BDNF signals survival and potentiation through TrkB; **proBDNF** preferentially binds the p75 receptor and drives the opposite program, facilitating *long-term depression (LTD)* and apoptosis (Kaplan & Sadock 2024). At the developing neuromuscular synapse the two act as a "reward" and "punishment" pair: activity-dependent proteases convert proBDNF to mature BDNF at *active* terminals (which are stabilised), while p75-expressing *inactive* terminals bind proBDNF and receive the retraction signal. Chronic stress raises hippocampal proBDNF in rodents, and this normalises with fluoxetine. Human peripheral proBDNF-to-BDNF studies are, however, mixed and do not yet serve as a reliable clinical biomarker.

> **PEARL**
>
> Think of the BDNF gene as producing a Jekyll-and-Hyde protein. The *mature* ligand acting through TrkB means survival, LTP and synapse-building. The uncleaved *proBDNF* acting through p75 means LTD, spine loss and pruning. Whether the balance tips toward growth or retraction is set by proteolytic cleavage and by which receptor is engaged, not merely by how much BDNF is present.

12.3 The two receptor systems: Trk tyrosine kinases and p75

Neurotrophins are unusual in signalling through two structurally unrelated receptors at once (Kaplan & Sadock 2024). The **Trk (tropomyosin-related kinase)** receptors are receptor tyrosine kinases mediating the trophic, pro-survival, pro-plasticity effects. The **p75 neurotrophin receptor (p75NTR)** is a member of the tumour-necrosis-factor receptor superfamily, carrying an intracellular *death domain*, and it can drive apoptosis.

Ligand-receptor specificity is a guaranteed exam item. Each mature neurotrophin has its own preferred Trk, while *all* neurotrophins can bind p75.

RECEPTOR	TYPE	PREFERRED LIGAND(S)	PRINCIPAL EFFECT
TrkA	Receptor tyrosine kinase	**NGF**	Survival of cholinergic and sympathetic/sensory neurons
TrkB	Receptor tyrosine kinase	**BDNF and NT-4**	Synaptic plasticity, LTP, the mood-relevant receptor
TrkC	Receptor tyrosine kinase	**NT-3**	Neuronal differentiation and survival
p75NTR	TNF-receptor superfamily (death domain)	All neurotrophins; proneurotrophins with high affinity	**Apoptosis, LTD; tunes Trk ligand selectivity**

Neurotrophin-receptor pairing. The discriminator to memorise: NGF to TrkA, BDNF (and NT-4) to TrkB, NT-3 to TrkC, and every neurotrophin to p75. Mature ligand plus Trk means survival; proneurotrophin plus p75 means death.

RULE **NGF-TrkA, BDNF-TrkB, NT-3-TrkC; every neurotrophin binds p75.** Mature ligand at Trk means survival, proneurotrophin at p75 means death.

Two refinements worth knowing. First, p75 sharpens specificity: NT-3 can weakly bind TrkA and TrkB, but co-expressed p75 restricts each Trk to its cognate ligand, so with p75 present only BDNF gives a functional TrkB response. Second, the "high vs low affinity" shorthand is technically loose, because proNGF actually binds p75 with high affinity; what really determines the cellular outcome is the ratio of Trk to p75 and whether the ligand is the mature or the pro form (Kaplan & Sadock 2024).

12.4 BDNF to TrkB signalling: three downstream cascades

When BDNF dimers bind TrkB, the receptor dimerises and *autophosphorylates* intracellular tyrosine residues, which become docking sites for adaptor proteins (notably Shc and PLC-gamma). Three signalling arms then diverge (Kaplan & Sadock 2024; Yang et al. 2020):

Ras to MAPK/ERK

Via Shc. The extracellular-signal-regulated kinase pathway drives neurite outgrowth, differentiation and the transcriptional changes of long-lasting plasticity.

PI3K to Akt

Via Shc. The principal *survival* pathway; Akt (protein kinase B) suppresses apoptotic programs and, importantly, feeds into **mTORC1**, the node that couples BDNF signalling to activity-dependent local

protein synthesis and spine remodelling.

PLC-gamma to Ca2+/PKC

Generates inositol phosphates and diacylglycerol, raising intracellular calcium and activating protein kinase C; central to TrkB-mediated hippocampal LTP.

The convergence point is transcription. All three arms converge on the transcription factor **CREB** (cyclic-AMP response element-binding protein), and CREB in turn induces the *BDNF gene itself* (Kaplan & Sadock 2024). This creates a self-amplifying loop and is precisely where the monoamine and neurotrophic hypotheses join hands: serotonin and noradrenaline reuptake inhibitors act through G-protein-coupled receptors and cyclic AMP to raise CREB, which raises BDNF, on a 10-to-20-day time course that matches the clinical latency of antidepressant response.

12.5 Activity-dependent plasticity: BDNF and LTP

BDNF is the archetypal **activity-dependent** neurotrophin: its transcription, dendritic transport, secretion and cleavage are all gated by neuronal activity, which is what lets it translate experience into lasting synaptic change (cross-reference the the Functional Neuroanatomy & Neurophysiology notes LTP topic for the induction machinery). BDNF messenger RNA is upregulated by the very high-frequency stimulation that induces LTP in the hippocampus (Yang et al. 2020).

The nuance is "promotes but is not strictly required". BDNF-TrkB signalling *facilitates* hippocampal LTP and is needed for its late, protein-synthesis-dependent phase, yet high-frequency-induced LTP can still occur without it in some paradigms (Kaplan & Sadock 2024). Mechanistically, BDNF acts both presynaptically (enhancing glutamate release) and postsynaptically (increasing synaptic trafficking and insertion of *AMPA receptors*, and driving actin-dependent dendritic-spine enlargement via ERK and Rho-GTPase pathways). Brief application of exogenous BDNF can itself produce lasting synaptic potentiation, a phenomenon termed "BDNF-LTP". BDNF also stimulates adult hippocampal neurogenesis in the dentate gyrus, tying the growth factor to the structural-plasticity face of depression.

12.6 The neurotrophic hypothesis of depression

The core claim. Stress lowers BDNF and antidepressant treatments raise it, and this bidirectional movement, rather than monoamine level per se, tracks the illness and its treatment (Duman et al. 1997; Kaplan & Sadock 2024; Stahl 2021). Several convergent lines support it:

1. Stress lowers BDNF and damages the hippocampus. In animal models, restraint and chronic stress reduce hippocampal BDNF expression and cause atrophy and death of hippocampal neurons, most markedly in the *CA3* region. Concordantly, MRI shows a small but reproducible reduction in **hippocampal volume** in depression and PTSD (Kaplan & Sadock 2024).

2. BDNF itself is antidepressant. Infusing BDNF into the rodent hippocampus produces antidepressant-like effects in the forced-swim and learned-helplessness paradigms comparable to chronic drug treatment (Shirayama et al. 2002).

3. Antidepressants, ECT and exercise all raise BDNF. Monoamine antidepressants upregulate BDNF, CREB and TrkB in the hippocampus over a time course matching clinical response. **Electroconvulsive therapy** is among the most potent inducers of BDNF transcription and hippocampal sprouting in rodents (though human serum data are mixed and BDNF is a poor predictor of ECT outcome). Physical *exercise* robustly elevates BDNF, the molecular substrate for its antidepressant and pro-cognitive effects (Kaplan & Sadock 2024; Phillips 2017).

Stahl frames the same idea as *neuroprogression*: stress, inflammation, early-life adversity, altered microbiome and disrupted sleep produce epigenetic silencing of the BDNF gene, and the resulting loss of growth factor leads first to failure of synaptic maintenance and then to frank synapse and neuron loss (Stahl 2021). In ICD-11 the relevant disorder is a depressive episode (single episode depressive disorder or recurrent depressive disorder), cross-mapped to DSM-5-TR major depressive disorder; the neurotrophic account is a mechanistic model, not a diagnostic category.

COMMON TRAP

Do not overstate serum BDNF as a diagnostic test. Peripheral (serum or plasma) BDNF tends to be lower in unmedicated depression and rises with treatment at a group level, but it is confounded by platelets, exercise, diet, smoking, storage and diurnal variation, and it does not reliably diagnose an individual or predict response (Kaplan & Sadock 2024). State it as a group-level correlate and candidate biomarker, never as a bedside test. Equally, do not claim the neurotrophic hypothesis has replaced the monoamine hypothesis: it sits downstream of it and explains the therapeutic delay.

12.7 The BDNF Val66Met polymorphism

What it is. Val66Met (rs6265) is a common single-nucleotide polymorphism in the *prodomain* of the human BDNF gene, substituting methionine for valine at codon 66. Because it sits in the pro-region, it does not change the mature protein's sequence; instead it impairs the *intracellular trafficking and activity-dependent secretion* of BDNF, so Met-allele carriers release less BDNF in response to neuronal activity, particularly at dendrites (Kaplan & Sadock 2024).

The phenotype. Met carriers show, on functional imaging, smaller hippocampal volumes and poorer episodic memory, and behaviourally they exhibit *less efficient fear extinction* and heightened anxiety under stress; parallel findings hold in a knock-in mouse carrying the human Met allele (Chen et al. 2006; Kaplan & Sadock 2024). A meta-analysis of gene-by-environment studies found the Met allele significantly moderates the relationship between stressful life events or childhood adversity and depression (Zhao et al. 2018).

Why it matters clinically. The impaired-extinction phenotype has a direct therapeutic implication: Met carriers may need a longer or more intensive course of *exposure therapy* to extinguish conditioned aversive cues, and the polymorphism has been reported to predict exposure-therapy response in PTSD (Felmingham et al. 2013; Kaplan & Sadock 2024). The same allele is also a genome-wide-significant signal for obesity and a risk factor for antipsychotic-associated weight gain and insulin resistance, reflecting BDNF-TrkB's role in hypothalamic (paraventricular) control of satiety and energy balance.

CLINICAL ANCHOR

Val66Met is the cleanest single example of pharmacogenomics touching psychotherapy rather than pharmacotherapy: a growth-factor variant that predicts how a patient will learn to un-fear a stimulus, and therefore how a course of exposure-based CBT should be dosed. It is not yet a routine clinical test, but it is the paradigm case examiners use to show that "biological" and "psychological" treatments share a final common substrate in activity-dependent BDNF release.

12.8 Ketamine to BDNF to mTOR: the rapid-acting pathway

The neurotrophic hypothesis found its sharpest confirmation in the mechanism of **ketamine**, whose antidepressant effect appears within hours and is, at its core, a BDNF phenomenon (cross-reference the glutamate topic for the receptor pharmacology). Two complementary accounts operate (Kaplan & Sadock 2024):

Route one, de-repressing BDNF translation. Blocking NMDA receptors deactivates *eEF2 kinase* (eukaryotic elongation factor-2 kinase); this lifts the brake on BDNF translation, producing a rapid rise in BDNF protein within about 30 minutes that drives spine remodelling and synaptogenesis.

Route two, the AMPA-to-mTOR surge. Transient NMDA blockade on GABAergic interneurons disinhibits cortical glutamate neurons, producing a brief glutamate burst that stimulates **AMPA receptors**. AMPA activation triggers local release of BDNF (and VEGF), which engage TrkB (and Flk-1) to activate *Akt and mTORC1*, driving translation of synaptic proteins and a rapid burst of synaptogenesis in the prefrontal cortex (Kaplan & Sadock 2024). Either way the antidepressant effect is not the NMDA block itself but the downstream **BDNF-mTOR synaptic rebuild** it unleashes.

This mechanism underwrites the newest therapeutics: intranasal **esketamine** (the S-enantiomer, approved 2019 for treatment-resistant depression and later for major depressive disorder with acute suicidality, given under supervision with an oral antidepressant), racemic IV ketamine off-label, and the investigational rapid agents that target the same pathway. It also explains why a TrkB-signalling requirement has been proposed as the common denominator of both slow (SSRI) and fast (ketamine) antidepressants, with the antidepressant binding site now mapped onto TrkB itself in recent work (Kaplan & Sadock 2024).

MNEMONIC

"Stress Bends, Treatment Mends: BDNF"

Stress Bends the synapse down (low BDNF, hippocampal atrophy, smaller volume). **Treatment Mends** it back up (SSRIs, ECT and exercise raise BDNF slowly via CREB; ketamine raises it fast via AMPA to mTOR). The molecule in the middle of both arrows is always BDNF, acting through TrkB.

HOLD THIS

Stress lowers BDNF and treatments raise it, and that movement (not the monoamine level) tracks the illness. Mature BDNF at TrkB builds synapses; uncleaved proBDNF at p75 does the opposite.

12.9 Neurotrophins beyond depression: development, neurodegeneration and pain

Development and critical periods. In the CNS, BDNF governs the maturation of inhibitory parvalbumin GABA interneurons and thereby the timing of experience-dependent *critical periods*, the classic example being ocular-dominance-column formation in visual cortex; BDNF overexpression accelerates visual-acuity development and closes the critical period early (Kaplan & Sadock 2024).

Neurodegeneration. The neurotrophic-deficit logic extends beyond mood. In **Huntington disease**, mutant huntingtin reduces cortico-striatal *anterograde transport of BDNF*, starving the striatal medium spiny neurons that degenerate. In **Alzheimer disease**, loss of NGF support to basal-forebrain cholinergic neurons contributes to the cholinergic deficit, and adding NGF or BDNF to entorhinal cortex or hippocampus improves spatial memory in models (Kaplan & Sadock 2024).

Pain, and the therapeutic difficulty of using neurotrophins. NGF sensitises nociceptors, and anti-NGF monoclonal antibodies (for example tanezumab) reduce osteoarthritis pain, showing the family cuts both ways. Direct delivery of neurotrophins as antidepressants has largely failed: they do not cross the blood-brain barrier, indiscriminate flooding risks seizures, and TrkB downregulates after unregulated BDNF exposure. The tractable strategy is therefore to raise BDNF *indirectly* through antidepressants, ECT, exercise, or small molecules and GPCR ligands (for example A2A and PACAP receptors) that transactivate TrkB, rather than to administer the protein itself (Kaplan & Sadock 2024).

INDIA

Two low-cost, high-yield levers on BDNF are directly relevant to Indian practice, where medication access and affordability are uneven: structured *physical exercise* and adequate *sleep* both raise BDNF and can be prescribed as adjuncts at no drug cost, and ECT (widely available and effective in Indian tertiary centres for severe and treatment-resistant depression) is among the most potent BDNF inducers. Framing exercise and sleep hygiene to patients as biologically active, "growth-factor-raising" interventions rather than soft lifestyle advice improves adherence and fits a resource-conscious, guideline-concordant stepped-care model.

Neuroendocrinology

13 · HPA axis, stress and cortisol

The endocrine home of stress. Of the three neuroendocrine axes on these notes, the hypothalamic-pituitary-adrenal (HPA) axis is the one examiners return to most, because it is where a psychological event becomes a measurable hormone and then a testable psychiatric

marker. the Functional Neuroanatomy & Neurophysiology notes drew the *neural* stress circuit (amygdala driving the paraventricular nucleus, with prefrontal and hippocampal brakes); this topic adds the *endocrine arm* on top of it and owns the full cascade, the receptor-level feedback, and the one classical laboratory test of the axis, the dexamethasone suppression test. Cross-reference the amygdala-to-PVN wiring back to the Functional Neuroanatomy & Neurophysiology notes and do not re-derive it here.

The single organising idea is a three-tier hormonal relay under negative feedback: a stressor drives hypothalamic **CRH**, which drives pituitary **ACTH**, which drives adrenal **cortisol**, and cortisol then shuts the loop off by acting back on the pituitary, hypothalamus and hippocampus. Kaplan and Sadock frame cortisol as the transmitter of the endocrine stress response, sharpening arousal, vigilance and memory encoding acutely, but corrosive to the hippocampus when chronically elevated (Kaplan & Sadock 2024). Learn the cascade forward, the feedback backward, and the disease signatures (depression high, PTSD paradoxically low) as the payoff.

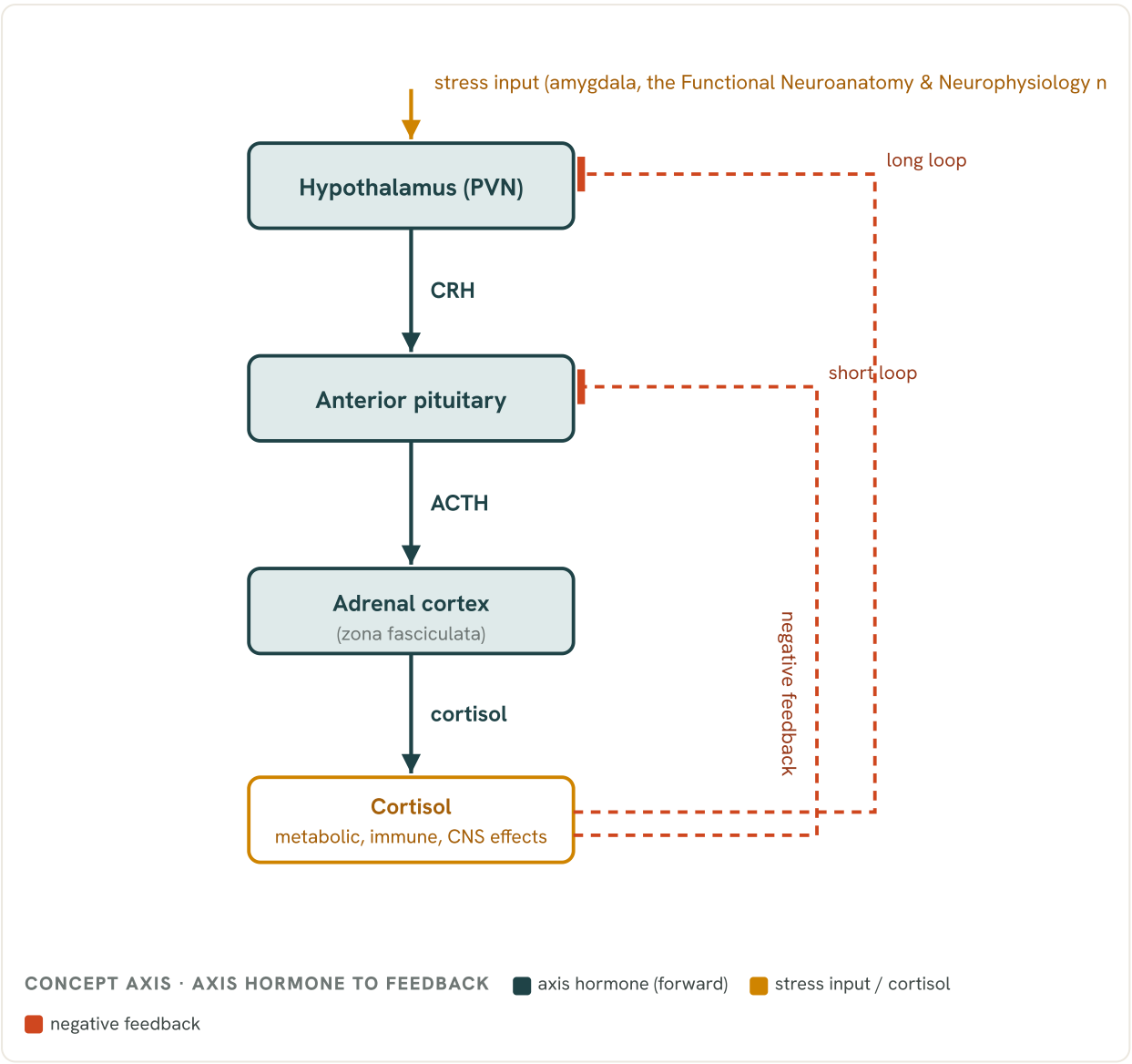


Fig 2.5 The HPA axis. A limbic stress signal (from the Functional Neuroanatomy & Neurophysiology circuit) drives the hypothalamic paraventricular nucleus to release CRH, which drives pituitary ACTH, which drives adrenal cortisol. Cortisol then closes two negative-feedback loops, a short loop onto the pituitary and a long loop onto the hypothalamus. The dexamethasone suppression test probes this feedback: failure to suppress cortisol (non-suppression) is the classic finding in melancholic depression.

13.1 The three-tier cascade: CRH to ACTH to cortisol

The anatomy of the relay. The axis is three glands in series, each secreting the signal for the next. Learn the source, the signal and the target at each tier.

Tier 1: hypothalamus (PVN)

Parvocellular neurons of the **paraventricular nucleus (PVN)** secrete **corticotropin-releasing hormone (CRH)**, a 41-amino-acid peptide, into the hypophyseal portal circulation. CRH is co-secreted with **arginine vasopressin (AVP)**, which is a weaker secretagogue on its own but strongly potentiates CRH at the pituitary (Kaplan & Sadock 2024).

Tier 2: anterior pituitary

CRH acts on corticotrophs of the **anterior pituitary** to release **adrenocorticotropic hormone (ACTH)**, cleaved from the precursor pro-opiomelanocortin (POMC). ACTH travels in the systemic circulation to the adrenal.

Tier 3: adrenal cortex

ACTH stimulates the **zona fasciculata of the adrenal cortex** to synthesise and release **cortisol**, the principal human glucocorticoid, from cholesterol. Cortisol is the effector hormone and the output that closes the loop.

MNEMONIC

CAP for the cascade, top to bottom

CRH (hypothalamic PVN) drives **A**CTH (anterior pituitary) drives cortisol from the adrenal **P**arenchyma (cortex, zona fasciculata). Read top-down for the forward cascade; the same three levels read bottom-up are exactly where cortisol feeds back.

13.2 The effector: what cortisol does acutely

Cortisol is adaptive in the short term and damaging when sustained, and the exam wants both faces. Acutely it increases arousal, vigilance and focused attention, mobilises energy (raising blood glucose via gluconeogenesis), contains the immune and inflammatory response, and facilitates the encoding of emotionally salient memory (Kaplan & Sadock 2024). This memory-enhancing effect is **contingent on noradrenaline**: glucocorticoid facilitation of emotional memory in the amygdala depends on concurrent arousal-driven noradrenergic activation, tying the endocrine arm back to the locus coeruleus circuit of the Functional Neuroanatomy & Neurophysiology notes.

PEARL

Cortisol has a **biphasic (inverted-U) effect** on hippocampal function and memory: a moderate rise sharpens memory consolidation, but high or sustained levels impair hippocampal-dependent cognition. This dose-dependence is why acute stress can sharpen recall while chronic stress dulls it, and it is the mechanistic bridge to the hippocampal atrophy seen with prolonged hypercortisolaemia.

13.3 Feedback: the two receptors, MR and GR

Two receptors, two thresholds. Cortisol closes its own loop through two intracellular corticosteroid receptors that differ critically in affinity, and this affinity difference is the single most examinable point in HPA feedback (Kaplan & Sadock 2024; Goodman & Gilman 2018).

FEATURE	MINERALOCORTICOID RECEPTOR (MR)	GLUCOCORTICOID RECEPTOR (GR)
Affinity for cortisol	**High affinity: occupied even at low, basal (trough) cortisol**	**Lower (moderate-to-low) affinity: recruited only when cortisol is high, at the diurnal peak and during stress**
Physiological role	Sets basal tone and maintains the circadian rhythm of the axis	Mediates the negative-feedback shut-off of the stress response and the return to baseline
Regional concentration	Dense in the hippocampus	Widespread; very high in hippocampus, also pituitary and hypothalamus
Feedback site	Tonic, permissive	**The main brake: GR at pituitary, hypothalamus and hippocampus terminates the surge**

The discriminator: MR is the high-affinity receptor that keeps the axis toned at rest, GR is the lower-affinity receptor that only engages when cortisol is high and is therefore the receptor that shuts stress off. Impaired GR feedback is the core lesion posited in melancholic depression.

RULE **MR is high-affinity and tones the axis at rest; GR is lower-affinity and only engages when cortisol is high, so GR is the brake that shuts stress off.** Impaired GR feedback is the posited melancholic lesion.

The **hippocampus** carries a very high density of both receptors and is the principal site of glucocorticoid negative feedback; this is why hippocampal damage both results from and worsens HPA dysregulation, a feed-forward loop of cortisol excess and hippocampal injury. Note also that MR responds to cortisol centrally because neurons lack the 11-beta-hydroxysteroid dehydrogenase type 2 that elsewhere protects MR from cortisol (Goodman & Gilman 2018).

13.4 Diurnal rhythm and the cortisol awakening response

Cortisol is not secreted flat: it follows a strong **diurnal (circadian) rhythm**, driven by the suprachiasmatic nucleus (cross-reference the circadian topic). Levels peak in the early morning, around waking, and fall to a nadir (trough) around midnight and the first hours of sleep. Superimposed on waking is the **cortisol awakening response (CAR)**, a sharp 50 to 75 percent rise in the 30 to 45 minutes after waking. The rhythm matters clinically for two reasons: it dictates *when* you must sample cortisol for any test to be interpretable, and its *flattening* (loss of the normal peak-to-trough amplitude) is itself a marker of chronic stress and HPA dysregulation.

COMMON TRAP

A single random cortisol is nearly uninterpretable because of the diurnal swing. The abnormality in depression is classically described not just as a raised mean but as an **elevated evening (nadir) cortisol with loss of the normal diurnal fall**, an earlier nadir and blunted amplitude. Always anchor a cortisol value to the time of day it was drawn.

13.5 Stress response and allostatic load

From adaptation to damage. The acute stress response is *allostasis*: the active process of achieving stability through change, mobilising the HPA axis and sympathetic system to meet a challenge, then switching off. **Allostatic load** (McEwen) is the cumulative physiological cost of this machinery when it is over-used or fails to shut off, that is, the wear-and-tear of a stress response that is too frequent, too prolonged, or inadequately terminated. Continuous high levels of hypothalamic and extrahypothalamic CRH are a strong contributor to allostatic load (Kaplan & Sadock 2024).

The four failure modes of the stress response that generate allostatic load are worth naming as a set: (a) too many stressors (repeated hits), (b) failure to habituate to a repeated stressor, (c) failure to shut off after the stressor ends (the GR-feedback problem), and (d) an inadequate response in one system leading to compensatory overactivity in another. The downstream cost of sustained cortisol is the peripheral syndrome of hypercortisolaemia (hypertension, insulin resistance, dyslipidaemia, osteoporosis, immunosuppression, visceral adiposity, procoagulant state) plus central hippocampal and prefrontal injury.

PEARL

Distinguish the terms cleanly. **Homeostasis** = keeping a fixed setpoint constant. **Allostasis** = achieving stability *through* change (the adaptive response itself). **Allostatic load** = the price paid for chronic or inefficient allostasis. **Allostatic overload** = the point where that load produces frank pathology. Examiners test the allostasis-versus-homeostasis distinction directly.

13.6 The dexamethasone suppression test (DST): protocol

The one test to know in full. The DST probes the integrity of glucocorticoid negative feedback. Dexamethasone is a potent synthetic glucocorticoid that suppresses pituitary ACTH (and hence cortisol) in a normal, feedback-intact axis. In the standard low-dose overnight protocol, **1 mg of dexamethasone is given orally at 11 PM**, and plasma cortisol is measured the next day, classically at 8 AM, 4 PM and 11 PM (Kaplan & Sadock 2024).

Normal (suppression)

Post-dexamethasone plasma cortisol falls and stays low, indicating an intact HPA feedback loop. This is the expected, healthy result.

Abnormal (non-suppression)

Plasma cortisol remains **above 5 micrograms/dL** (the classical cut-off), meaning the axis has escaped feedback: this is a positive test. Non-suppression reflects impaired GR-mediated feedback and is the finding of interest in depression (Kaplan & Sadock 2024).

COMMON TRAP

The DST is **not diagnostic of depression** and is not used clinically to make the diagnosis. Its low sensitivity, its escape as mood improves, and its non-specific positives (it is also positive in Cushing syndrome, and confounded by weight loss, alcohol, and enzyme-inducing drugs like carbamazepine and phenytoin that speed dexamethasone metabolism) mean it never entered routine practice. Know it as a historical and mechanistic marker, not a diagnostic test.

13.7 DST performance: melancholia, psychosis and the DEX/CRH refinement

The numbers are examinable and specific. In the pooled literature the 1 mg DST shows about **67 percent sensitivity and 96 percent specificity for melancholic depression** (Carroll's original claim), but sensitivity for major depression in general is only about **44 percent** (Contreras 2013). Non-suppression rates rise with biological severity: roughly **43 percent in MDD overall, but 67 percent in MDD with psychotic features** (Varghese 2001). Non-suppression is also **age-dependent**, climbing from about 34 percent in patients under 18 to 64 percent in those over 60, and correlates with the number of past depressive episodes.

The **combined dexamethasone/CRH (DEX/CRH) test** is the more sensitive research refinement: the axis is first suppressed with dexamethasone, then challenged with CRH. In dysregulated patients cortisol paradoxically rises despite pre-treatment, and the test reaches **sensitivity up to 90 percent** for detecting depression (Varghese 2001). Elevated CSF CRH is a fairly specific, *state* marker of depression (normal in mania, schizophrenia and dementia) that normalises with treatment.

67%	96%	44%	90%
1 MG DST SENSITIVITY IN MELANCHOLIA	SPECIFICITY FOR MELANCHOLIA	SENSITIVITY IN MDD OVERALL	DEX/CRH TEST SENSITIVITY

CLINICAL ANCHOR

Persistent non-suppression predicts relapse. DST non-suppression typically normalises as depression remits; a DST (or DEX/CRH) that *fails* to normalise despite symptomatic improvement flags a substantially higher risk of early relapse. This prognostic use, not diagnosis, is the clinically meaningful signal, and non-suppression also predicts better response to somatic (drug, ECT) than to placebo treatment.

13.8 HPA in depression: the hypercortisolaemic signature

Major depressive disorder (ICD-11 6A70-6A71; DSM-5-TR major depressive disorder), particularly the **melancholic** subtype, is the archetype of HPA *over*-activity. The composite signature (Varghese 2001; Kaplan & Sadock 2024) is: hypercortisolaemia with a flattened diurnal rhythm and raised evening cortisol; adrenal and pituitary hypertrophy on imaging; elevated CSF CRH with CRH-neuron overactivity in the PVN; a **blunted ACTH response to exogenous CRH** (from chronic CRH-driven pituitary downregulation); DST non-suppression; and reduced hippocampal volume. The mechanistic story is impaired GR-mediated feedback: the brake fails,

CRH drive is sustained, and the resulting cortisol excess is itself hippocampally toxic, a self-reinforcing loop.

COMMON TRAP

Atypical depression breaks the pattern. The hypercortisolaemia story is specific to *melancholic/endogenous* depression. Atypical depression (with hyperphagia, hypersomnia, leaden paralysis, mood reactivity) shows lower basal cortisol and a higher proportion of normal DSTs, closer to the *hypo*-cortisol pattern. Do not claim hypercortisolaemia across all depression.

13.9 HPA in PTSD: the low-cortisol paradox

The counter-intuitive case. Post-traumatic stress disorder (ICD-11 6B40; DSM-5-TR PTSD) is the examiner's favourite trap because, despite chronic stress, the classic finding is **low, not high, cortisol** (Yehuda). The paradox resolves through **enhanced negative feedback**: PTSD is associated with reduced urinary free cortisol, increased glucocorticoid-receptor density and sensitivity on lymphocytes, and consequently an over-active feedback brake that keeps cortisol low. CRH, by contrast, is *elevated* in CSF, so the abnormality is a hypersensitive GR feedback loop clamping down on the output, not a quiet axis (Contreras 2013).

The signature laboratory demonstration is **hypersuppression on a low-dose DST**: at **0.5 mg dexamethasone (half the usual dose)**, PTSD patients still suppress cortisol (indeed over-suppress) whereas depressed patients do not, a dissociation historically used to distinguish the two (Yehuda 2004).

MNEMONIC

Depression is HIGH and escapes; PTSD is LOW and over-suppresses

MDD: high cortisol, blunted feedback, DST *non*-suppression. PTSD: low cortisol, *enhanced* feedback (up-regulated, hypersensitive GR), *hyper*-suppression on the 0.5 mg DST. The two disorders sit at opposite poles of the same feedback axis.

HOLD THIS

Melancholic depression is high-cortisol and escapes feedback (DST non-suppression); PTSD is low-cortisol and hyper-suppresses on the 0.5 mg DST. Opposite poles of one feedback axis, driven by GR sensitivity.

13.10 HPA and suicide

HPA dysregulation carries independent prognostic weight for suicide. Across studies, DST non-suppression and evidence of HPA over-activity in depressed patients are associated with an **increased risk of completed suicide** (Varghese 2001). A widely cited meta-analytic finding is that DST non-suppressors have a substantially higher long-term risk of eventual suicide than suppressors, making persistent HPA dysregulation one of the few biological markers with replicated links to suicidal outcome. Post-mortem work adds convergent evidence of altered CRH signalling and reduced frontal-cortex CRH-binding in suicide, consistent with sustained central CRH hyperdrive.

13.11 Early-life programming of the axis

Where the setpoint is set. The HPA axis is developmentally plastic, and early-life stress durably resets its sensitivity, a central theme in the diathesis-stress and developmental-psychiatry literature. Preclinical work shows basal CSF CRH is persistently higher in primates that experienced early-life stress, and that excessive early CRH exposure produces hippocampal damage in later life (Kaplan & Sadock 2024). The best-characterised mechanism is **epigenetic**: early caregiving quality alters DNA methylation of the glucocorticoid-receptor (NR3C1) promoter in the hippocampus, changing lifelong GR expression and therefore feedback set-point (Meaney and Szyf, in the maternal-care model).

PEARL

Early-life adversity produces a **gene-environment interaction at the HPA axis**: the FKBP5 polymorphism (which regulates GR sensitivity) interacts with childhood trauma to predict adult depression and PTSD. This is the molecular embodiment of the diathesis-stress model and links the endocrine axis directly to developmental-psychiatry and epigenetics stems.

13.12 Therapeutics targeting the axis

Because the axis is a mechanism, it is a drug target, and current agents are examinable. **Mifepristone (RU-486)**, a glucocorticoid-receptor (GR) antagonist, has been trialled for **psychotic depression** (rapid reversal reported) and, in older adults with elevated cortisol, for cognitive and worry symptoms (Kaplan & Sadock 2024). Direct **CRH-1 receptor antagonists** were a rational strategy but have disappointed: no CRH-1 antagonist has shown efficacy in a phase III trial for a stress-related disorder, and pexacerfont failed against placebo in generalised anxiety disorder. Conceptually, standard antidepressants themselves partly work by *normalising* HPA feedback (restoring GR function and DST suppression) as mood improves, which is why persistent non-suppression on treatment signals inadequate response.

INDIA

The DST and DEX/CRH test are research and teaching instruments, not part of routine Indian (or international) clinical workup for depression: HPA-axis testing does not feature in IPS or NICE depression pathways, and diagnosis remains clinical. Know the axis for its mechanistic and viva value, and reserve endocrine testing for when a genuine endocrinopathy (Cushing syndrome, Addison disease) is in the differential.

14 · HPT and HPG axes in psychiatry

After the HPA axis, the two neuroendocrine loops most often examined in psychiatry are the **hypothalamic-pituitary-thyroid (HPT)** axis and the **hypothalamic-pituitary-gonadal (HPG)** axis. Both illustrate the same organising idea: a hypothalamic releasing hormone drives an anterior-pituitary trophic hormone, which drives a peripheral endocrine gland, whose product feeds back negatively on the two levels above it. Each axis touches psychiatric practice at three points: the endocrinopathy itself can present as a psychiatric syndrome (hypothyroid depression, menopausal mood change), the axis can be used diagnostically or therapeutically (the TRH

stimulation test, T3 augmentation), and psychotropic drugs perturb it (lithium and the thyroid, antipsychotics and prolactin). This topic also gathers the two remaining anterior-pituitary hormones of exam interest, **prolactin** (the antipsychotic problem) and **growth hormone** (the clonidine challenge test), because they share the same hypothalamic-pituitary anatomy.

The examiner reliably wants three things in this territory: the exact feedback logic of each axis, the numbers attached to the challenge tests and to lithium-induced thyroid disease, and a rational, prolactin-sparing approach to antipsychotic hyperprolactinaemia. The through-line is that dopamine is the hidden regulator of both prolactin (inhibitory) and TSH (inhibitory), which is why the neuroleptic that blocks dopamine raises prolactin, and why the axes are never fully separable from the transmitter pharmacology of these notes.

14.1 The HPT axis: TRH to TSH to T3/T4, and its feedback

Three hormones, one negative-feedback loop. Hypothalamic **thyrotropin-releasing hormone (TRH)**, a tripeptide from the paraventricular nucleus, drives the anterior pituitary to release **thyroid-stimulating hormone (TSH, thyrotropin)**, which drives the thyroid follicular cells to synthesise and release **thyroxine (T4)** and **triiodothyronine (T3)** from the thyroglobulin precursor. Low circulating thyroid hormone releases the brake on both TRH and TSH; high thyroid hormone suppresses them (Kaplan & Sadock 2024). Two facts have direct psychiatric relevance. First, **T4 is the main hormone reaching the brain, whereas T3 is the metabolically active hormone at peripheral tissues**, and much brain T3 is generated locally by deiodination of T4, which is part of the rationale for using T3 (not T4) in depression augmentation. Second, **central dopamine and glucocorticoids inhibit TSH secretion**, coupling the thyroid axis to the same monoamine and stress systems that dominate the rest of these notes.

Protein binding

T3 and T4 are tightly bound to thyroxine-binding globulin (TBG); only about 0.3% of T3 and 0.02% of T4 circulate free. Because oestrogen raises TBG, pregnancy and oral contraceptives raise *total* T4 without raising free hormone, whereas androgens lower TBG. This is why free-hormone indices, not total levels, are used to judge thyroid status (Kaplan & Sadock 2024).

Where the level points

An *elevated* TSH with low free T4 localises the lesion to the thyroid gland (primary hypothyroidism). A *low or normal* TSH with low free T4 points instead to the pituitary or hypothalamus (central hypothyroidism), the pattern to remember when a depressed patient has low thyroid hormone but an inappropriately unraised TSH.

Euthyroid sick syndrome

In serious non-thyroidal illness (myocardial infarction, chronic kidney disease, anorexia nervosa, cirrhosis) peripheral T4-to-T3 conversion falls, giving a low T3 with a normal TSH. It is a confound, not thyroid disease, and must not be treated as hypothyroidism (Kaplan & Sadock 2024).

TRAP A low T3 with a normal TSH in serious non-thyroidal illness is euthyroid sick syndrome, a confound, not hypothyroidism; do not start levothyroxine for it.

CLINICAL ANCHOR

Serum TSH is the single most useful screen and belongs in the initial workup of any new mood, cognitive or treatment-resistant presentation, alongside electrolytes, fasting glucose and calcium. Psychiatric symptoms arising from an endocrinopathy will not remit until the endocrine disturbance is corrected, and may worsen if psychotropics are added over an untreated axis.

14.2 Subclinical hypothyroidism, overt hypothyroidism and depression

The commonest endocrine mimic of depression. Overt hypothyroidism (raised TSH, low free T4) classically produces depressed mood, apathy, psychomotor retardation and a cognitive picture of slowed processing with prominent *verbal memory* and working-memory deficits (Kaplan & Sadock 2024). **Subclinical hypothyroidism (SCH)**, defined as a raised TSH with a still-normal free T4, is the more exam-relevant entity because it is easy to miss: it too is associated with cognitive impairment (mainly under age 75) and with depressive symptoms, and even *euthyroid but thyroid-antibody-positive* patients show a higher prevalence of depression. Worldwide the commonest cause of hypothyroidism is iodine deficiency; where salt is iodised, autoimmune **Hashimoto thyroiditis** (with anti-thyroglobulin and anti-thyroid-peroxidase antibodies) predominates.

Why it matters for treatment. Both overt hypothyroidism and SCH predict a *poorer antidepressant response* in major depressive disorder, and correcting the thyroid state does not always fully lift the neuropsychiatric symptoms, so thyroid disease is a genuine cause of apparent treatment resistance (Kaplan & Sadock 2024). In ICD-11 the correct label when a mood syndrome is driven by thyroid disease is a *secondary mood syndrome* (mood disorder due to thyroid disease), cross-mapped to DSM-5-TR "depressive disorder due to another medical condition"; the diagnosis of primary major depressive disorder should be withheld until the axis is corrected.

CLINICAL ANCHOR

Two named traps in one axis. **Hashimoto encephalopathy** is a rare autoimmune presentation with altered sensorium, delusions, auditory hallucinations, catatonia, seizures and even coma; it is steroid-responsive, with 90 to 98% responding to corticosteroids, and is the reason antithyroid antibodies belong in an atypical psychosis or catatonia workup. **Postpartum thyroiditis** occurs in roughly 5 to 9% of women after delivery, may cycle through a hyperthyroid then hypothyroid phase, and is a recognised organic contributor to postnatal mood disturbance (Kaplan & Sadock 2024).

14.3 Lithium and the thyroid (and parathyroid)

Lithium is itself a common cause of hypothyroidism. Lithium concentrates in the thyroid and inhibits the iodination of tyrosine and, principally, the *release* of thyroid hormone from the gland, driving a compensatory rise in TSH and often a goitre. The examinable figures: after long-term lithium, roughly **20% of patients develop overt hypothyroidism with goitre and a further ~20% develop subclinical hypothyroidism** (Kaplan & Sadock 2024). Risk is higher in

women, in patients with pre-existing **antithyroid antibodies**, and with **longer exposure**. Lithium can also raise serum calcium and parathyroid hormone (lithium-associated hyperparathyroidism), an easily forgotten cause of lethargy, cognitive change and renal effects in a lithium-treated patient.

~20%	~20%	25%
OVERT HYPOTHYROIDISM ON LONG-TERM LITHIUM	SUBCLINICAL HYPOTHYROIDISM	EUTHYROID DEPRESSED WITH BLUNTED TSH-TO-TRH

PEARL

Lithium-induced hypothyroidism is *not* a reason to stop a working mood stabiliser: it is managed by adding levothyroxine and continuing lithium. This is why baseline and periodic TSH (and calcium) monitoring is a hard rule of lithium prescribing, and why a new depressive relapse in a euthymic lithium-treated patient should prompt a TSH before it prompts an antidepressant.

14.4 The TRH stimulation test and the blunted-TSH finding

A historical biological marker of depression. In the **TRH stimulation test (TRH infusion test)** a baseline TSH is taken, TRH is given intravenously, and TSH is remeasured over the following half hour. The *normal* response is a rise in TSH of **at least 5 mIU/mL above baseline within 30 minutes**. The response is *exaggerated* in hypothyroidism and *blunted* in hyperthyroidism (Kaplan & Sadock 2024).

The psychiatric result. Around **25% of euthyroid patients with major depression show a blunted TSH response to TRH**, a finding widely reported as a putative state marker of depression, alongside the observation that many depressed patients have a subtly activated HPT axis (raised CSF TRH, blunting of the normal nocturnal TSH surge). The prevailing interpretation is that this thyroid activation is a *compensatory* response to the depressive process rather than its cause (Kaplan & Sadock 2024). With the arrival of highly sensitive TSH assays in the 1990s the test fell out of routine clinical use and is now essentially a viva-and-theory topic, paired with the dexamethasone suppression test (DST) as the two classic, non-specific "biological markers" of depression.

COMMON TRAP

Do not confuse the two blunting phenomena. A *blunted TSH response to TRH* is the depression marker (about a quarter of euthyroid depressed patients) and is not diagnostic. A blunted response in a non-depressed patient with normal T4 instead defines *subclinical hyperthyroidism*. Neither the TRH test nor the DST is sensitive or specific enough to diagnose depression, which remains a clinical diagnosis.

14.5 T3 augmentation and thyroid hormone in mood disorder

Using the axis therapeutically. Two distinct thyroid strategies appear in mood-disorder pharmacology, and the examiner wants them kept apart. First, **liothyronine (T3) augmentation** of an antidepressant: adding low-dose T3 (typically about 25 to 50 micrograms daily) to an SSRI or a tricyclic can convert non-responders to responders in unipolar depression, and this benefit is

seen even in *euthyroid* patients, with a particular signal where treatment resistance coincides with subclinical hypothyroidism (Kaplan & Sadock 2024). T3 is preferred over T4 here because T3 is the active hormone and acts faster. In the STAR*D programme T3 augmentation and lithium augmentation were compared at an equivalent step, with T3 at least as well tolerated. Second, in *bipolar* disorder, **high-dose (supraphysiological) thyroxine** has been used adjunctively for rapid-cycling and refractory illness, a separate and more specialist use.

Mechanistic thread. Thyroid hormone interacts with the serotonin system that dominates antidepressant pharmacology: hypothyroidism reduces brain 5-HT synthesis, and thyroid hormone reduces the sensitivity of inhibitory 5-HT1A autoreceptors in the raphe while increasing 5-HT2 sensitivity, an arrangement that plausibly disinhibits serotonergic output and rationalises T3 augmentation (Kaplan & Sadock 2024).

MNEMONIC

"T3 to Treat, T4 to the Thinker"

Use **T3** to **treat** (augment antidepressants; active, fast, peripheral). Remember **T4** reaches **the thinker** (T4 is the main hormone crossing into the brain, converted locally to T3). This keeps the augmentation choice and the brain-delivery fact straight.

14.6 The HPG axis: GnRH to LH/FSH to the sex steroids

A pulsatile axis unlike the others. Hypothalamic **gonadotropin-releasing hormone (GnRH)** is released in *pulses*, and it is this pulsatility, not a steady level, that drives the anterior pituitary gonadotrophs to secrete **luteinising hormone (LH)** and **follicle-stimulating hormone (FSH)** (Kaplan & Sadock 2024). LH and FSH act on the gonads: in the ovary they drive follicular oestradiol and, after ovulation, corpus-luteum progesterone; in the testis LH drives Leydig-cell testosterone and FSH supports Sertoli-cell spermatogenesis. The sex steroids feed back on the hypothalamus and pituitary, mostly negatively, with the mid-cycle oestrogen surge providing the one physiological example of *positive* feedback (triggering the LH surge and ovulation). Continuous, non-pulsatile GnRH agonism paradoxically *suppresses* the axis by desensitising the gonadotroph, the basis of GnRH-agonist "chemical castration" used in paraphilic and hypersexuality disorders.

Why psychiatry cares. Gonadal steroids are neuroactive. Oestradiol modulates dopaminergic, serotonergic and glutamatergic transmission and increases dopamine availability; this underlies the **oestrogen-protection hypothesis** of schizophrenia, which explains the later mean onset in women, the symptomatic worsening during low-oestrogen phases of the cycle, and the second incidence peak at menopause (Matuszewska 2023). Progesterone's metabolite **allopregnanolone** is a positive allosteric modulator of GABA-A receptors and dampens the HPA axis, linking the gonadal and stress axes and setting up the perinatal pharmacology below.

CLINICAL ANCHOR

The oestrogen-protection idea is now a therapeutic target. Adjunctive **selective oestrogen-receptor modulators (SERMs)**, notably *raloxifene*, have shown benefit for positive, negative and cognitive symptoms in some trials of postmenopausal women with schizophrenia, exploiting brain-oestrogenic action while avoiding the feminising and thromboembolic risks of oestrogen itself (Matuszewska 2023). Results are mixed, so this remains adjunctive and investigational rather than standard care.

14.7 Reproductive-cycle mood syndromes: PMDD, perinatal, menopause

Three windows where HPG shifts drive psychiatric risk. The shared principle is *sensitivity to change* in gonadal steroids rather than an abnormal absolute level.

Premenstrual dysphoric disorder (PMDD)

A luteal-phase disorder of affective, irritable and somatic symptoms that remit within a few days of menses, coded in ICD-11 in the gynaecological chapter and cross-listed, and given a discrete diagnosis in DSM-5-TR. Circulating oestrogen and progesterone are *normal*; the disorder reflects an abnormal central sensitivity to normal luteal-phase falls in these steroids and their neuroactive metabolites. SSRIs are first-line and, unusually, work rapidly and can be given *luteal-phase only*, consistent with a serotonergic rather than a slow neurotrophic mechanism; ovulation suppression is a second-line option.

Perinatal (postpartum) depression

The postpartum period carries the highest lifetime risk for a new or recurrent mood episode. The precipitous *fall* in oestrogen and progesterone (and in allopregnanolone) at delivery is the leading endocrine hypothesis, which motivated the allopregnanolone-based drugs below. Postpartum thyroiditis (14.2) is an organic differential that must be excluded.

Perimenopause and menopause

The menopausal transition, with its erratic then declining oestradiol, is a window of raised risk for depressive episodes and, in women with psychotic illness, the second peak of schizophrenia incidence (Matuszewska 2023). Transdermal oestradiol has antidepressant evidence for perimenopausal (but not established postmenopausal) depression, again pointing to change-sensitivity.

CLINICAL ANCHOR

The allopregnanolone story is the modern, examinable payoff of HPG-HPA cross-talk. **Brexanolone**, an intravenous allopregnanolone, and **zuranolone**, an oral neuroactive-steroid GABA-A positive modulator, are approved for postpartum depression with a rapid onset over days, directly replacing the neurosteroid that crashes after delivery. This is the clearest example of reproductive endocrinology yielding a novel psychiatric drug class.

14.8 Prolactin and antipsychotics: recognition and management

The one anterior-pituitary hormone under tonic dopamine inhibition. Prolactin is unique in being held *down* by hypothalamic dopamine acting on lactotroph D2 receptors (dopamine is the physiological prolactin-inhibiting factor). Any drug that blocks D2 in the tuberoinfundibular pathway therefore *raises* prolactin. The high offenders are the potent D2 blockers that bind

tightly and do not dissociate rapidly: **risperidone, paliperidone, amisulpride** and the typical antipsychotics (Maudsley 2021). The prolactin-sparing drugs are those that are partial agonists or dissociate rapidly from D2: **aripiprazole, brexpiprazole, cariprazine, quetiapine and clozapine**. Note that transient physiological rises also follow a generalised seizure, which is used clinically to distinguish an epileptic seizure from a psychogenic non-epileptic attack.

Recognition. Symptomatic hyperprolactinaemia causes *menstrual irregularity or amenorrhoea, galactorrhoea, gynaecomastia, reduced libido and sexual dysfunction*, and, through hypogonadism, longer-term **reduced bone mineral density**. Before ascribing a raised prolactin to the drug, exclude pregnancy, primary hypothyroidism (raised TRH also drives prolactin), a prolactinoma when the level is very high, and laboratory *macroprolactin*. Antipsychotics typically produce modest elevations; a markedly high prolactin unexplained by dose warrants pituitary imaging.

Management. The rational sequence is: confirm the elevation is symptomatic and drug-attributable, then either *reduce the dose*, *switch to a prolactin-sparing agent*, or add low-dose **aripiprazole**, whose partial D2 agonism at the lactotroph lowers antipsychotic-induced prolactin in placebo-controlled trials (Maudsley 2021). A dopamine agonist such as cabergoline is a last resort in psychosis because it can worsen the illness. Asymptomatic, modest elevations may simply be monitored.

PROLACTIN EFFECT	ANTIPSYCHOTICS	MECHANISM NOTE
High prolactin-raising	Risperidone, paliperidone, amisulpride, typicals (e.g. haloperidol)	**Potent, persistent D2 blockade; poor CNS-selectivity**
Prolactin-sparing	Aripiprazole, brexpiprazole, cariprazine	D2 partial agonism at the lactotroph
Prolactin-sparing	Quetiapine, clozapine	Low affinity and rapid D2 dissociation

Antipsychotics ranked by prolactin liability. The discriminator is D2 pharmacology: potent persistent antagonists raise prolactin, partial agonists and loose binders spare it.

HOLD THIS

Dopamine is the physiological prolactin-inhibiting factor, so any tuberoinfundibular D2 blocker raises prolactin. The rational fix is a prolactin-sparing switch or add-on aripiprazole (D2 partial agonism at the lactotroph), not a dopamine agonist.

INDIA

Risperidone is among the most-prescribed antipsychotics in Indian public and private practice on cost grounds, so antipsychotic hyperprolactinaemia is common and frequently missed, especially amenorrhoea and sexual dysfunction that patients do not volunteer. Switching to, or augmenting with, aripiprazole is usually affordable here and is the pragmatic first move; cabergoline needs cautious specialist use given psychosis-worsening risk.

14.9 Growth hormone and the clonidine challenge test

A probe of central noradrenergic (alpha-2) function. Growth hormone (GH) is released from the anterior pituitary under dual hypothalamic control: **growth hormone-releasing hormone (GHRH)** stimulates it and **somatostatin** inhibits it. GH secretion is driven partly by central alpha-2 adrenoceptor activation, which is the basis of the challenge test. In the **clonidine challenge test**, the alpha-2 agonist clonidine is given and the GH rise is measured; a *blunted GH response to clonidine* is the most consistent neuroendocrine finding in **major depression** and is interpreted as evidence of reduced sensitivity of post-synaptic hypothalamic **alpha-2 adrenoceptors** (Kaplan & Sadock 2024). A similar blunting has been reported in generalised anxiety disorder and panic disorder.

Reading the result. Like the TRH and dexamethasone tests, the clonidine-GH test is a research and viva instrument, not a clinical diagnostic: it is neither sensitive nor specific enough to diagnose depression, but it is the standard example when a question asks how the noradrenergic system is probed pharmacologically, and it complements the serotonergic fenfluramine challenge (which measures a prolactin or cortisol response). Growth-hormone regulation is also disturbed in eating disorders, where chronic undernutrition produces GH resistance with high GH but low IGF-1.

> **COMMON TRAP**
>
> Match each challenge test to the transmitter it probes. *Clonidine to GH* probes noradrenergic alpha-2 function and is blunted in depression; *fenfluramine to prolactin/cortisol* probes serotonergic function; *TRH to TSH* probes the thyroid axis; *dexamethasone to cortisol* probes HPA feedback. Confusing the agonist with the axis it interrogates is the classic marks-losing error here.

15 · Circadian rhythms and melatonin

A clock built from a gene loop, wired to the eye, read out through a hormone. The circadian system is the one piece of "basic" neuroscience the paper can turn into clinical questions from three directions at once: molecular biology (the clock-gene feedback loop), neuroendocrinology (melatonin and the cortisol rhythm), and psychopharmacology (the melatonin-agonist antidepressants and hypnotics). The examinable spine is a single causal chain. A self-sustaining transcription-translation loop in the suprachiasmatic nucleus keeps time with a near-24-hour period; light, sensed by a specialised retinal pathway, resets it each day; the reset clock drives an output rhythm of melatonin, cortisol and core temperature; and when that output drifts out of phase with the environment or the sleep-wake schedule, mood and psychotic disorders track the disruption. Get the loop, the light input and the melatonin output straight and the clinical material (seasonal depression, the bipolar phase-advance, agomelatine, ramelteon, tasimelteon) falls out of it.

Two framing facts to carry into the detail. First, the endogenous human period is not exactly 24 hours: free-running, the suprachiasmatic clock runs at roughly 24.2 hours, so it must be actively re-entrained daily, and the direction a person's clock naturally drifts (long period gives an

evening "owl", short period gives a morning "lark") is largely genetic (Kaplan & Sadock 2024). Second, melatonin is biochemically continuous with serotonin (it is synthesised from it), which is why the serotonergic and circadian systems are examined together and why the one drug that sits at their junction, agomelatine, is both a melatonin agonist and a 5-HT2C antagonist (Stahl 2021). This topic cross-references the the Functional Neuroanatomy & Neurophysiology notes material on sleep physiology and the two-process model of sleep regulation.

15.1 The suprachiasmatic nucleus: the master pacemaker

Location and anatomy. The primary circadian oscillator in mammals is the **suprachiasmatic nucleus (SCN)**, a paired nucleus in the anterior hypothalamus lying immediately dorsal to the optic chiasm (the name is literally "above the chiasm"). Its neurons are among the smallest in the brain, densely packed with short, sparsely branched dendrites. The SCN is anatomically divided into a **core** (ventral, calbindin-positive, receiving the main retinal input) and a surrounding **shell** (Kaplan & Sadock 2024).

Master and slave clocks. The circadian system is a hierarchy. The SCN is the master oscillator, but near-identical molecular clocks run autonomously in peripheral tissues (liver, kidney, lung, heart) and in other brain regions; the SCN's job is to keep these **peripheral oscillators** synchronised to each other and to environmental time. A key exam point is that the SCN is self-sustaining: an isolated SCN neuron, or even a dissociated SCN culture, continues to generate a circadian rhythm with no external cue, proving the clock is *endogenous* and not merely a passive response to the light-dark cycle.

15.2 The molecular clock: the transcription-translation feedback loop

The clock is a gene circuit that takes about a day to complete one cycle. The mammalian clockwork is a set of interlocking **transcription-translation feedback loops (TTFL)** built from a handful of core clock genes. The **positive limb** is a heterodimer of two transcriptional activators, **CLOCK** and **BMAL1**. This CLOCK-BMAL1 complex binds E-box enhancer elements in the promoters of the **Period (PER1, PER2, PER3)** and **Cryptochrome (CRY1, CRY2)** genes and drives their transcription.

The negative limb. The PER and CRY proteins accumulate in the cytoplasm, dimerise, and translocate back into the nucleus, where they *inhibit their own transcription* by repressing the CLOCK-BMAL1 complex that made them (Kaplan & Sadock 2024). As PER and CRY proteins are then degraded, the repression lifts, CLOCK-BMAL1 becomes active again, and the cycle restarts. This delayed negative feedback is the oscillator, and the delays (transcription, translation, protein complex formation, nuclear entry, degradation) are what set the roughly 24-hour period.

The stabilising secondary loop and post-translational timing. CLOCK-BMAL1 also drives the nuclear receptor genes **REV-ERBα** and **ROR**, whose products respectively repress and activate BMAL1 transcription; this second interlocked loop confers robustness and precision. Crucially, the period is fine-tuned not just by transcription but by **post-translational modification**: phosphorylation of PER proteins by **casein kinase 1 (isoforms epsilon and delta)** governs their

nuclear entry and degradation rate, so a mutation here shortens the whole period. This is the mechanism of familial advanced sleep phase syndrome and the molecular reason casein kinase surfaces in exam stems.

MNEMONIC

"CB builds it, PC breaks it"

CLOCK and **B**MAL1 (positive limb) build the loop by activating transcription; **P**ER and **C**RY (negative limb) break it by repressing their own makers. The two pairs chase each other around a roughly 24-hour cycle. Bolt on the secondary loop (REV-ERB and ROR set BMAL1) and the tuner (casein kinase phosphorylates PER) and you have the whole clockwork.

HOLD THIS

The clock is a transcription-translation loop: CLOCK-BMAL1 build it, PER-CRY break it, over roughly 24 hours. Melatonin is biochemically made from serotonin, which is why agomelatine (MT1/MT2 agonist plus 5-HT2C antagonist) sits at their junction.

15.3 Light entrainment: the retinohypothalamic tract and melanopsin

The photic input pathway. Because the endogenous period is not exactly 24 hours, the clock must be reset daily, and the dominant resetting cue is light. Light is transduced not by rods and cones for this purpose but by a distinct population of **intrinsically photosensitive retinal ganglion cells (ipRGCs)** that express the photopigment **melanopsin** and are maximally sensitive to short-wavelength **blue light** (around 480 nm). These cells project directly to the SCN via the **retinohypothalamic tract (RHT)**, whose neurotransmitter is **glutamate** (Kaplan & Sadock 2024).

Why blue light and screens matter clinically. The blue-light sensitivity of melanopsin is the mechanistic basis for the sleep-disrupting effect of evening screen exposure and for the therapeutic use of bright light and blue-enriched light. It also explains why totally blind individuals with no light perception lose entrainment: roughly 50 to 70 percent develop **non-24-hour sleep-wake rhythm disorder**, their clock free-running at its intrinsic period so their sleep drifts progressively later each day (Kaplan & Sadock 2024).

15.4 Zeitgebers: photic and non-photic time cues

Zeitgeber

German "time-giver": any external cue that entrains (resets) the endogenous clock to the 24-hour environmental day. The clock without zeitgebers free-runs at its intrinsic near-24.2-hour period.

Photic zeitgeber

Light, the strongest and dominant cue, acting through the melanopsin-RHT pathway to the SCN.

Non-photic zeitgebers

Feeding and meal timing, physical exercise and locomotor activity, social interaction (the basis of "social zeitgebers"), ambient temperature, and certain drugs (amphetamines). Non-photic signals reach the SCN largely via the thalamus and the midbrain raphe (Kaplan & Sadock 2024).

Entrainment

The process by which a zeitgeber locks the endogenous clock to the external cycle, holding a stable phase relationship rather than letting it free-run.

The phase-response curve. The direction in which a cue shifts the clock depends on *when* in the circadian cycle it arrives, described by the **phase-response curve (PRC)**. For light, exposure in the early biological night (evening) produces a **phase delay** (pushes the clock later), whereas exposure in the late night or early morning produces a **phase advance** (pulls it earlier). Melatonin has an almost mirror-image PRC: evening melatonin advances the clock, morning melatonin delays it. This is the pharmacological logic behind timing light and melatonin to treat delayed and advanced phase disorders and jet lag, and it is a favourite exam discriminator.

RULE **Evening light delays the clock, morning light advances it; melatonin has the mirror-image curve.** Evening melatonin advances, morning melatonin delays.

15.5 Melatonin synthesis: from serotonin in the pineal gland

The biosynthetic pathway. Melatonin (**N-acetyl-5-methoxytryptamine**) is synthesised in the pinealocytes of the **pineal gland** from serotonin in two enzymatic steps. Serotonin is first N-acetylated by **arylalkylamine N-acetyltransferase (AANAT)**, the rate-limiting enzyme whose activity rises steeply at night, to N-acetylserotonin; this is then O-methylated by **acetylserotonin O-methyltransferase (ASMT, formerly HIOMT)** to melatonin (Kaplan & Sadock 2024). Adding an acetyl group to serotonin's amine and a methoxy group in place of its hydroxyl makes melatonin markedly more lipophilic than serotonin, so it crosses the blood-brain barrier and the placenta freely and is not stored but released as fast as it is made.

The neural drive is noradrenergic and dark-gated. The SCN controls melatonin through a multisynaptic efferent path: SCN to the hypothalamic paraventricular nucleus, then down to the spinal cord, out to the **superior cervical ganglion**, and finally by sympathetic fibres to the pineal. At the pinealocyte, **noradrenaline acts on beta-1 and alpha-1 adrenergic receptors** to switch on AANAT and drive melatonin synthesis. Because the SCN *inhibits* this pathway during the day and releases it at night, **melatonin synthesis rises when SCN activity falls**: light suppresses it, darkness permits it.

PEARL

Melatonin is the body's chemical signal for "biological night", not for sleep as such. It marks darkness and the timing of the internal clock to every organ, which is why it works better as a chronobiotic (a clock-shifter, taken in the early evening to advance the clock) than as a pure hypnotic. This distinction, phase-shifting versus sedating, separates melatonin and ramelteon from the benzodiazepine-receptor hypnotics.

15.6 Melatonin dynamics and the DLMO marker

The nocturnal profile. Plasma melatonin is low by day (around 40 pmol/L) and high at night, peaking near 2 to 3 a.m. (around 400 pmol/L), a roughly tenfold nocturnal rise, then falling to baseline by morning just as cortisol peaks (Kaplan & Sadock 2024). Its receptors are the G-protein-coupled **MT1** and **MT2** subtypes, both densely expressed in the SCN itself: broadly,

MT1 mediates the acute suppression of SCN firing (the sleep-promoting, "opening the gate" effect) and MT2 mediates the phase-shifting (clock-resetting) effect, a mechanistic pairing worth naming.

Dim-light melatonin onset. The single most useful clinical marker of circadian phase is the **dim-light melatonin onset (DLMO)**, the evening time at which melatonin begins to rise measured under dim light (bright light would suppress it). DLMO normally precedes habitual sleep onset by about 2 to 4 hours; a *late* DLMO indicates a delayed clock (as in delayed sleep phase and much of adolescent and depressive presentation) and an *early* DLMO a phase-advanced clock (Kaplan & Sadock 2024).

15.7 Circadian output rhythms and the two-process model of sleep

What the clock drives. The SCN imposes a circadian rhythm on melatonin, on **core body temperature** (which reaches its nadir in the early morning, roughly 5 to 6 a.m., just before natural waking), and on the **HPA axis**: cortisol peaks in the early morning (about 6 to 8 a.m.) via an SCN to paraventricular-nucleus to CRH to ACTH pathway, and this early-morning cortisol surge is a robustly examinable output rhythm. The temperature minimum is the reference point around which sleep is best timed.

Interaction with the sleep homeostat (cross-reference the Functional Neuroanatomy & Neurophysiology notes). Sleep timing is the product of two processes (Borbely's model): **Process S**, the homeostatic sleep drive that builds with time awake (adenosine accumulation is the leading substrate, and caffeine promotes wakefulness by antagonising adenosine), and **Process C**, the circadian drive for arousal that the SCN steadily raises across the day to oppose the mounting sleep pressure, peaking in the evening "wake-maintenance zone" before melatonin rises and it wanes. Chronotype (lark versus owl) is driven almost entirely by Process C, not Process S, because the homeostat is similar between people of similar age (Kaplan & Sadock 2024). See the the Functional Neuroanatomy & Neurophysiology notes sleep-physiology topic for sleep architecture and the two-process model in full.

15.8 Circadian disruption in depression and bipolar disorder

Circadian disturbance is a near-universal feature of mood disorder, and probably not just a symptom of it. In **depression** the most consistent circadian findings are a **phase advance** of several rhythms, classically expressed as *early-morning awakening* and a *shortened REM latency*, together with lower and phase-shifted nocturnal melatonin, loss of the normal nocturnal fall in core temperature, and the diurnal mood variation (worse in the morning) of melancholia. The **phase-advance hypothesis** of depression is the classical formulation the exam wants.

Bipolar disorder. Here circadian instability is arguably a trait, not just a state. Sleep loss is one of the most reliable triggers of a switch into mania, and mood episodes cluster with disruption of the sleep-wake and social rhythm. Polymorphisms in clock genes (including CLOCK, BMAL1, PER, CRY, TIMELESS, NR1D1 and CSNK1 isoforms) are associated with bipolar disorder, illness course and treatment response (Bunney 2015). Two mechanistic anchors are high-yield: the **ClockΔ19 mutant mouse** shows a mania-like phenotype (hyperactivity, reduced sleep,

increased reward-seeking) driven by raised dopaminergic activity in the ventral tegmental area, a phenotype normalised by lithium; and **lithium inhibits GSK-3beta**, an enzyme that regulates the clock (it phosphorylates clock proteins and sets the period), giving a molecular link between the circadian system and the mood-stabilising action of lithium.

CLINICAL ANCHOR

Interpersonal and Social Rhythm Therapy (IPSRT) operationalises this biology for bipolar disorder: it targets the regularity of daily social zeitgebers (wake time, meals, activity, social contact) on the premise that stabilising social rhythms stabilises the underlying circadian clock and so reduces relapse. It is the therapy the exam pairs with the circadian model of bipolar disorder.

15.9 Seasonal affective disorder and the seasonal-pattern specifier

Nomenclature. What older texts call **seasonal affective disorder (SAD)** is, in current nosology, not a standalone diagnosis but a course specifier applied to a recurrent mood disorder: DSM-5-TR uses **"with seasonal pattern"** for major depressive disorder (recurrent) and for bipolar disorder, requiring a regular temporal relationship between episode onset and a particular time of year, most typically winter depression remitting in spring (DSM-5-TR 2022). ICD-11 similarly captures this as a seasonal pattern qualifier of a recurrent depressive or bipolar disorder rather than a separate entity.

Proposed mechanisms. The leading accounts are circadian: the **phase-shift hypothesis** holds that the shorter winter photoperiod delays the circadian clock relative to the sleep-wake cycle (a phase delay in most patients), which is why morning bright light, which phase-advances the clock, is therapeutic. Reduced light also lengthens the duration of nocturnal melatonin secretion in winter, and serotonergic hypofunction is implicated.

CLINICAL ANCHOR

Bright-light therapy is first-line for seasonal winter depression: typically **10,000 lux for about 30 minutes on waking**, timed in the early morning to phase-advance a delayed clock. Response is often faster than to antidepressants (within a week). The main cautions are precipitation of hypomania or mania in bipolar patients and, rarely, retinal considerations.

15.10 Chronotherapeutics: light, wake therapy and exogenous melatonin

Non-pharmacological. **Bright-light therapy** is used for seasonal depression, delayed sleep phase (morning light) and, in the evening, for advanced sleep phase, always exploiting the light PRC. **Total or partial sleep deprivation (wake therapy)** produces a rapid but transient antidepressant response in a substantial minority of patients, often lost after the next night's sleep; it is combined with sleep-phase advance and light to sustain the effect. **Chronotherapy** proper, the systematic timed shifting of the sleep schedule, treats circadian sleep-wake disorders.

Exogenous melatonin. Used in low physiological doses (often 0.5 to 5 mg) as a **chronobiotic**, timed in the early evening to phase-advance a delayed clock (delayed sleep phase disorder, jet lag travelling eastward, non-24 disorder), and as a mild hypnotic in older adults where endogenous

melatonin is reduced. A prolonged-release preparation is licensed for insomnia in adults over 55 in several jurisdictions; melatonin is also widely used for insomnia in children with neurodevelopmental disorders (Maudsley Prescribing Guidelines).

15.11 Melatonin receptor agonists: ramelteon, agomelatine, tasimelteon

Three synthetic agonists, each defined by its receptor profile and its indication. All are structural analogues of melatonin, all are highly lipophilic, cross the blood-brain barrier, are metabolised principally by **CYP1A2** (a major interaction caveat: fluvoxamine, a potent CYP1A2 inhibitor, dramatically raises their levels and is contraindicated or cautioned with all three), and all have short elimination half-lives of under about two hours (Kaplan & Sadock 2024).

AGENT	RECEPTOR ACTION	LICENSED USE	KEY CAUTION
Ramelteon	MT1 / MT2 agonist	**Sleep-onset insomnia (no scheduled-drug / abuse liability)**	Avoid with fluvoxamine (CYP1A2)
Agomelatine	**MT1 / MT2 agonist plus 5-HT2C antagonist**	Major depressive disorder	Hepatotoxicity: monitor LFTs; contraindicated in hepatic impairment
Tasimelteon	MT1 / MT2 agonist	**Non-24-hour sleep-wake rhythm disorder (esp. totally blind)**	CYP1A2 / CYP3A4 metabolism
Melatonin (prolonged-release)	MT1 / MT2 agonist	Insomnia in adults over 55; paediatric neurodevelopmental insomnia	Generally well tolerated

The four melatonergic agents compared: the discriminators are agomelatine's added 5-HT2C antagonism (which gives it antidepressant efficacy and is why it is the one used for depression rather than insomnia) and tasimelteon's niche in non-24 disorder.

Agomelatine, the key drug. Its combination of MT1/MT2 agonism with **5-HT2C antagonism** is what distinguishes it: the 5-HT2C blockade disinhibits frontocortical dopamine and noradrenaline release, giving antidepressant and pro-sleep effects, while resynchronising disrupted circadian rhythms. It is notable for being relatively free of the sexual dysfunction, weight gain and discontinuation effects of SSRIs, but carries a dose-related risk of **hepatotoxicity** that mandates baseline and periodic liver function tests and precludes use in hepatic impairment (Stahl 2021).

COMMON TRAP

Do not lump the melatonin agonists with the benzodiazepine-receptor hypnotics. Ramelteon and melatonin act on MT1/MT2 with *no* action at the GABA-A benzodiazepine site, so they carry no meaningful dependence, tolerance, abuse or next-day psychomotor liability, and are not scheduled drugs. Their trade-off is a modest hypnotic effect confined largely to sleep *onset*. Agomelatine is an antidepressant, not a hypnotic, and its examinable hazard is hepatic, not sedative.

INDIA

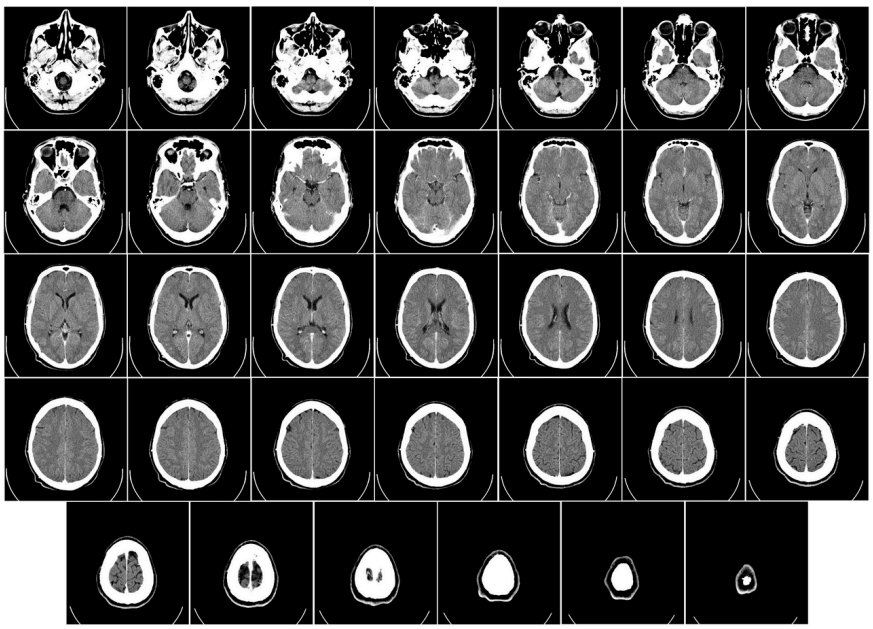
Melatonin is inexpensive and widely available over the counter in India and is a pragmatic first choice for jet lag, delayed sleep phase and adjunctive insomnia. Agomelatine is marketed and used for depression, but the mandatory liver-function monitoring (baseline and periodic) is easily neglected in practice and must be counselled and arranged, particularly given variable follow-up. Ramelteon and tasimelteon are far less commonly available.

Neuroimaging

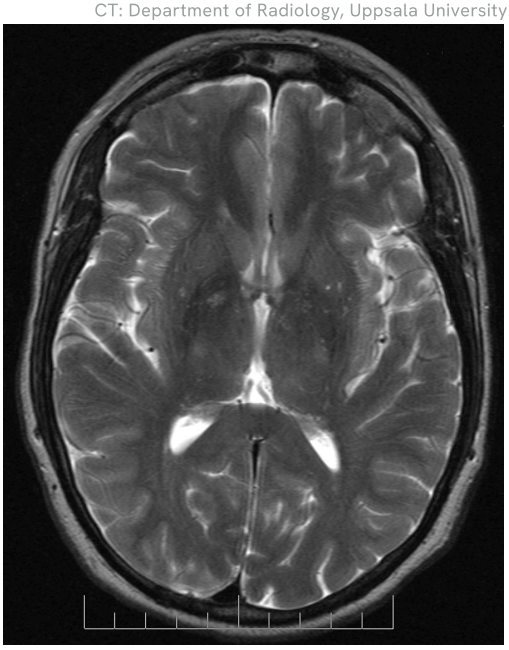
16 · Structural imaging (CT/MRI) findings in psychiatric disorders

Start at the scanner, not the syndrome. Before any disorder-specific finding means anything, you have to be able to look at a film and say *what* it is and *why it looks the way it does*. Structural imaging is the layer that shows the machinery the Functional Neuroanatomy & Neurophysiology notes mapped: it does not measure activity (that is the functional topic next door), it measures shape, tissue, and gross lesion. In psychiatry its role is almost entirely one of **exclusion** and correlation: no structural scan diagnoses a primary psychiatric disorder, but a scan can unmask the organic mimic hiding inside a first-episode presentation, and group-level structural signatures (enlarged ventricles in schizophrenia, white-matter hyperintensities in late-life depression, medial-temporal atrophy in Alzheimer disease) are examined precisely because they are reproducible.

The single most examinable skill is the one most easily skipped: telling a **CT** from an **MRI** at a glance, and knowing what is bright and dark on each MRI sequence and why. Get that physics right and every disorder finding below reads itself off the film. This topic is the imaging deep home for this material; it cross-references the Functional Neuroanatomy & Neurophysiology structures (hippocampus, ventricles, frontal and temporal cortex) rather than re-teaching them.



CT: Department of Radiology, Uppsala University Hospital, CC0, via Wikimedia Commons



MRI (T2): Afiller, CC BY-SA 3.0, via Wikimedia Commons

Fig 2.6 What a normal CT and MRI actually look like. On the CT series (top, skull base to vertex), bone is bright white, air and CSF are dark, and grey-white differentiation is modest; CT is fast and is the emergency scan for acute blood and bone. On the T2 MRI (below), CSF is bright, grey and white matter separate cleanly, and the soft-tissue detail is far greater; MRI carries the psychiatric yield. Read this real appearance alongside the sequence signal grid in Fig 2.7.

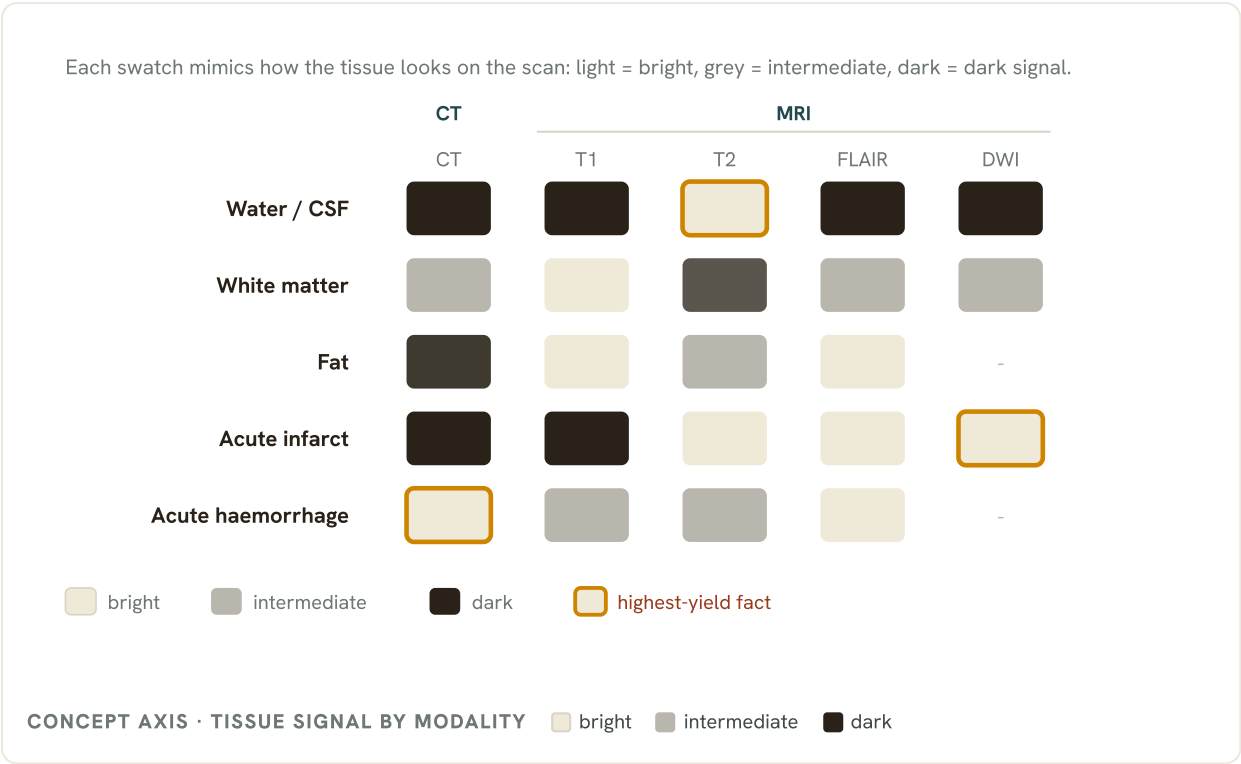


Fig 2.7 How to read the sequences at a glance. Anchor on water: CSF is bright only on T2, and FLAIR is a T2 with the CSF signal suppressed (so a periventricular lesion stands out). Fat is bright on T1. Acute haemorrhage is bright (hyperdense) on CT, which is why CT is the emergency scan; an acute infarct is bright on DWI before it shows anywhere else. The two one-liners: "water is white on T2" and "acute stroke is bright on DWI".

16.1 Telling a CT from an MRI at a glance, and in principle

The physics decides the picture. CT (computed tomography) is X-ray based: a rotating X-ray tube measures how much tissue attenuates the beam, and a voxel's brightness is its **density**, expressed in Hounsfield units. It uses ionising radiation, is fast (seconds), is widely available and cheap, and is the workhorse of the emergency setting. Dense things stop X-rays and appear white (**hyperdense**): bone and the skull vault, fresh clotted blood, and calcification. Water-like things appear dark (**hypodense**): CSF, oedema, and old infarct. On a plain CT the skull is brilliant white, CSF in the ventricles is black, and grey-white differentiation is only modest.

MRI (magnetic resonance imaging) uses no ionising radiation. A strong magnetic field aligns hydrogen protons and radiofrequency pulses tip them; the signal comes from how protons relax back (the T1 and T2 relaxation times) and from proton (water) density. This gives superb **soft-tissue contrast** and multiplanar imaging without moving the patient. The trade-off: it is slow, expensive, less available, contraindicated with many ferromagnetic implants and pacemakers, and cortical *bone* gives almost no signal (few mobile protons), so the skull is dark rather than white. The instant tell at the console: **if the skull is bright white, it is CT; if the skull is dark, it is MRI.**

PEARL

The one-line discriminator to carry into the exam and the ward: *bone bright, blood bright, fast, radiation, emergency* is CT; *bone dark, exquisite soft tissue, slow, no radiation, elective and definitive* is MRI. CT answers "is there acute blood or a fracture, right now?"; MRI answers "what exactly is the soft-tissue lesion?"

16.2 When each modality is chosen

The choice is not preference, it is the clinical question and the clock. **CT is chosen** when speed and blood detection matter: acute head trauma, suspected acute intracranial haemorrhage, the confused or newly seizing patient in the emergency room, screening before lumbar puncture, and any patient who cannot have an MRI (pacemaker, certain metallic implants, agitation, instability). Acute haemorrhage is the classic CT strength: fresh blood is reliably hyperdense on CT from the first minutes, whereas it is deceptively subtle on standard early MRI. **MRI is chosen** for the elective, definitive soft-tissue question: characterising a mass, demyelination, mesial temporal sclerosis, subtle cortical dysplasia, posterior-fossa and brainstem lesions (where CT bone-hardening artefact obscures the view), and the great majority of the psychiatric organic workup, where the yield is in grey-matter volume, white-matter change, and small structural lesions that CT would miss.

FEATURE	CT	MRI
Physical basis	X-ray attenuation (density, Hounsfield units)	**Proton relaxation in a magnetic field (T1/T2/proton density)**
Ionising radiation	**Yes**	No
Speed / availability	**Seconds; ubiquitous, cheap**	Minutes; scarcer, expensive
Skull / cortical bone	**Bright white (hyperdense)**	Dark (little signal)
Acute haemorrhage	**Reliably hyperdense from the outset (modality of choice)**	Subtle early on standard sequences
Soft-tissue / grey-white contrast	Modest	**Superb; multiplanar**
Best clinical question	**"Acute blood or fracture, now?"**	"What exactly is the soft-tissue lesion?"
Main contraindications	Radiation dose (pregnancy, repeated scans)	**Pacemaker, ferromagnetic implants, uncooperative patient**

The exam discriminator is the two-line summary: CT is the fast, radiation-based, blood-and-bone modality for the emergency; MRI is the slow, radiation-free, soft-tissue modality for the definitive elective workup that carries the psychiatric yield.

16.3 The MRI sequences, made concrete: what is bright and dark, and why

This is the load-bearing table of the topic. An MRI is not one image; it is a set of sequences, each weighted to make a different tissue property the source of contrast. The examiners want you to state, for a given sequence, what appears bright and what appears dark, and the single physical

reason. Anchor everything to **CSF**: it is the reference tissue that flips brightness across sequences, and reading CSF tells you which sequence you are looking at.

T1-weighted (anatomy)

The anatomy sequence. **Fat is bright, CSF is dark; white matter is brighter than grey matter** (myelin is fat-rich). Grey-white boundaries and gross morphology are crisp, so T1 is the volumetric and structural workhorse (and the sequence on which gadolinium contrast enhances). Memory hook: on T1 the picture looks "anatomical", water is black, and fat is white.

T2-weighted (pathology / water)

The pathology sequence. **Water is bright: CSF is bright, and most pathology (oedema, gliosis, demyelination, tumour, inflammation) is bright** because pathology increases tissue water. Grey matter is brighter than white matter (the reverse of T1). Memory hook: "WW2", *Water is White on T2*; if it is wet or diseased, it lights up.

FLAIR (fluid-attenuated inversion recovery)

A T2 image with the bright CSF signal deliberately nulled (inverted out). **CSF is dark, but pathology stays bright.** This is the trick that makes periventricular and cortical lesions visible: on plain T2 a bright lesion next to bright CSF is camouflaged; on FLAIR the CSF goes black and the lesion stands out. FLAIR is the go-to for white-matter hyperintensities, periventricular MS plaques, and cortical/juxtacortical lesions.

DWI (diffusion-weighted imaging)

The acute-ischaemia sequence. It maps the random (Brownian) motion of water. In acute infarction, cytotoxic oedema restricts water diffusion, so the infarct is **bright on DWI and dark on the ADC map** (restricted diffusion) within minutes to hours, long before CT or conventional MRI changes. "Bright on DWI, dark on ADC" is the signature of acute stroke; it also lights up the abscess core and, classically, cortical ribboning in Creutzfeldt-Jakob disease.

DTI (diffusion tensor imaging)

An extension of diffusion imaging that measures the *direction* of water diffusion. In white-matter tracts water diffuses preferentially along the axon (anisotropic diffusion), quantified as **fractional anisotropy (FA)**. DTI indexes the integrity and myelination of tracts and enables tractography; reduced FA is the standard readout of disrupted connectivity (Kaplan & Sadock 2024).

TISSUE / LESION	T1	T2	FLAIR	DWI (ACUTE)
CSF (ventricles, sulci)	Dark	**Bright**	Dark (suppressed)	Dark
White matter	**Bright (brighter than grey)**	Darker than grey	Intermediate	Intermediate
Grey matter	Intermediate (darker than white)	**Brighter than white**	Intermediate	Intermediate
Fat (scalp, marrow)	**Bright**	Intermediate/bright	Bright	Variable
Oedema / most pathology	Dark	**Bright**	Bright	Variable

TISSUE / LESION	T1	T2	FLAIR	DWI (ACUTE)
White-matter hyperintensity, MS plaque	Dark to iso	Bright	**Bright with CSF nulled (best seen)**	Usually iso
Acute infarct (cytotoxic oedema)	Iso early	Bright (hours later)	Bright	**Bright (restricts within minutes; dark on ADC)**

Read the table by anchoring on CSF: bright CSF means T2, dark CSF with bright lesions means FLAIR, dark CSF with bright fat and bright white matter means T1. The two highest-yield one-liners are "Water is White on T2" and "acute stroke is bright on DWI, dark on ADC".

MNEMONIC

WW2, and "T1 = anatomy, fat white; FLAIR = T2 minus water"

WW2 fixes the pivot: *Water (CSF) is White on T2*. From there T1 is simply the inverse for water (CSF black) and the sequence where *fat is white and white matter is white*, i.e. the anatomy scan. FLAIR is "T2 with the water taken out", so CSF turns black while disease stays bright. DWI is the odd one out and easiest to remember by its job: the acute-stroke sequence.

HOLD THIS

Bright skull means CT (blood and bone, the emergency); dark skull means MRI (soft tissue, the definitive scan). Anchor the sequences on water: Water is White on T2, FLAIR is T2 with the CSF nulled, acute stroke is bright on DWI.

16.4 When to image the psychiatric patient: red flags and the organic workup

Routine structural imaging is *not* indicated for every psychiatric presentation; the yield in an otherwise typical young patient with a classic picture is low. Imaging earns its place when the presentation carries features that raise the pre-test probability of an organic lesion. The examinable trigger list is the **first-episode psychosis red flags** and the broader organic-workup indications.

First-episode psychosis red flags for imaging

Atypical age of onset (very young or new onset in later life), any focal neurological sign, seizures, an abrupt or fluctuating course with clouding of consciousness (suggesting delirium rather than a primary psychosis), headache, rapid cognitive decline, focal or catatonic features, or any finding pointing to a space-occupying, inflammatory, or vascular cause.

Broader organic-workup indications

New cognitive impairment or suspected dementia (structural imaging is part of the standard dementia assessment), new personality change with frontal features, first psychiatric presentation in the elderly, head injury, focal deficit, and treatment-resistant or otherwise unexplained presentations where an occult lesion must be excluded before committing to a primary psychiatric label.

CLINICAL ANCHOR

The governing principle is exclusion, not diagnosis: a scan in psychiatry is ordered to *rule out* the organic mimic (tumour, subdural, demyelination, hydrocephalus, vascular lesion) that would change management, and to support a dementia workup, not to confirm schizophrenia or depression. A normal scan does not exclude a primary psychiatric disorder, and a group-level finding (enlarged ventricles) is never diagnostic in the individual patient.

16.5 Schizophrenia: enlarged ventricles, reduced grey matter, and the hippocampus

The oldest and most robust structural story in psychiatry. The landmark study was Johnstone and colleagues in 1976, who used the then-novel technique of CT and found significantly enlarged lateral ventricles in patients with schizophrenia (Semple & Smyth 2019), reviving a finding first hinted at by pneumoencephalography decades earlier. Modern MRI has confirmed and extended this into a reproducible signature.

Ventricular enlargement

Enlargement of the lateral and third ventricles is the single most replicated structural finding. The large meta-analysis by Haijma and colleagues (2013), pooling over 18,000 subjects, put the increase in ventricular volume at roughly **30%** (Semple & Smyth 2019).

Reduced brain and grey-matter volume

Total brain volume is reduced by about **2.6%** and intracranial volume by about **2%** in the same meta-analysis; the reduced intracranial volume argues that much of the change is neurodevelopmental and present early in life. Grey-matter loss exceeds white-matter loss, and cortical grey matter is thinner, especially in frontal and superior-temporal regions.

Hippocampus and thalamus

Effect sizes were largest for the **hippocampus and thalamus**, both smaller in schizophrenia. Reduced hippocampal volume is among the most consistent regional findings, and smaller superior temporal gyri have been associated specifically with formal thought disorder.

~30%	~2.6%	~2%
LARGER VENTRICULAR VOLUME IN SCHIZOPHRENIA	LOWER TOTAL BRAIN VOLUME	LOWER INTRACRANIAL VOLUME (DEVELOPMENTAL)

The pathology is neurodevelopmental, not neurodegenerative: there is an *absence of gliosis* and no neuronal loss of the degenerative kind, with reductions instead in synaptic and dendritic markers. Findings are broadly similar in antipsychotic-naive and medicated patients, which argues that the core changes are not simply a drug effect, though the contribution of progressive change versus medication over the illness course remains debated (Semple & Smyth 2019). Schizophrenia, in ICD-11, is classified under schizophrenia and other primary psychotic disorders (DSM-5-TR: schizophrenia spectrum and other psychotic disorders); the imaging is a research and exclusion tool, never a diagnostic test.

COMMON TRAP

Do not describe the schizophrenia changes as "atrophy" in the degenerative sense: there is no gliosis and no Alzheimer-type neurodegeneration. The changes are a neurodevelopmental shift in the whole distribution of ventricular and brain volumes, present in part before symptom onset. Equally, ventricular enlargement is a group finding; you cannot diagnose schizophrenia from an individual patient's ventricles.

16.6 Mood disorders: white-matter hyperintensities and hippocampal volume

The two examinable structural themes in mood disorder are **white-matter hyperintensities** (the vascular-depression story) and reduced **hippocampal volume** (the neurotrophic story).

White-matter hyperintensities (WMH)

Hyperintense signals on T2/FLAIR in the **deep and periventricular white matter**, seen in normal ageing but increased in major depression, especially late-onset illness. In depression, greater deep-WMH burden is associated with greater illness severity, poorer treatment response, late onset, apathy and psychomotor retardation, and vascular risk factors (Semple & Smyth 2019). This gave rise to the **vascular depression** hypothesis: that late-life depression with these clinical and radiological features is driven by cerebrovascular disease disrupting mood-regulatory pathways (Aizenstein and colleagues 2011).

Hippocampal volume

Decreased hippocampal volume is a consistent finding in recurrent major depression, more marked with longer and more recurrent illness, and in the elderly it correlates with cognitive deficits. The favoured explanation is the **neurotrophic hypothesis**: chronic stress and cortisol hypersecretion drive neuronal atrophy and downregulate adult hippocampal neurogenesis (Semple & Smyth 2019).

Bipolar disorder and the lithium effect

Volumetric findings in bipolar disorder are inconsistent and heavily confounded by illness stage and medication. The examinable nuance is lithium: in bipolar patients *not* taking lithium, hippocampal volumes are lower as in recurrent depression, but this reduction is **reversed in patients taking lithium**, consistent with lithium's neurotrophic and neuroprotective action (Hallahan and colleagues 2011). There is also evidence of cerebral volume reduction over the course of bipolar illness and DTI abnormalities in frontal and temporal white-matter tracts.

Depressive disorders sit under mood disorders in ICD-11 (DSM-5-TR: depressive disorders); bipolar type I and II are the bipolar and related disorders. As in schizophrenia, none of these findings is diagnostic; they are group-level correlates and, in the WMH case, a marker that flags a vascular subtype with prognostic weight.

PEARL

Two clean mood-disorder pairings for the exam: *white-matter hyperintensities to vascular depression* (late-onset, poor response, vascular risk) and *reduced hippocampus to the neurotrophic/cortisol hypothesis*. The lithium point is the high-value discriminator: lithium *reverses* the hippocampal volume loss in bipolar disorder, a rare instance where a drug's structural effect is neuroprotective rather than a confound to explain away.

16.7 Dementia subtypes: the atrophy pattern is the diagnosis

In dementia, structural imaging shifts from exclusion to positive pattern recognition: *where* the atrophy sits discriminates the subtype, and the regional pattern is the examinable content. Imaging is a formal part of the dementia workup, both to exclude reversible causes and to read the atrophy signature.

DEMENTIA	STRUCTURAL SIGNATURE	DISCRIMINATING FEATURE
Alzheimer disease	Medial-temporal-lobe atrophy (hippocampus, entorhinal cortex), later temporoparietal and generalised cortical atrophy with ventricular enlargement	**Early medial-temporal (hippocampal) atrophy is the imaging hallmark; disproportionate hippocampal loss out of keeping with age**
Frontotemporal dementia	Focal, often asymmetric atrophy of the frontal and anterior temporal lobes	**Frontal / anterior-temporal atrophy with relative posterior sparing; "knife-edge" gyri; matches behavioural or language onset**
Vascular dementia	Multiple infarcts, extensive deep and periventricular white-matter change (leukoaraiosis), lacunes	**Vascular lesion load and strategic infarcts rather than a single atrophy focus**
Dementia with Lewy bodies	Relative preservation of the medial temporal lobe (hippocampus) compared with Alzheimer disease	**Medial temporal lobe relatively spared, unlike AD (a useful negative discriminator)**
Late/advanced or unspecified	Generalised cortical atrophy with widened sulci and enlarged ventricles	Non-specific; must be read against age and clinical picture

The single highest-yield contrast is Alzheimer disease (early medial-temporal/hippocampal atrophy) versus frontotemporal dementia (frontal and anterior-temporal atrophy) versus dementia with Lewy bodies (medial temporal lobe relatively preserved). Generalised atrophy alone is non-specific and expected with age.

RULE **The atrophy pattern is the diagnosis: medial-temporal for Alzheimer, frontal/anterior-temporal for FTD, medial-temporal spared in dementia with Lewy bodies.**

COMMON TRAP

Generalised cortical atrophy and widened ventricles are common in normal ageing and cannot, by themselves, diagnose dementia: the atrophy must be disproportionate to age and matched to the clinical syndrome. The classic error is over-reading age-appropriate atrophy as pathology, or missing the specificity of a *focal* pattern (medial temporal for AD, frontal for FTD) by calling everything "generalised atrophy".

16.8 Normal-pressure hydrocephalus and the reversible mimic

The reason you scan the cognitively declining patient. **Normal-pressure hydrocephalus (NPH)** is the flagship reversible mimic that imaging catches. The clinical triad is the classic examinable trio: **gait apraxia** (typically first and most prominent, a magnetic, shuffling gait), **cognitive impairment**, and **urinary incontinence** ("wet, wobbly, and wacky"). The structural

signature is **ventricular enlargement out of proportion to sulcal (cortical) atrophy**: the ventricles are markedly dilated but the surface sulci are not correspondingly widened, which is the key that separates NPH from the ex-vacuo ventricular enlargement of generalised atrophy, where ventricles and sulci enlarge together.

CLINICAL ANCHOR

NPH matters because it is potentially treatable by CSF shunting, and gait typically responds best. The imaging discriminator is the mismatch: *big ventricles, normal-sized sulci* in NPH, versus *big ventricles and wide sulci together* in atrophy. Miss the mismatch and a reversible cause of the "dementia with gait disturbance" presentation is lost.

TRAP Big ventricles alone do not mean NPH. NPH is ventricles enlarged *out of proportion* to the sulci; when sulci widen too, it is ex-vacuo atrophy.

16.9 Organic mimics on structural imaging

Beyond NPH, a defined set of structural lesions can present with psychiatric or cognitive symptoms and is the reason the scan is ordered. Each has a characteristic look that the examiners may show.

Space-occupying lesions

Frontal and temporal tumours (gliomas, meningiomas) can present with personality change, apathy, disinhibition, or new psychosis before any focal sign; a mass with surrounding vasogenic oedema (bright on T2/FLAIR) and mass effect is the picture.

Chronic subdural haematoma

A crescent-shaped extra-axial collection over the convexity in an older or alcohol-dependent patient, presenting as fluctuating confusion or "dementia"; its density on CT evolves from hyperdense (acute) to isodense to hypodense (chronic).

Demyelination (multiple sclerosis)

Periventricular and juxtacortical FLAIR-bright ovoid white-matter plaques, classically presenting with mood disorder, euphoria, or cognitive change; FLAIR is the sequence that makes the periventricular lesions visible.

Vascular lesions

Strategic infarcts (thalamic, caudate) and extensive small-vessel white-matter disease can produce cognitive and mood syndromes; the vascular-depression and vascular-dementia links above are the psychiatric face of this.

Other

Herpes and limbic encephalitis (medial temporal T2/FLAIR signal), Wilson disease (basal-ganglia change), and the atrophy of chronic alcohol use and thiamine deficiency each have a structural face worth recognising as a mimic.

16.10 Voxel-based morphometry and the quantitative structural toolkit

The disorder findings above increasingly come not from a radiologist's eye on a single film but from automated group analysis of high-resolution MRI. Three methods are examinable.

Voxel-based morphometry (VBM)

An automated, whole-brain method that identifies voxels where grey-matter (or white-matter) volume or concentration differs between groups, inferred from signal-intensity differences on structural MRI (Kaplan & Sadock 2024). Its strength is that it is unbiased by prior region-of-interest choice: it surveys the whole brain and localises where differences fall, which is how the distributed grey-matter reductions of schizophrenia were mapped.

Volumetric MRI (vMRI)

Automated or semi-automated segmentation of specified regions of interest to obtain volumes, cortical thickness, and shape indices; the method behind the hippocampal and ventricular volume figures (Kaplan & Sadock 2024).

Diffusion tensor imaging (DTI)

Indexes white-matter tract integrity and myelination through anisotropic diffusion (fractional anisotropy), enabling tractography; reduced FA is the standard marker of disrupted connectivity in schizophrenia and mood disorder (Kaplan & Sadock 2024).

PEARL

Keep the toolkit paired to its output: *VBM* asks "where in the whole brain does grey matter differ?"; *vMRI* asks "how big is this specific structure?"; *DTI/FA* asks "how intact is this white-matter tract?". These three are how a modern structural paper turns anatomy into a group-level finding, and each is fair game as a short-note stem.

16.11 Cross-references to the Functional Neuroanatomy & Neurophysiology notes and the one-line synthesis

This topic deliberately does not re-teach the structures; it reads findings off the anatomy the Functional Neuroanatomy & Neurophysiology notes established. The **hippocampus and medial temporal lobe** (the Functional Neuroanatomy & Neurophysiology notes limbic system) are the shared site across schizophrenia, depression, and Alzheimer disease. The **lateral and third ventricles** (the Functional Neuroanatomy & Neurophysiology notes ventricular system) are the schizophrenia and NPH readout. The **frontal and temporal cortex** (the Functional Neuroanatomy & Neurophysiology notes lobar anatomy) carry the frontotemporal-dementia and thought-disorder signatures. The **white-matter tracts** (the Functional Neuroanatomy & Neurophysiology notes connectivity) are what DTI and the WMH story index.

MNEMONIC

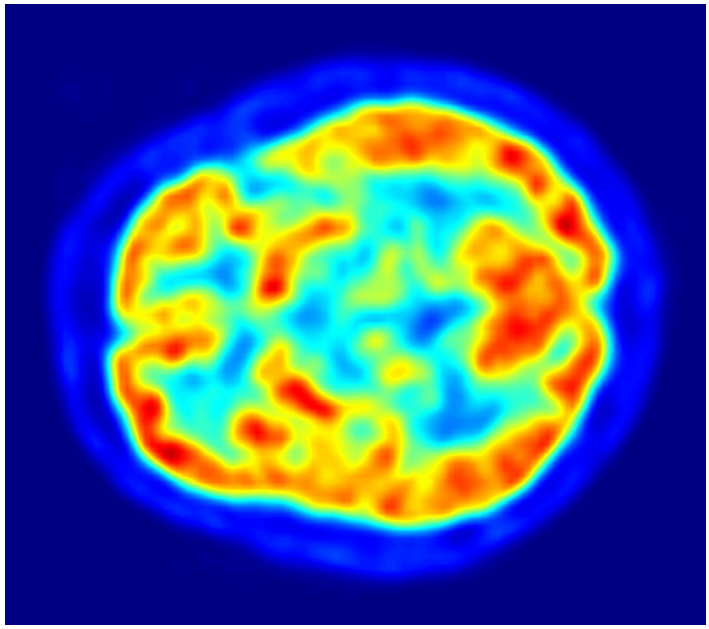
"Ventricles up, hippocampus down, white matter bright, atrophy where the syndrome lives"

The whole topic in one line. *Ventricles up*: schizophrenia (and NPH, but with spared sulci). *Hippocampus down*: schizophrenia, recurrent depression, and Alzheimer disease. *White matter bright*: FLAIR hyperintensities of vascular depression and demyelination. *Atrophy where the syndrome lives*: medial temporal for AD, frontal for FTD. Underneath it all sits the physics: CT for blood and bone in the emergency, MRI with "Water is White on T2" for the soft-tissue answer.

17 · Functional imaging (fMRI/PET/SPECT) principles and findings

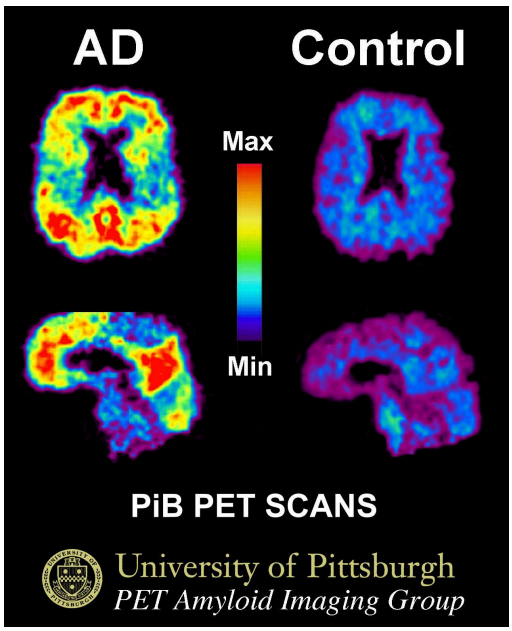
Functional imaging is where the molecular material of this paper meets the phenomenology of the clinical papers, and examiners exploit that junction relentlessly. Structural imaging shows what the brain *is*; functional imaging shows what the brain *is doing*, either through a haemodynamic surrogate for neural activity (**fMRI**) or through a radiotracer that reports metabolism, perfusion, or the density and occupancy of a named receptor (**PET and SPECT**). The single most useful mental move for the exam is to keep two questions apart: *what does the modality physically measure*, and *which finding maps to which syndrome*. Almost every Step-5 discrimination item is really the second question in disguise, "here is an imaging signature, name the disorder", and it rewards a clean lookup table more than any amount of prose.

Exam framing. Very little of this is clinical-grade. With three exceptions (FDG-PET and amyloid/tau PET in the dementia work-up, D2 occupancy PET as a pharmacological reference, and DAT-SPECT for parkinsonian syndromes), functional imaging in psychiatry remains a *research and group-level* tool: it separates cohorts, not individual patients, and no scan diagnoses schizophrenia, depression, or OCD. Say this explicitly in a viva before you recite findings; it is the discriminating maturity examiners look for. Cross-reference the the Functional Neuroanatomy & Neurophysiology notes material on resting-state networks: the default mode, salience, and central executive networks are the substrate on which most of the disorder findings below are now framed.



FDG-PET: Jens Maus, public domain, via Wikimedia Commons

Fig 2.8 A normal FDG-PET slice. 18F-fluorodeoxyglucose maps regional glucose metabolism, brightest in grey-matter cortex and deep grey. The *pattern of hypometabolism* then localises disease: temporoparietal in Alzheimer disease, frontal in frontotemporal dementia, occipital in dementia with Lewy bodies. In schizophrenia, reduced frontal activation on cognitive tasks is the hypofrontality finding.



PiB amyloid PET: Klunkwe, CC BY-SA 3.0, via Wikimedia Commons

Fig 2.9 Amyloid PET with Pittsburgh compound B. The Alzheimer brain (left) retains tracer diffusely across the cortex; the control (right) shows only non-specific white-matter signal. Amyloid and tau PET are molecular markers that can support an Alzheimer diagnosis in a living patient, distinct from the FDG metabolic map and from structural atrophy.

17.1 BOLD fMRI: what the signal actually is

Functional MRI does not measure neuronal firing directly. It measures the **blood-oxygen-level-dependent (BOLD)** signal, an indirect haemodynamic proxy discovered by Ogawa in 1990 (Kaplan & Sadock 2024).

The physical basis

Deoxyhaemoglobin is *paramagnetic* and distorts the local magnetic field, shortening T2*; oxyhaemoglobin is diamagnetic and does not. When a region becomes active, local blood flow rises out of proportion to the oxygen actually extracted, so the venous blood becomes *relatively more oxygenated*. The fall in deoxyhaemoglobin reduces field distortion and the T2*-weighted signal **rises**. The BOLD signal is therefore a report on the neurovascular coupling that follows neural activity, not on the spikes themselves.

Neurovascular coupling

BOLD tracks **local field potentials** (synaptic and dendritic input) more faithfully than output spiking, which matters when interpreting a "hyperactivity" finding: it may reflect greater afferent processing rather than more firing.

The haemodynamic response function

The signal lags the neural event by roughly 4 to 6 seconds and is sluggish, giving fMRI excellent *spatial* resolution (millimetres) but poor *temporal* resolution, the mirror image of EEG. This is the classic paired contrast in exams.

Task versus rest. Task-based fMRI contrasts BOLD during a cognitive or emotional challenge (an n-back for working memory, fearful faces for the amygdala) against a baseline. **Resting-state fMRI** requires no task: it measures spontaneous low-frequency (below 0.1 Hz) BOLD

fluctuations and infers **functional connectivity** from the correlation of these fluctuations between regions. Resting-state work is the engine behind the network models below and needs no patient cooperation, a practical advantage in psychosis and dementia.

COMMON TRAP

BOLD is a signal about *oxygenation*, and the counter-intuitive point examiners test is the sign: an active region ends up with *less* deoxyhaemoglobin and therefore a *higher* T2* signal, because the flow response overshoots the metabolic demand. Do not say activity "uses up oxygen and lowers the signal"; the net effect is the reverse.

17.2 PET and SPECT: three things a radiotracer can report

Both PET and SPECT inject a radiolabelled tracer and image where it accumulates; the difference is physics. **PET** uses positron-emitters (fluorine-18, carbon-11, oxygen-15) and detects the paired 511 keV photons of annihilation, giving higher resolution and quantification. **SPECT** uses single-photon emitters (technetium-99m, iodine-123), is cheaper and more available, but has lower resolution. What the tracer reports depends entirely on which tracer you choose (Kaplan & Sadock 2024).

WHAT IS MEASURED	REPRESENTATIVE TRACER	READS OUT
Glucose metabolism	**[18F]-FDG (fluorodeoxyglucose)**	Regional metabolic rate; the workhorse of dementia imaging
Cerebral perfusion	[99mTc]-HMPAO, [99mTc]-ECD (SPECT); [15O]-water (PET)	Regional blood flow, a proxy for activity
Presynaptic dopamine synthesis	**[18F]-FDOPA (FDOPA-PET)**	Dopamine synthesis and storage capacity in striatum
Presynaptic dopamine transporter	[123I]-FP-CIT (DaTSCAN, SPECT)	Nigrostriatal terminal integrity; parkinsonian syndromes
Postsynaptic receptor density / occupancy	[11C]-raclopride, [123I]-IBZM (D2)	Available D2 receptors and drug occupancy
Amyloid burden	**[11C]-PIB, [18F]-florbetapir/flutemetamol**	Cortical fibrillar amyloid-beta
Tau burden	[18F]-flortaucipir	Neurofibrillary tangle load

The tracer decides the question. The discriminator to fix: FDG reports metabolism, FDOPA reports presynaptic dopamine *synthesis*, raclopride/IBZM report postsynaptic D2 *availability and occupancy*, and DaTSCAN reports the presynaptic *transporter*. Confusing FDOPA (synthesis) with raclopride (receptor) is a standard trap.

PEARL

The two axes to keep straight are *presynaptic versus postsynaptic* and *synthesis versus transporter versus receptor*. FDOPA and DaTSCAN are presynaptic (synthesis capacity and transporter respectively); raclopride and IBZM are postsynaptic (D2 availability). This single grid answers most molecular-imaging single-best-answer items.

TRAP Schizophrenia does not show raised D2 receptors on PET. The durable finding is raised *presynaptic* dopamine synthesis on FDOPA-PET; do not swap FDOPA (synthesis) for raclopride (receptor).

17.3 Receptor occupancy and the therapeutic window

The most clinically anchored use of PET in psychiatry is measuring how much of a receptor pool a drug occupies. By comparing tracer binding before and after a drug, PET quantifies **receptor occupancy** as a percentage, and this reshaped antipsychotic dosing (Kapur 2000).

The D2 occupancy window

Kapur's double-blind PET work in first-episode schizophrenia established that antipsychotic response and side effects track striatal D2 occupancy on a threshold basis: clinical response emerges above roughly **65%** occupancy, while **extrapyramidal side effects** rise steeply above about **80%**. The practical *therapeutic window* is therefore approximately 65 to 80% D2 occupancy, and **hyperprolactinaemia** appears at the upper end (around 72% and above). This is the single most examinable number in the whole topic.

SERT occupancy

Antidepressant SSRIs occupy about 80% of the serotonin transporter at standard clinical doses, an occupancy reached at the bottom of the dose range, which is why pushing SSRI doses higher rarely adds efficacy (Maudsley Prescribing Guidelines).

The clozapine exception

Clozapine is antipsychotic at strikingly *low* D2 occupancy (often below 60%), one of the arguments that its efficacy in treatment resistance is not primarily D2-mediated. Occupancy imaging is the evidence base for that claim.

CLINICAL ANCHOR

The 65 to 80% window explains a common ward error: escalating an antipsychotic dose in a non-responder who is already at 80% occupancy adds no benefit and only buys EPS and prolactinaemia. If a patient is fully occupied and still psychotic, the problem is unlikely to be more D2 blockade; consider adherence, the non-dopaminergic (glutamatergic) subgroup, and clozapine. Occupancy plateaus while dose keeps climbing, the pharmacological argument against reflexive dose increases.

HOLD THIS

The antipsychotic window is roughly 65 to 80% striatal D2 occupancy: response above 65%, EPS above 80%. Escalating a fully-occupied non-responder buys only EPS and prolactinaemia.

65%	80%	~80%
D2 OCCUPANCY FOR ANTIPSYCHOTIC RESPONSE	D2 OCCUPANCY WHERE EPS RISES	SERT OCCUPANCY AT STANDARD SSRI DOSE

17.4 Resting-state networks and the triple-network model

Resting-state connectivity reframed psychiatric findings from "which region" to "which network", and one framework recurs across disorders (Kaplan & Sadock 2024; Menon 2011).

Default mode network (DMN)

Precuneus/posterior cingulate, medial prefrontal cortex, and inferior parietal and lateral temporal regions. It is *more* active at rest and during self-referential thought, and deactivates during external tasks. Linked to rumination and self-focus.

Salience network

Anterior insula and dorsal anterior cingulate cortex. Detects behaviourally relevant stimuli and switches control between the DMN and the executive network.

Central executive network

Dorsolateral prefrontal cortex and posterior parietal cortex. Supports working memory and goal-directed cognition.

The triple-network model. Menon's synthesis holds that many disorders share a common architecture of dysfunction: aberrant salience-network gating fails to toggle correctly between an over-engaged DMN (self-referential, ruminative) and an under-engaged executive network. In depression this reads as DMN hyperconnectivity and rumination; in schizophrenia as failure to deactivate the DMN with a hyperactive salience system (the imaging correlate of aberrant salience). This is a research model, but it is the current language of the field and worth naming.

17.5 Schizophrenia: hypofrontality, the striatal window, and presynaptic dopamine

Schizophrenia carries three separable imaging signatures across three modalities, and the exam wants all three held apart (Companion to Psychiatric Studies; Howes & Kapur 2009).

- **Activation fMRI/perfusion, hypofrontality.** Reduced **dorsolateral prefrontal cortex** activation during executive tasks (the Wisconsin Card Sort, n-back), the classic *hypofrontality*, correlating with negative and cognitive symptoms. It is task-dependent and may follow an initial hyperactivity; a resting scan can look normal, which is why the finding is elicited with a cognitive challenge.
- **Postsynaptic D2 (raclopride/IBZM PET/SPECT).** The therapeutic window sits at **65 to 80% striatal D2 occupancy** (see 17.3). Baseline postsynaptic D2 density is *not* reliably raised once antipsychotic exposure is accounted for, which was the downfall of the crude receptor hypothesis.
- **Presynaptic dopamine (FDOPA-PET).** The robust, replicated positive finding is *elevated presynaptic striatal dopamine synthesis capacity*, present even in the prodrome and in unmedicated patients. This is the imaging cornerstone of the version III "final common pathway" hypothesis: the lesion is presynaptic, not at the receptor.

> **COMMON TRAP**
>
> Do not answer "schizophrenia shows increased D2 receptors on PET". The durable finding is raised *presynaptic dopamine synthesis and release capacity* on FDOPA-PET; postsynaptic D2 density is at best marginally and inconsistently elevated. FDOPA (synthesis) versus raclopride (receptor) is exactly the presynaptic/postsynaptic discrimination from 17.2, applied to the highest-yield disorder.

17.6 Depression: subgenual cingulate and prefrontal hypoactivity

Mood disorder imaging centres on a limbic-cortical imbalance, and one region has become the emblematic node (Kaplan & Sadock 2024; Mayberg 1997).

Subgenual anterior cingulate cortex (sgACC, Brodmann area 25)

Hyperactivity here (raised resting metabolism on FDG-PET, raised BOLD) is the signature finding of the depressed state, normalising with recovery. It is Mayberg's rationale for deep brain stimulation of area 25 in treatment-resistant depression, and appears across FDG-PET, task fMRI, and resting EEG, a rare convergence.

Dorsolateral prefrontal cortex (DLPFC)

Reduced dorsolateral prefrontal activity, the correlate of psychomotor retardation and cognitive slowing. The left DLPFC is the target of therapeutic repetitive TMS.

Amygdala

Exaggerated amygdala response to negative emotional stimuli (fearful faces), reflecting a negative processing bias that predates and predicts response to treatment.

The circuit summary. Depression reads as a *hyperactive ventral/limbic compartment* (subgenual cingulate, amygdala) with a *hypoactive dorsal/cortical compartment* (DLPFC), and treatments, whether SSRI, TMS, or DBS, act to rebalance the two. This dorsal-down, ventral-up shorthand is highly examinable.

MNEMONIC

"Ventral UP, Dorsal DOWN"

In depression the **ventral** limbic node (subgenual cingulate/BA25, amygdala) is **up** (hypermetabolic), and the **dorsal** cortical node (DLPFC) is **down** (hypoactive). Treatments push the balance back the other way. If you can only remember one region, remember subgenual cingulate hyperactivity.

17.7 Bipolar disorder: amygdala up, prefrontal down

Bipolar imaging shares the amygdala theme with unipolar depression but is defined by a *frontolimbic dysconnection* that is present across mood states (New Oxford Textbook of Psychiatry; Strakowski 2012).

- **Amygdala hyperactivity.** Heightened amygdala response to emotional (especially facial) stimuli, more state-independent than in unipolar depression, and a candidate trait marker.
- **Prefrontal (especially ventrolateral/ventromedial) hypoactivity.** Reduced ventral prefrontal engagement, read as failure of top-down cortical control over limbic drive, the imaging correlate of affective instability and impulsivity.
- **Reduced VLPFC-amygdala connectivity.** Weakened functional coupling between the medial/ventrolateral prefrontal cortex and the amygdala distinguishes the bipolar from the unipolar depressed brain in some studies.

Discriminator. The bipolar signature is best given as "amygdala hyperactivity with prefrontal hypoactivity and a failure of prefrontal-limbic modulation", which contrasts with depression's more specific subgenual-cingulate emphasis. All of this is research-grade; no scan diagnoses bipolar disorder.

17.8 OCD: the hyperactive cortico-striato-thalamo-cortical loop

OCD has the tightest, most reproducible circuit signature in the whole topic, and it is a favourite because the same loop explains the imaging, the surgery, and the treatment response (Kaplan & Sadock 2024; Saxena 1998).

The CSTC loop

A hyperactive **cortico-striato-thalamo-cortical (CSTC) circuit**: the *orbitofrontal cortex*, the *anterior cingulate cortex*, the *caudate nucleus* (head), and the *thalamus* show raised resting metabolism on FDG-PET. The model is a failure of the striatal "brake", so an excitatory orbitofronto-thalamic drive runs unchecked, generating the intrusive urge.

Treatment normalisation

The distinguishing feature is that this hypermetabolism *normalises* with successful treatment, whether SSRI or cognitive-behavioural therapy, and the degree of orbitofrontal/caudate reduction predicts response. Few functional findings in psychiatry are so cleanly state-dependent.

> **CLINICAL ANCHOR**
>
> The CSTC model is the rationale for neurosurgery and neuromodulation in refractory OCD: anterior *cingulotomy* and *capsulotomy*, and deep brain stimulation of the ventral capsule/ventral striatum, all interrupt the same overactive loop the imaging identifies. Symptom relief tracks reduced orbitofrontal-caudate metabolism, closing the loop between the scan and the intervention.

17.9 Anxiety and PTSD: amygdala up, ventromedial prefrontal down

The fear-circuit disorders share a two-node signature that is the direct imaging translation of extinction failure (Kaplan & Sadock 2024; Rauch 2006).

- **Amygdala hyperactivity.** Exaggerated amygdala response to threat and trauma cues, the substrate of hypervigilance and the exaggerated startle of PTSD, seen across anxiety disorders.
- **Ventromedial prefrontal cortex hypoactivity.** Reduced **vmPFC** activity, the region that normally exerts top-down inhibitory control over the amygdala and mediates extinction of conditioned fear. Its underactivity leaves the amygdala disinhibited.
- **Hippocampal changes (PTSD).** Reduced hippocampal volume and function, linked to contextual (mis)appraisal of safe situations as dangerous. This is the finding most specific to PTSD within the group.

Discriminator. The clean pairing to hold is *amygdala hyper- plus vmPFC hypoactivity* (failed prefrontal inhibition of fear), which recurs for panic, social anxiety, specific phobia, and PTSD. PTSD adds the hippocampal element.

COMMON TRAP

Depression, bipolar, anxiety, and PTSD all feature amygdala hyperactivity, so "amygdala hyperactivity" alone cannot discriminate them. The *partner cortical region* is the discriminator: subgenual cingulate for unipolar depression, ventrolateral/ventromedial prefrontal for bipolar, and specifically the *ventromedial* prefrontal (extinction) node plus hippocampus for anxiety/PTSD. Always name the second node.

17.10 Dementia subtypes: the FDG-PET metabolic map and the ATN framework

This is the one area where functional imaging is genuinely **clinical-grade** and diagnostically deployed. FDG-PET distinguishes the dementias by the *location* of hypometabolism, and molecular PET now anchors the biological diagnosis of Alzheimer disease (Kaplan & Sadock 2024; Stahl 2021).

DEMENTIA	FDG-PET HYPOMETABOLISM PATTERN	MOLECULAR / DISTINGUISHING MARKER
Alzheimer disease	**Temporoparietal and posterior cingulate/precuneus, later frontal**	Amyloid PET positive; tau PET in medial temporal to neocortex
Frontotemporal dementia	**Frontal and anterior temporal (asymmetric)**	Amyloid PET typically negative; helps separate from AD
Dementia with Lewy bodies	**Occipital hypometabolism; posterior cingulate "island sign" spared**	Reduced DaTSCAN uptake (nigrostriatal loss); MIBG cardiac
Vascular dementia	Patchy, multifocal, following vascular territories	Structural infarcts on MRI

The metabolic map of the dementias. The three highest-yield discriminators: AD is temporoparietal, FTD is frontotemporal, and DLB is occipital with the cingulate island sign (relative sparing of posterior cingulate against reduced occipital and precuneus metabolism). Amyloid-negative PET argues against AD.

The A/T/N biomarker framework

Alzheimer biology is now defined biologically: **A** (amyloid, by amyloid PET or CSF Abeta42/Abeta40), **T** (tau, by tau PET or CSF phospho-tau), and **N** (neurodegeneration, by FDG-PET, structural MRI, or CSF total tau). FDG-PET is an *N* marker, not specific to AD; amyloid and tau PET are the specific molecular markers.

DLB and DaTSCAN

Reduced striatal dopamine transporter uptake on *DaTSCAN* (SPECT) is a supportive DLB criterion, reflecting nigrostriatal degeneration and separating DLB from AD, where DaTSCAN is normal.

Currency (through 2026)

The *anti-amyloid monoclonal antibodies* (lecanemab, donanemab) require *amyloid PET or CSF confirmation of amyloid positivity* before treatment, so molecular imaging has moved from research tool to a gatekeeper for disease-modifying therapy, and treatment response is now monitored by falling amyloid PET signal.

PEARL

The **cingulate island sign** is the DLB pearl: on FDG-PET the posterior cingulate is *relatively preserved* (an "island") against surrounding occipital and precuneus hypometabolism, the reverse of AD, where the posterior cingulate is among the first to fail. Occipital hypometabolism plus a preserved cingulate island points to Lewy bodies.

17.11 ADHD: fronto-striatal hypoactivation

ADHD imaging maps onto the dopaminergic hypofunction model from the dopamine topic (Kaplan & Sadock 2024; Cortese 2012).

- **Fronto-striatal hypoactivation.** Reduced activation of the *prefrontal cortex* (especially inferior frontal and dorsolateral) and the *striatum* during inhibitory-control and attention tasks (go/no-go, stop-signal), the correlate of impaired response inhibition and executive control.
- **Fronto-parietal and ventral attention networks.** Under-recruitment of the networks that sustain and reorient attention, with failure to deactivate the default mode network during tasks (DMN intrusion, linked to lapses of attention).
- **Stimulant normalisation.** Methylphenidate and amphetamine tend to *increase* the deficient fronto-striatal activation toward control levels, consistent with raising synaptic dopamine and noradrenaline.

Grade. Research-only. There is no imaging diagnosis of ADHD, and a scan cannot confirm or exclude it in an individual; the diagnosis remains clinical.

17.12 The finding-to-syndrome discrimination table

This is the Step-5 anchor for the whole topic: given an imaging signature, name the syndrome. Read it in both directions, and note the clinical grade in the final column.

IMAGING SIGNATURE	MODALITY	SYNDROME	GRADE
Hypofrontality (DLPFC) on activation	Task fMRI / perfusion SPECT	Schizophrenia (negative/cognitive symptoms)	Research
Raised presynaptic striatal dopamine synthesis	FDOPA-PET	Schizophrenia (final common pathway)	Research
65 to 80% striatal D2 occupancy = therapeutic window	Raclopride/IBZM PET-SPECT	Antipsychotic dosing reference	**Clinical (pharmacology)**
Subgenual anterior cingulate (BA25) hyperactivity	FDG-PET / fMRI	Major depression	Research
Reduced dorsolateral prefrontal activity	Task fMRI	Major depression (retardation)	Research

IMAGING SIGNATURE	MODALITY	SYNDROME	GRADE
Amygdala hyper- + prefrontal hypoactivity	Task fMRI	Bipolar disorder	Research
Hyperactive orbitofrontal-caudate-thalamus (CSTC), normalises with treatment	FDG-PET / fMRI	OCD	Research
Amygdala hyper- + ventromedial prefrontal hypoactivity (± small hippocampus)	Task fMRI	Anxiety disorders / PTSD	Research
Temporoparietal + posterior cingulate hypometabolism	FDG-PET	Alzheimer disease	**Clinical**
Frontal + anterior temporal hypometabolism	FDG-PET	Frontotemporal dementia	**Clinical**
Occipital hypometabolism + cingulate island sign; low DaTSCAN	FDG-PET / DaTSCAN	Dementia with Lewy bodies	**Clinical**
Cortical amyloid tracer retention	Amyloid PET	Alzheimer disease (gates anti-amyloid mAbs)	**Clinical**
Fronto-striatal hypoactivation on inhibitory tasks	Task fMRI	ADHD	Research

The master discrimination grid. When two syndromes share amygdala hyperactivity, the partner cortical node discriminates them: subgenual cingulate (unipolar depression), ventrolateral prefrontal (bipolar), ventromedial prefrontal plus hippocampus (anxiety/PTSD). The clinical-grade rows (D2 occupancy, the three dementia FDG patterns, amyloid PET) are the only ones used in individual patients.

INDIA

Functional and molecular imaging remain scarce and expensive in Indian practice: PET is confined to metropolitan tertiary centres, and FDOPA, amyloid, tau, and DaTSCAN tracers are rarely available or affordable outside research and a handful of private centres. The exam-relevant consequence is that the dementia work-up in most Indian settings still leans on clinical criteria plus structural MRI, with FDG-PET or DaTSCAN reserved for genuinely ambiguous cases (AD versus FTD, or DLB versus AD). Know the findings for the exam, but frame their availability realistically in a viva.

Basic psychopharmacology

18 · Pharmacokinetics (ADME)

What the body does to the drug. Pharmacokinetics is the mirror-image of pharmacodynamics: dynamics is what the drug does to the body, kinetics is what the body does to the drug. Every psychotropic decision you make, the dose, the interval, whether to load, when to check a level, whether to halve it in the elderly, is a kinetic decision. The four processes are packaged in one acronym, **ADME** (absorption, distribution, metabolism, excretion), and the exam rewards you for knowing not just the definitions but the three or four equations that tie them together and the handful of psychiatric drugs where getting the kinetics wrong is dangerous.

Frame the whole topic as a journey of a single molecule (Kaplan & Sadock 2024). It is swallowed and must survive the gut and the first pass through the liver to reach the blood (absorption); it is carried by plasma proteins and must be lipophilic enough to cross the blood-brain barrier to reach its target (distribution); the liver dismantles it in two phases (metabolism); and the kidney clears the water-soluble remains (excretion). Absorption and distribution set how fast and how much drug reaches the brain; metabolism and excretion set how long it stays and therefore the dosing interval. The one number that governs steady state, drug interactions and toxicity monitoring all at once is the **half-life**, so build toward it.

18.1 Absorption and the two things that erode oral dose

Bioavailability is the survivors. **Bioavailability (F)** is the fraction of an administered dose that reaches the systemic circulation in unchanged form (StatPearls 2023). Intravenous dosing is the reference: F is 1.0 (100%) by definition, because the drug is placed directly into the blood. Everything given by any other route is measured against that IV standard, quantified as the ratio of the areas under the plasma concentration-time curves (AUC-oral divided by AUC-IV). Two hurdles cut F for an oral psychotropic: incomplete absorption across the gut wall, and **first-pass metabolism**.

First-pass (presystemic) metabolism is the extraction of drug by the gut wall and, chiefly, the liver before it ever reaches the systemic circulation, because the entire venous drainage of the gut passes through the portal vein into the liver first (Tripathi/KDT 2019). A drug with heavy first-pass metabolism (the classic psychiatric example being the older tricyclics and beta-blockers such as propranolol) has a low and highly variable oral F, so oral and parenteral doses differ markedly and interindividual variation is large. Bypassing first-pass is precisely why some routes matter clinically: sublingual (asenapine, buprenorphine), intramuscular, intravenous and transdermal all skip the portal circulation.

CLINICAL ANCHOR

Route choice in psychiatry is a bioavailability decision. **Asenapine** is given sublingually because its oral (swallowed) bioavailability is under 2% from near-total first-pass metabolism, so a swallowed tablet is inert. Long-acting intramuscular antipsychotic depots deliberately trade a slow, complete absorption for months of steady levels. Intranasal **esketamine** is chosen to bypass hepatic first-pass and give rapid CNS entry.

RULE **Sublingual, intramuscular, intravenous and transdermal routes exist to bypass first-pass metabolism.** Swallowed asenapine is inert (oral bioavailability under 2%).

18.2 Order of kinetics: first-order versus zero-order, and why it is examined

The rate at which a drug is eliminated defines its kinetics, and the distinction is high-yield because a few dangerous psychiatric drugs are the exceptions. In **first-order kinetics** a constant *fraction* of the drug is eliminated per unit time; the absolute amount cleared is proportional to plasma concentration, so the half-life is constant regardless of dose. This is the ordinary case for most drugs. In **zero-order (saturation) kinetics** a constant *amount* is eliminated per unit time because the metabolising enzymes are saturated; there is no fixed half-life, and a small dose increase produces a disproportionately large rise in plasma level (StatPearls 2023).

COMMON TRAP

The examined zero-order drugs are **ethanol**, **phenytoin** and high-dose **salicylate**. Phenytoin is the psychiatry-adjacent trap: near the top of its range its kinetics flip from first- to zero-order, so a routine dose increase can push a patient into toxicity. Some sources add high-dose fluoxetine and fluvoxamine as showing non-linear (saturable) kinetics. Do not state these have a "fixed half-life."

18.3 Distribution: volume of distribution and what a high or low number tells you

A number that is not a real volume. The **apparent volume of distribution (Vd)** is the theoretical volume into which the total amount of drug in the body would have to be dissolved to give the measured plasma concentration (Vd = total drug in body divided by plasma concentration). It is not an anatomical space; it is an index of how widely a drug leaves the plasma for the tissues. A drug confined to plasma has a small Vd; a drug that partitions deeply into fat and tissue has a very large Vd, far exceeding total body water (StatPearls 2023).

Read Vd off two properties: lipophilicity and protein binding. A small, lipophilic molecule distributes into cells and adipose tissue and has a huge Vd (the non-psychiatric teaching example is chloroquine at around 140 L/kg); a large, charged or highly protein-bound molecule stays intravascular with a low Vd. In psychiatry the lipophilic psychotropics (most antipsychotics, TCAs, fluoxetine) have large volumes of distribution, which is why they are not effectively removed by haemodialysis and why lipophilic long-half-life drugs accumulate in body fat.

PEARL

Vd drives the loading dose; clearance drives the maintenance dose. Loading dose = Vd times target plasma concentration divided by F. This is why lithium, with a small Vd close to total body water, reaches a predictable level, and why a drug with a very large Vd cannot be cleared by dialysis. Half-life is the bridge between the two: it rises with Vd and falls with clearance.

18.4 Protein binding: the free-drug principle and its interaction traps

In plasma a drug exists as a protein-bound fraction and a free fraction, and only the **free (unbound) drug** is pharmacologically active: only free drug crosses membranes, reaches receptors, is metabolised and is excreted (StatPearls 2023). The two principal binding proteins are **albumin** (binds acidic drugs, for example valproate, phenytoin, diazepam) and **alpha-1-acid glycoprotein** (binds basic drugs, for example many antipsychotics and TCAs). A fall in albumin (malnutrition, hepatic or renal disease, the elderly, pregnancy) raises the free fraction of a highly bound drug and can produce toxicity at an apparently therapeutic total level.

CLINICAL ANCHOR

Valproate is the canonical psychiatric protein-binding trap. It is roughly 90% albumin-bound, but binding is saturable: as the total level rises, the free fraction rises disproportionately, and in hypoalbuminaemia (elderly, hepatic disease) a "therapeutic" total valproate level can conceal a toxic free level. Displacement interactions (valproate displacing warfarin, or aspirin displacing valproate) matter most for highly bound, narrow-index drugs.

18.5 Crossing into the brain: the blood-brain barrier and lipophilicity

A psychotropic can only work if it reaches the CNS, and the **blood-brain barrier (BBB)** is the gate. The BBB is formed by tight junctions between brain capillary endothelial cells that abolish the porous, fenestrated permeability seen elsewhere, so passive entry is restricted to small, lipophilic, uncharged, unbound molecules; hydrophilic and highly protein-bound drugs are largely excluded unless carried by a transporter (Nursing Pharmacology 2021). Efflux pumps, chiefly **P-glycoprotein**, actively push many drugs back out, further limiting brain penetration.

The design consequence runs both ways. Psychotropics are deliberately lipophilic to enter the brain, which is also why they have large volumes of distribution and cross the placenta. Conversely, unwanted CNS entry by a peripheral drug causes central side effects: sedating first-generation antihistamines (diphenhydramine) are the standard example of a drug crossing the BBB to cause drowsiness, whereas second-generation agents are engineered not to cross.

18.6 Metabolism: phase I and phase II, and the CYP450 system that matters most

Two phases, one goal. Hepatic metabolism converts lipophilic drugs into water-soluble metabolites the kidney can excrete, usually in two sequential phases (StatPearls 2023).

Phase I

Non-synthetic functionalisation reactions (oxidation, reduction, hydrolysis) that add or expose a reactive polar group. Oxidation by the **cytochrome P450 (CYP)** mono-oxygenase family is the dominant route. Metabolites may be inactive, active, or occasionally toxic.

Phase II

Synthetic conjugation reactions (glucuronidation by UGT, sulfation, acetylation, methylation, glutathione conjugation) that attach a large polar group to make the compound water-soluble for excretion. Products are almost always inactive. Phase II can occur without a prior phase I step.

The examined CYP isoenzymes in psychiatry are **CYP3A4** (the highest-abundance isoform, metabolises many antipsychotics and benzodiazepines), **CYP2D6** (metabolises risperidone, aripiprazole, many TCAs and SSRIs; genetically polymorphic), **CYP1A2** (clozapine and olanzapine; induced by tobacco smoke), and **CYP2C19** (citalopram, escitalopram, sertraline; polymorphic). An **inhibitor** raises the substrate's level (fluvoxamine and fluoxetine are potent inhibitors); an **inducer** lowers it (carbamazepine, and the polycyclic aromatic hydrocarbons in cigarette smoke induce CYP1A2). These are the mechanistic backbone of psychotropic drug interactions.

ISOENZYME	KEY PSYCHIATRIC SUBSTRATES	CLASSIC INDUCER / INHIBITOR WITH EXAM RELEVANCE
CYP1A2	Clozapine, olanzapine, duloxetine	**Induced by cigarette smoke (not nicotine): stopping smoking, or a smoking ban on admission, raises clozapine levels and can precipitate toxicity; fluvoxamine is a potent inhibitor**
CYP2D6	Risperidone, aripiprazole, TCAs, many SSRIs; codeine to morphine activation	**Highly polymorphic: poor and ultrarapid metaboliser phenotypes; paroxetine and fluoxetine are potent inhibitors of this pathway**
CYP3A4	Quetiapine, pimozide, many benzodiazepines, carbamazepine	**Inhibited by ketoconazole and grapefruit juice; carbamazepine is a strong inducer and also autoinduces its own metabolism**
CYP2C19	Citalopram, escitalopram, sertraline, diazepam	**Polymorphic; regulatory QTc-based dose caps on citalopram reflect concentration-dependent risk**

The four isoenzymes to hold cold are CYP1A2 (clozapine and smoking), CYP2D6 (polymorphism), CYP3A4 (highest abundance, most substrates) and CYP2C19. Two special metabolic behaviours are examined by name: carbamazepine autoinduction, and lithium being an outlier that undergoes no hepatic metabolism at all.

18.7 Excretion, clearance and the equations that link them

The kidney clears the water-soluble remains. Most metabolised drug is excreted by the kidney (glomerular filtration, active tubular secretion, passive reabsorption), with a biliary and faecal route for others. **Clearance (CL)** is the volume of plasma completely cleared of drug per unit time; it is the single best index of the body's efficiency at eliminating a drug and it sets the maintenance dose (maintenance rate = CL times target concentration divided by F).

The **elimination half-life (t-half)** is the time for the plasma concentration to fall by 50%. It is a derived parameter tying together the two primary ones: t-half = 0.693 times Vd divided by CL. So half-life lengthens if the drug distributes more widely (higher Vd) or is cleared more slowly (lower CL, as in renal or hepatic impairment or old age). Half-life governs two clinically decisive quantities (StatPearls 2023, Pharmaceutical Press 2023):

Time to steady state

On regular dosing, plasma level plateaus after approximately **4 to 5 half-lives**, independent of the dose or interval. This is when to check a trough level and when to judge full effect of a dose change.

Time to elimination

After stopping, a drug is effectively cleared (about 94 to 97% gone) after 4 to 5 half-lives; this sets safe washout before switching drugs.

CLINICAL ANCHOR

Fluoxetine's long half-life is the clinical exception you must know. Fluoxetine (1 to 4 days) and its active metabolite norfluoxetine (7 to 15 days) mean steady state takes weeks and washout takes about 5 to 6 weeks, which is why a long drug-free interval is needed before starting an MAOI. Conversely, the very short half-life of immediate-release venlafaxine or paroxetine explains their prominent discontinuation syndrome.

18.8 Loading, maintenance and the dosing interval

Two everyday decisions fall straight out of the parameters. The **loading dose** (Vd times target level divided by F) rapidly fills the volume of distribution to reach a therapeutic level without waiting the 4 to 5 half-lives, used when speed matters. The **maintenance dose and interval** replace what is eliminated each period and are set by clearance. The dosing interval is chosen relative to the half-life: an interval much longer than the half-life gives large peak-to-trough swings, while an interval near or shorter than the half-life gives smoother levels, which is the rationale for modified-release formulations and for once-daily dosing of long-half-life drugs.

PEARL

Because a long-half-life drug is self-buffering, once-daily dosing is rational and a single missed dose matters little (fluoxetine, aripiprazole). Because a short-half-life drug swings, it needs divided dosing or a modified-release form and punishes missed doses with withdrawal (venlafaxine IR, lithium in some regimens). Match the schedule to the half-life, not to habit.

18.9 Special populations: hepatic, renal, elderly, pregnancy and lactation

Every ADME step shifts in the populations you actually treat, and the exam tests the direction of change and the drug that is the exception.

POPULATION	DOMINANT KINETIC CHANGE	PRACTICAL RULE AND THE DRUG IT TURNS ON
Hepatic impairment	Reduced first-pass and phase I metabolism; low albumin raises free fraction; reduced clearance of hepatically cleared drugs	**Prefer drugs with minimal hepatic handling; among benzodiazepines choose lorazepam, oxazepam, temazepam (phase II glucuronidation only, no active metabolites, spared in liver disease)**
Renal impairment	Reduced excretion of renally cleared drugs and active metabolites	**Lithium is the critical one: it is renally excreted and unmetabolised, so any fall in GFR (dehydration, NSAIDs, ACE inhibitors, thiazides) raises the level toward toxicity; amisulpride and paliperidone are also renally cleared**
Elderly	Falling GFR and hepatic mass, reduced albumin, and increased fat-to-water ratio enlarging the Vd of lipophilic drugs, all prolonging half-life; increased BBB permeability and receptor sensitivity	**"Start low, go slow"; avoid long-half-life benzodiazepines (diazepam accumulates); anticholinergic load and orthostasis compound the kinetic risk**
Pregnancy	Increased plasma volume and GFR, increased hepatic metabolism (induction of some CYPs), fall in albumin; net effect often lowers plasma levels of some drugs as pregnancy advances	**Lithium clearance rises with GFR in pregnancy then falls abruptly at delivery, so the level must be tracked and the dose reduced around delivery to avoid postpartum toxicity; lamotrigine levels fall substantially and often need upward adjustment**
Lactation	Transfer into milk favours lipophilic, low-protein-bound, low-molecular-weight, unionised drugs; infant clearance is immature	**The relative infant dose (infant dose per kg as a percentage of the maternal dose per kg) under about 10% is generally considered acceptable; sertraline is a preferred SSRI on this metric, lithium is relatively contraindicated**

Lithium recurs in four of the five rows because it is the drug whose kinetics (renal, unmetabolised, narrow index, small Vd) leave no margin for a physiological shift. Learn the special-population section through lithium first, then generalise.

INDIA

Genetic variation in drug-metabolising enzymes is clinically relevant in Indian populations: **CYP2C19** poor-metaboliser frequency is appreciable, affecting escitalopram and clozapine handling, and slow-acetylator status affects isoniazid (relevant when co-prescribing with psychotropics in patients on antitubercular therapy). Formal pharmacogenomic testing is not yet routine in most Indian settings, so dose titration and clinical monitoring remain the practical safeguard.

18.10 Therapeutic drug monitoring: lithium, valproate and clozapine

When to measure the blood level. **Therapeutic drug monitoring (TDM)** is justified when a drug has a narrow therapeutic index, a clear concentration-effect (or concentration-toxicity) relationship, wide interindividual kinetic variability, and a level that is not easily read off the clinical picture (Maudsley 2021). In psychiatry the three drugs for which TDM is mandatory or strongly indicated are lithium, valproate and clozapine; sampling is standardised as a **trough level**, taken just before the next dose once steady state is reached.

Lithium

The archetypal narrow-index drug. Standard maintenance range approximately **0.6 to 0.8 mmol/L** (some target up to 1.0, and up to about 1.2 in acute mania); toxicity climbs above roughly 1.5 mmol/L and is serious above 2.0. Sample a **12-hour post-dose trough**, check 5 to 7 days after any dose change (its half-life is around 18 to 24 hours), then routinely every 3 to 6 months with renal and thyroid function.

Valproate

Reference range approximately **50 to 100 mg/L (about 350 to 700 micromol/L)** in the epilepsy tradition; the concentration-response relationship in mania is weaker, so TDM is used more for adherence, toxicity and the free-fraction caveat than for titration. Trough sampling; watch the saturable protein binding described above.

Clozapine

A plasma **clozapine level around 350 to 600 ng/mL (micrograms/L)** is the usual therapeutic threshold, with response unlikely below about 350; seizure risk and toxicity rise steeply above roughly 600 to 1000. Because CYP1A2 drives its metabolism, levels swing with smoking status and interacting drugs, and the clozapine-to-norclozapine ratio helps flag adherence and metabolic changes (Maudsley 2021, Stahl 2020).

0.6-0.8	50-100	350-600
LITHIUM MAINTENANCE MMOL/L (12H TROUGH)	VALPROATE MG/L	CLOZAPINE NG/ML

COMMON TRAP

A lithium level is meaningful only as a standardised **12-hour trough**; a random or peak sample is uninterpretable and a common error. For clozapine, the highest-yield trap is the **smoking-cessation surge**: cigarette smoke induces CYP1A2, so a patient stabilised on clozapine who stops smoking (planned quit, hospital admission, or a ward smoking ban) can see plasma levels rise by 50% or more into the toxic range within days. Reduce the dose and monitor when smoking status changes.

18.11 Pharmacogenomics: the modern kinetic frontier (currency to 2026)

The 2020s addition to this topic is **pharmacogenomic (PGx)** testing, which reads the genotype of drug-metabolising enzymes to predict phenotype before dosing. The best-evidenced psychiatric applications are the polymorphic CYP2D6 and CYP2C19 loci: a **poor metaboliser** accumulates a substrate (risk of toxicity at a standard dose), while an **ultrarapid metaboliser** subtherapeutically clears it (risk of non-response). International consortia (CPIC and DPWG) publish genotype-guided dosing guidance for several antidepressants, and regulators have added PGx information to the labels of drugs such as the CYP2D6-metabolised agents. The examinable principle is that PGx individualises the metabolism step of ADME, converting population dosing into genotype-informed dosing, though clinical uptake, and cost-effectiveness, remain uneven and it is not yet standard of care in most settings including India.

MNEMONIC

ADME, and "Load with Vd, Maintain with Clearance"

The four steps are **A**bsorption, **D**istribution, **M**etabolism, **E**xcretion. The two dosing rules hang off two parameters: the **loading dose fills the Vd** (loading dose = Vd times target level divided by F) and the **maintenance dose replaces what clearance removes.** Half-life, t-half = 0.693 times Vd divided by CL, is the bridge, and 4 to 5 half-lives is the answer to both "when is it at steady state" and "when is it washed out."

HOLD THIS

Loading dose fills the Vd, maintenance dose replaces what clearance removes, and steady state (or washout) takes 4 to 5 half-lives. Half-life is the bridge: t-half = 0.693 times Vd divided by clearance.

19 · Pharmacodynamics, receptor theory and dose-response

Pharmacodynamics is "what the drug does to the body": the quantitative relationship between a drug at its molecular target and the biological effect that follows, as distinct from pharmacokinetics ("what the body does to the drug"). For psychiatry this is the grammar underneath every prescription, because almost all psychotropics act by occupying a **receptor** (or a transporter or enzyme, covered elsewhere) and shifting its output up or down. The examiner tests this topic as a set of clean, high-yield definitions plus their drug exemplars: the difference between affinity and efficacy, the agonist spectrum from full agonist to inverse agonist, the two flavours of antagonism, and the numbers that describe a dose-response curve. Get these right and

a large slice of clinical pharmacology (why aripiprazole is not just another D2 blocker, why buprenorphine has a ceiling, why flumazenil reverses a benzodiazepine) falls out for free (Stahl 2021, Kaplan & Sadock 2024).

This fragment builds from the binding event outward: first receptor occupancy and the two independent properties a ligand can have (affinity, efficacy); then the full agonist spectrum and the two-state model that makes sense of inverse agonism; then the dose-response curve and its landmark numbers (EC50, therapeutic index); then the competitive/non-competitive distinction, spare receptors and allosteric modulation; and finally the three canonical worked examples. It cross-references the receptor-transduction machinery (GPCRs, ion channels) from the transporters-and-receptors topic of these notes. A concept figure of the agonism spectrum overlaid on log dose-response curves is flagged in metadata.

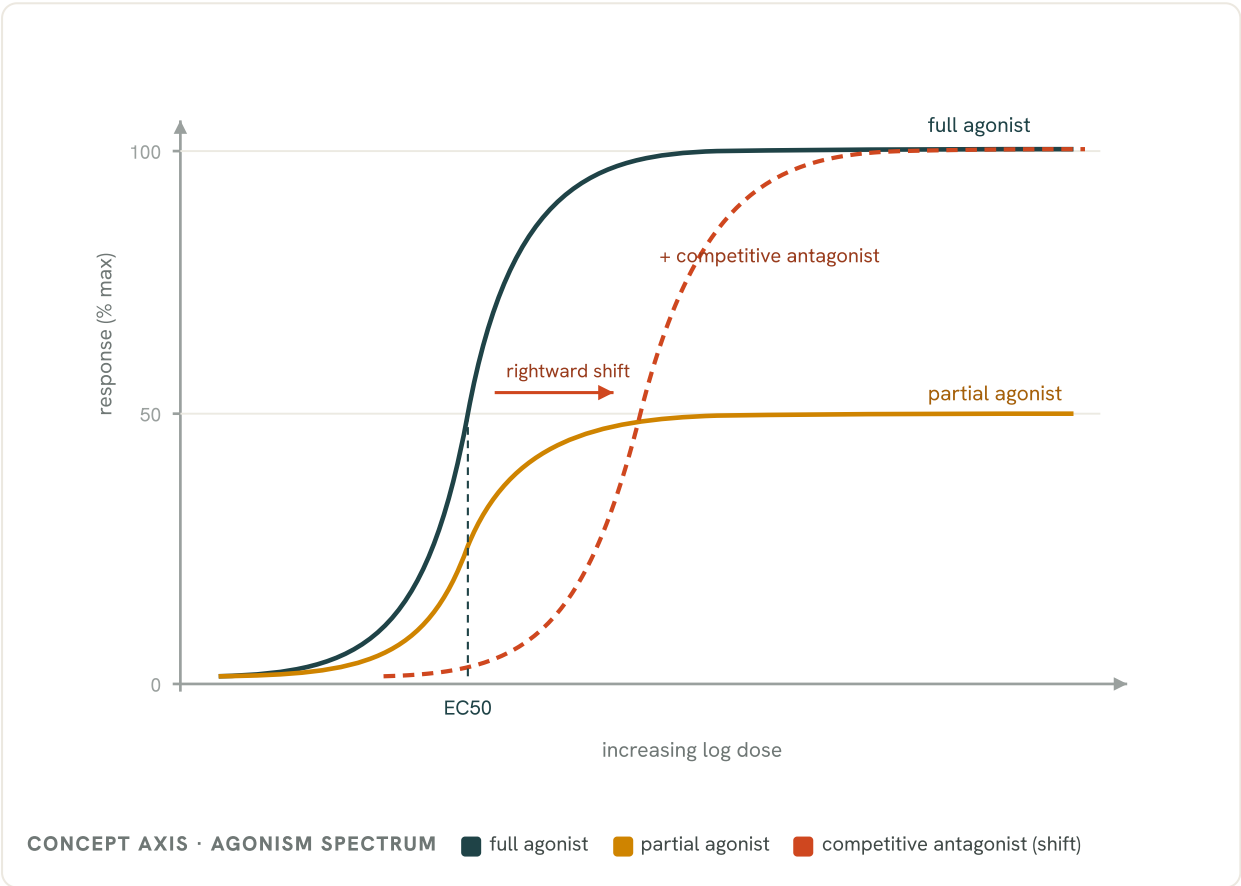


Fig 2.10 The log dose-response curve and the agonism spectrum. A full agonist reaches the maximal response; a partial agonist has lower intrinsic activity and plateaus below maximum (aripiprazole at D2, buprenorphine at mu); a competitive antagonist shifts the agonist curve rightward without lowering its maximum (surmountable). EC50, the dose giving half-maximal response, indexes potency; the plateau height indexes efficacy.

19.1 Receptor binding: occupancy, affinity and the two independent properties

Two things a ligand does, and they are separable. A drug that acts at a receptor has two logically distinct properties. **Affinity** is the tendency to bind, the strength of the drug-receptor association, and it determines what fraction of the receptor population a given concentration will occupy; it is captured by the dissociation constant **Kd** (the concentration occupying half the receptors), so a lower Kd means higher affinity. **Efficacy** (intrinsic efficacy, older term *intrinsic activity*) is a separate property: once bound, does the ligand change receptor activity, and by how

much? Agonists have both affinity and non-zero intrinsic efficacy (they bind and produce a response); antagonists have affinity but *zero* intrinsic efficacy (they bind and do nothing themselves, but occupy the site) (Kenakin 2010).

Why the separation matters clinically. A drug can bind avidly yet do nothing (a high-affinity antagonist such as many antipsychotics), or bind and only partly activate (a partial agonist). This is the conceptual root of the whole agonist spectrum in 19.2: affinity puts the drug on the receptor, efficacy decides what happens next. In the classical framework the response of a tissue is a function of both the fraction occupied and the intrinsic efficacy of the occupying ligand.

Affinity

The strength of drug-receptor binding, indexed by Kd (lower Kd = higher affinity). Governs occupancy at a given concentration but says nothing about what the bound drug does.

Efficacy / intrinsic activity

The capacity of the bound ligand to change receptor activity and generate a response. Full agonist = maximal, partial agonist = submaximal, antagonist = zero, inverse agonist = negative.

Occupancy

The proportion of the receptor population bound at a given drug concentration; a function of affinity and concentration. Occupancy is necessary but, because of spare receptors (19.7), not always proportional to response.

19.2 The agonist spectrum: full, partial, antagonist, inverse

One continuum, four named positions. Stahl frames the ligands acting at a G-protein-linked receptor as sitting along a single **agonist spectrum**, ordered by their effect on signal transduction (Stahl 2021). At one end the naturally occurring neurotransmitter, or a drug mimicking it, is a **full agonist**: it drives the receptor to its maximal conformational change and the full downstream cascade (maximal second-messenger synthesis, maximal phosphorylation). A **partial agonist** ("stabilizer") produces a conformational change intermediate between the full agonist and the resting receptor, so it turns the signal up from baseline but not to maximum. A **silent antagonist** has affinity but no efficacy: alone it does nothing, it simply occupies the site and holds the receptor at its no-agonist conformation, blocking anything else. An **inverse agonist** is the true opposite of an agonist: it not only blocks but drives receptor output *below* the baseline, resting level (Stahl 2021).

The partial-agonist dual personality. The examiner-favourite property is that a partial agonist behaves differently depending on the prevailing tone. Where the endogenous full agonist is scarce (low dopaminergic tone, mesolimbic), the partial agonist acts as a *net agonist* and raises signalling; where the full agonist is abundant (high tone, mesocortical or with a full agonist present), it competes it off and acts as a *net antagonist*, dimming the excess. This is Stahl's rheostat/"Goldilocks" idea: a partial agonist finds a stable level "not too hot, not too cold." It is exactly why aripiprazole (19.8) stabilises dopamine rather than simply blocking it.

COMMON TRAP

An antagonist is *not* the opposite of an agonist. A silent antagonist has no action of its own in the absence of agonist; it is the **inverse agonist** that has the opposite action, reducing constitutive activity below baseline. Also do not call a partial agonist "weak" and stop there: partial agonism means a submaximal ceiling and dual behaviour, not simply reduced efficacy, and this distinction drives real clinical differences (Stahl 2021).

19.3 Constitutive activity, the two-state model and inverse agonism

Receptors work when no drug is present. Inverse agonism only makes sense once you accept that many receptors, especially GPCRs, have **constitutive activity**: even with no agonist bound, a fraction of the population spontaneously adopts the active conformation and generates a low baseline signal, most visibly where receptor density is high (Stahl 2021). The **two-state model** formalises this: receptors sit in equilibrium between an inactive state (R) and an active state (R*), and a ligand's behaviour depends on which state it prefers. A ligand with higher affinity for R* enriches the active pool and acts as an agonist; a ligand with higher affinity for R depletes the active pool below baseline and acts as an **inverse agonist**; a ligand with equal affinity for both does not change the balance and behaves as a neutral antagonist, though it still blocks other ligands from binding (Costa & Herz 1989).

Why this is not academic. Many drugs historically labelled "antagonists" are, on careful testing, inverse agonists: the point is easy to miss because inverse agonism is only observable in a system with measurable constitutive activity; where constitutive activity is low, an inverse agonist looks like a plain competitive antagonist (Costa & Herz 1989). Pimavanserin, a 5-HT2A inverse agonist licensed for Parkinson-disease psychosis, is the clean psychiatric exemplar of a drug developed explicitly as an inverse agonist rather than a blocker.

PEARL

A useful three-line ladder: full agonist drives R toward R* (signal up to max); neutral antagonist locks the existing R/R* balance and blocks others (no change alone); inverse agonist pushes the balance toward R (signal below baseline). Constitutive activity is the hidden variable, and it is why the same molecule can read as "antagonist" in one tissue and "inverse agonist" in another (Stahl 2021).

19.4 Dose-response, the log curve and EC50

The sigmoid you must be able to read. Plot effect against drug concentration and you get a hyperbola; plot effect against the *logarithm* of concentration and it straightens into the familiar sigmoid, which is why dose-response curves are conventionally drawn on a log x-axis. The key landmark on the curve is the **EC50**, the concentration producing 50 percent of that drug's own maximal effect (the equivalent term for the fraction bound is the Kd; when measuring effect in a whole tissue it is the EC50). The **height** of the plateau reflects *efficacy* (the maximal attainable effect, Emax), and the **horizontal position** reflects *potency* (how much drug is needed to get there).

Potency versus efficacy, the classic discriminator. These are independent and constantly confused. **Potency** is a matter of dose: a more potent drug sits further left on the log axis (lower EC50), so less is needed, but potency alone says nothing about how good the drug is. **Efficacy** is the ceiling: the maximal effect the drug can produce however high the dose. A low-potency, high-efficacy drug given at the right dose can outperform a high-potency, low-efficacy one. In antipsychotics, haloperidol is high-potency (milligram doses) and chlorpromazine low-potency (hundred-milligram doses), yet their antipsychotic efficacy is broadly comparable: potency here reflects D2 affinity and daily dose, not clinical superiority (Kaplan & Sadock 2024).

HOLD THIS

Potency is horizontal position (EC50, the dose needed); efficacy is the ceiling (Emax). Haloperidol is more potent than chlorpromazine but not more efficacious; affinity puts a drug on the receptor, efficacy decides what it does there.

EC50

Concentration producing half of that drug's maximal effect; the standard index of potency for a graded (continuous) response. The steeper and further-left the curve, the more potent the drug.

ED50

The dose producing a specified effect (or the response of interest) in 50 percent of a population; used for quantal (all-or-none) responses and to derive the therapeutic index.

Emax

The maximal effect a drug can produce; the plateau of the curve. Reflects efficacy, not potency.

19.5 Therapeutic index and the safety window

How much room between working and harming. The **therapeutic index (TI)** is the ratio of the dose (or exposure) that produces toxicity to the dose that produces the therapeutic effect, classically TD50/ED50 in animals or LD50/ED50 for lethality. A large TI means a wide safety margin; a *narrow* TI means therapeutic and toxic doses are dangerously close, so the drug needs plasma-level monitoring and careful titration. In psychiatry this single concept explains the monitoring burden of **lithium** (narrow index, routine levels, toxicity just above the therapeutic range) and to a lesser degree some anticonvulsant mood stabilisers, versus the very wide index of the SSRIs, which are correspondingly hard to fatally overdose on their own (Kaplan & Sadock 2024).

CLINICAL ANCHOR

Narrow therapeutic index is the reason lithium is level-monitored (target trough roughly 0.6 to 0.8 mmol/L for maintenance, higher in acute mania), why dehydration, NSAIDs, thiazides and ACE inhibitors are dangerous (they raise lithium levels), and why lithium is a poor choice where adherence and monitoring cannot be assured. Contrast the SSRIs, whose wide index underlies their first-line status and relative overdose safety compared with the TCAs (narrow index, cardiotoxic in overdose).

INDIA

The wide-versus-narrow-index divide is directly practical here. Lithium remains cheap and widely used, but reliable serum-lithium assay access is uneven outside district and tertiary centres, which sharpens the case for SSRIs and low-toxicity agents where monitoring is impractical. Where TCAs are still prescribed for cost reasons, their narrow index and lethality in overdose warrant caution in patients at suicide risk and limited dispensing.

19.6 Competitive versus non-competitive antagonism

Can more agonist overcome the block, or not? A **competitive antagonist** binds reversibly at the same (orthosteric) site as the agonist, so the two compete; adding more agonist raises its probability of occupancy and eventually *surmounts* the block. On the dose-response curve this shifts the agonist curve to the right (higher EC50, reduced potency) but the same maximal effect (Emax) is still reachable at a high enough dose (Kenakin 2010). Most clinically used receptor antagonists are of this type, and it is why a benzodiazepine antagonist can be titrated and why beta-blocker effects can, in principle, be overridden by intense sympathetic drive.

Non-competitive / irreversible. A **non-competitive antagonist** either binds irreversibly to the orthosteric site or acts at a separate (allosteric) site to reduce the response in a way that added agonist cannot overcome. Here the curve is depressed downward: *Emax falls* and cannot be restored by more agonist (insurmountable block); potency (EC50) may be unchanged until spare receptors are exhausted. Phenoxybenzamine (irreversible alpha-blocker) is the standard general-pharmacology exemplar; in the CNS, channel-blocking NMDA antagonists such as ketamine and memantine act within the ion-channel pore, a use-dependent, non-competitive style of block.

FEATURE	COMPETITIVE ANTAGONIST	NON-COMPETITIVE / IRREVERSIBLE
Binding site	Same (orthosteric) site as agonist	Irreversible orthosteric, or a separate allosteric site
Effect of adding more agonist	**Block surmounted; response restored**	**Block insurmountable; response not fully restored**
Log dose-response curve	Parallel rightward shift	Downward depression of the curve
EC50 (potency)	Increased (curve shifts right)	Often unchanged until spare receptors exhausted
Emax (ceiling)	Unchanged	**Reduced**
Exemplar	Naloxone, flumazenil, propranolol	Phenoxybenzamine; ketamine/memantine (channel block)

Competitive versus non-competitive antagonism read off the dose-response curve. The single most testable discriminators are surmountability (does extra agonist win?) and whether Emax is preserved (competitive) or lowered (non-competitive).

RULE **Competitive block shifts the curve right but keeps Emax (surmountable); non-competitive block lowers Emax and cannot be overcome by more agonist.**

19.7 Spare receptors, receptor reserve and occupancy-response uncoupling

Maximal effect before full occupancy. Because postreceptor signalling machinery can saturate, an agonist can produce its maximal tissue response while occupying only a fraction of the receptor population; the unoccupied remainder are the **spare receptors** or *receptor reserve* (Kenakin 2010). The term is a mild misnomer, since all receptors participate and none are literally spare, but the phenomenon is real: one agonist might need only 25 percent occupancy for Emax where a lower-efficacy agonist needs 75 percent, the difference reflecting intrinsic efficacy. A large receptor reserve means the EC50 for effect lies well to the left of the Kd for binding, so occupancy and response are uncoupled.

Consequences worth knowing. A receptor reserve raises tissue sensitivity (small occupancy suffices) and buffers against a competitive or even a partial irreversible antagonist: the block must first consume the reserve before Emax starts to fall, which is one reason irreversible antagonists can leave potency intact until a threshold. It also underlies why receptor *occupancy* (from PET studies, for example the roughly 65 to 80 percent striatal D2 occupancy window associated with antipsychotic efficacy without extrapyramidal side-effects) is a more useful clinical readout than plasma level alone (Kaplan & Sadock 2024).

19.8 Allosteric modulation and functional selectivity

Acting from the side, not the front door. An **allosteric modulator** binds at a site distinct from the orthosteric (agonist) site and changes the receptor's response to the endogenous agonist without necessarily activating the receptor on its own. A **positive allosteric modulator (PAM)** increases the agonist's effect, a **negative allosteric modulator (NAM)** decreases it. The archetype in psychiatry is the **benzodiazepine**, a PAM at the GABA-A receptor: it has no action without GABA but, when GABA is present, increases the frequency of chloride-channel opening, enhancing inhibition. This "only works in the presence of the natural transmitter" property gives allosteric drugs a ceiling and a generally safer profile than direct agonists, and is being pursued for muscarinic and metabotropic-glutamate targets.

Functional selectivity (biased agonism). A modern refinement of receptor theory: a single receptor couples to more than one downstream pathway (classically G-protein versus beta-arrestin), and a ligand can preferentially activate one over the other, so intrinsic efficacy is not a single fixed number but is pathway-dependent (Kenakin 2010). The mu-opioid receptor is the worked example: G-protein signalling mediates analgesia while beta-arrestin recruitment is linked to constipation and respiratory depression, motivating G-protein-biased agonists such as oliceridine that aimed to separate analgesia from those adverse effects. Aripiprazole's actions at D2 have likewise been attributed partly to functional selectivity, not partial agonism alone (de Bartolomeis 2015).

MNEMONIC

PAM Pushes, NAM Nixes; benzos are the PAM

Positive **A**llosteric **M**odulators *push* the transmitter's effect up, **N**egative ones *nix* it. Anchor the whole class to benzodiazepines at GABA-A: no GABA, no benzodiazepine effect, which is exactly why an allosteric drug has a self-limiting ceiling.

19.9 Worked examples: aripiprazole, buprenorphine, flumazenil

Three drugs that make the theory concrete. These are the canonical viva exemplars, one for each of partial agonism, ceiling-effect partial agonism, and competitive antagonism.

Aripiprazole: the D2 partial agonist

A high-affinity **partial agonist at the dopamine D2 receptor** (Burris 2002), and a partial agonist at 5-HT1A with 5-HT2A antagonism. As a "dopamine stabiliser" it dampens excess mesolimbic dopamine (net antagonist where tone is high, giving antipsychotic effect) while providing enough tone in mesocortical and tuberoinfundibular pathways to reduce parkinsonism and, characteristically, to spare or even lower prolactin. Its ceiling on D2 activation explains the low extrapyramidal and prolactin burden; functional selectivity at D2 is thought to contribute (de Bartolomeis 2015). Brexpiprazole and cariprazine share the D2 partial-agonist mechanism.

Buprenorphine: partial mu agonism with a ceiling

A **partial agonist at the mu-opioid receptor** (with kappa antagonism) and high mu affinity (Tripathi/KDT 2019). The partial agonism gives a *ceiling effect* on respiratory depression, making it far safer in overdose than full agonists and a mainstay of opioid-use-disorder maintenance (usually combined with naloxone to deter injection). Its high affinity means it can displace and block full agonists, which is why starting buprenorphine in a patient still opioid-dependent can precipitate withdrawal, the practical corollary of "high affinity, submaximal efficacy."

Flumazenil: the competitive benzodiazepine antagonist

A **competitive antagonist at the benzodiazepine binding site** of the GABA-A receptor, used to reverse benzodiazepine sedation and overdose (Kaplan & Sadock 2024). Because the block is competitive and surmountable, and because flumazenil's short half-life is briefer than most benzodiazepines, re-sedation can occur and repeat dosing may be needed. In the benzodiazepine-dependent patient it can precipitate withdrawal seizures, the mirror-image caution to buprenorphine.

PEARL

Line the three up against the spectrum: aripiprazole (partial agonist, stabiliser), buprenorphine (partial agonist with a safety ceiling), flumazenil (competitive antagonist). Add naloxone/naltrexone as the mu competitive antagonists and pimavanserin as the 5-HT2A inverse agonist, and you have one drug for every position on the agonist spectrum, a common single-best-answer pattern.

20 · CYP450 system and drug metabolism

The cytochrome P450 (**CYP450**) superfamily is the single most examinable pharmacokinetic topic in psychiatry, because almost every psychotropic drug is a substrate, inhibitor, or inducer of one or more of its isoenzymes, and because the resulting drug interactions are a leading cause of

avoidable toxicity and treatment failure. **Why it matters.** A candidate who can name the five psychiatrically relevant isoenzymes, the flagship substrate for each, and the small set of high-yield inhibitors and inducers can predict and explain the majority of clinically significant interactions asked in vivas and MCQs. The examiner is rarely testing rote lists; the test is whether you can reason from "drug A inhibits enzyme X" and "drug B is a substrate of enzyme X" to "drug B accumulates and becomes toxic."

CYP450 enzymes are haem-containing mono-oxygenases concentrated in the hepatic endoplasmic reticulum and the enterocytes of the small intestine, where they mediate the bulk of oxidative **Phase I metabolism** (Kaplan & Sadock 2024). Nomenclature follows sequence homology: the number is the family (CYP2), the letter the subfamily (CYP2D), and the final number the specific gene (CYP2D6). Roughly 90% of clinically used drugs are handled by just six isoenzymes, of which CYP3A4, CYP2D6, CYP2C19, CYP1A2, and CYP2C9 dominate psychiatric practice.

20.1 Phase I versus Phase II, and where CYP450 sits

Biotransformation in two phases. **Phase I** reactions (oxidation, reduction, hydrolysis) introduce or unmask a functional group and are catalysed overwhelmingly by CYP450; they usually inactivate the drug but can also generate active metabolites (for example, fluoxetine to norfluoxetine, or risperidone to 9-hydroxyrisperidone/paliperidone). **Phase II** reactions conjugate the drug or its Phase I metabolite with an endogenous moiety, most importantly glucuronidation by the UDP-glucuronosyltransferase (UGT) family, rendering it water-soluble for excretion. A drug that is cleared purely by Phase II conjugation (lorazepam, oxazepam, temazepam, lamotrigine) largely bypasses CYP450 and is therefore relatively protected from CYP-mediated interactions, a point of high clinical value in hepatic impairment and polypharmacy (Kaplan & Sadock 2024).

20.2 CYP3A4: the highest-volume isoenzyme

Substrates. CYP3A4 is the most abundant hepatic and intestinal CYP and metabolises the largest share of drugs, including most benzodiazepines (alprazolam, midazolam, triazolam), buspirone, most statins, quetiapine, ziprasidone, pimozide, carbamazepine, aripiprazole (with 2D6), and lurasidone. **Inhibitors.** The potent inhibitors are the azole antifungals (ketoconazole, itraconazole, fluconazole), macrolides (clarithromycin, erythromycin), protease inhibitors (ritonavir, indinavir), and grapefruit juice, which inhibits intestinal 3A4; among psychotropics, fluvoxamine and nefazodone are strong inhibitors. **Inducers.** Carbamazepine, phenytoin, phenobarbital, rifampicin, and St John's wort are the classic inducers. The magnitude can be dramatic: lurasidone exposure rises roughly 10-fold with ketoconazole, so potent 3A4 inhibitors are contraindicated, while potent inducers such as rifampicin can render it subtherapeutic (Spina 2015).

20.3 CYP2D6: the polymorphic workhorse

Substrates. CYP2D6 handles a disproportionate share of psychotropics relative to its modest hepatic abundance: most tricyclic antidepressants, many SSRIs (paroxetine, fluoxetine),

venlafaxine, duloxetine, atomoxetine, vortioxetine, risperidone, aripiprazole, iloperidone, haloperidol, thioridazine, and the analgesic prodrugs codeine and tramadol (which require 2D6 to form their active opioid metabolites). **Inhibitors.** The strong psychiatric inhibitors are bupropion, fluoxetine, and paroxetine, with quinidine and terbinafine as potent non-psychiatric inhibitors; duloxetine is moderate. **A defining feature.** CYP2D6 is not inducible, so it has no clinically important inducers; interactions occur only through inhibition or genetic variation (Spina 2015). This makes 2D6 the isoenzyme most affected by pharmacogenetic phenotype (see 20.7).

CLINICAL ANCHOR

Paroxetine or fluoxetine added to a patient on a tricyclic antidepressant is a classic 2D6 interaction: the TCA level rises, risking anticholinergic delirium and cardiac conduction effects. Obtain a TCA level and reduce the dose. The same inhibition of 2D6 blocks codeine's conversion to morphine, so an analgesic dose of codeine may simply fail to work in a patient on paroxetine.

20.4 CYP2C19: benzodiazepines, PPIs, and citalopram

Substrates. CYP2C19 metabolises diazepam, citalopram and escitalopram, sertraline (partly), amitriptyline and clomipramine (demethylation), the proton pump inhibitors, and clopidogrel (activation). **Inhibitors and inducers.** Fluvoxamine and fluoxetine inhibit 2C19; omeprazole, cimetidine, and ticlopidine also inhibit it; carbamazepine, phenytoin, phenobarbital, and rifampicin induce it (Spina 2015). **Genetics matter here too.** 2C19 is highly polymorphic, and the FDA advises a maximum citalopram dose of 20 mg/day in CYP2C19 poor metabolisers because of QT-prolongation risk from elevated exposure.

20.5 CYP1A2: clozapine, olanzapine, and the smoking effect

Substrates. CYP1A2 metabolises clozapine and its active metabolite norclozapine, olanzapine, asenapine, duloxetine, caffeine, and theophylline. **The key inhibitor is fluvoxamine,** a potent 1A2 inhibitor that can multiply clozapine levels several-fold and precipitate toxicity; fluoroquinolones (ciprofloxacin) and oral contraceptives also inhibit 1A2. **The key inducer is tobacco smoke,** specifically the polycyclic aromatic hydrocarbons (not nicotine), which increase olanzapine clearance by about 98% and comparably reduce clozapine levels (Spina 2015). This is the highest-yield induction fact in the syllabus.

CLINICAL ANCHOR

A stable smoker on clozapine who is admitted to a smoke-free ward, or who quits smoking abruptly, loses 1A2 induction over about a week: clozapine levels rebound and can reach toxic, seizure-provoking or myocarditis-associated concentrations. Anticipate a dose reduction of roughly 30 to 40% and monitor levels. The reverse (a non-smoker who starts smoking) needs an upward adjustment. Charcoal-grilled meat is a weaker dietary inducer of the same enzyme.

20.6 CYP2C9: warfarin and the anticonvulsants

Substrates and interactions. CYP2C9 metabolises warfarin (the active S-isomer), phenytoin, several NSAIDs, and sulfonylureas. It is inhibited by valproate and fluoxetine and by fluconazole and amiodarone, and induced by carbamazepine and rifampicin. The examinable interaction is valproate or fluoxetine plus warfarin, which raises the INR and bleeding risk, mandating INR monitoring (Spina 2015). Carbamazepine, conversely, induces 2C9 and lowers warfarin effect.

20.7 Genetic polymorphism: poor and ultrarapid metabolisers

Four metaboliser phenotypes. For polymorphic enzymes (2D6, 2C19, 2C9) the population divides into **poor metabolisers** (PM, two non-functional alleles, minimal enzyme activity), **intermediate metabolisers** (IM), **extensive/normal metabolisers** (EM, the reference), and **ultrarapid metabolisers** (UM, gene duplication or multiduplication with supranormal activity).

Consequences depend on the drug. For a drug inactivated by the enzyme, a PM accumulates the parent drug and risks toxicity, whereas a UM sub-therapeutically clears it and may fail treatment. For a prodrug activated by the enzyme (codeine, tramadol, clopidogrel), the logic inverts: the PM fails to form the active metabolite and gets no effect, while the UM over-activates and risks toxicity (the basis of codeine-related opioid deaths in ultrarapid children). **Population frequencies.** Across world populations the predicted CYP2D6 PM frequency ranges from about 0.4% to 5.4%, highest in Europeans (about 5.4%) and lowest in East Asians (about 0.4%); 1 to 21% of individuals are UM depending on ancestry (Gaedigk 2017, cited in Kaplan & Sadock 2024). CYP2C19 PM status is notably more common in East Asian populations. This cross-population variability makes pharmacogenetics directly relevant to Indian practice; the mechanism is developed further in the the Psychiatric Genetics notes pharmacogenetics topic.

> **COMMON TRAP**
>
> Do not assume "poor metaboliser equals low drug level." That is true only for prodrugs. For the far more common situation of a drug inactivated by the enzyme, the poor metaboliser has a HIGH level and is the one at risk of toxicity. Read the stem carefully for whether the drug is the active moiety or a prodrug.

> **PEARL**
>
> Enzyme inhibition is immediate (competition at the active site, effect within a day or two) whereas induction is delayed and gradual (it requires new enzyme protein synthesis, taking one to two weeks to develop and a similar time to wane after the inducer stops). This asymmetry explains both the delayed fall in clozapine levels when smoking starts and the delayed rebound when it stops.

20.8 P-glycoprotein: the efflux transporter

A transport-level determinant, not a metabolising enzyme. **P-glycoprotein** (P-gp; MDR1, gene ABCB1) is an ATP-dependent efflux pump expressed at the intestinal wall, the biliary and renal canaliculi, and the blood-brain barrier, where it pumps substrates back out of cells and limits their absorption and CNS penetration (Tasman 2015). Many psychotropics (TCAs, SSRIs, atypical antipsychotics, carbamazepine, lamotrigine) and digoxin are substrates. Inhibitors such

as verapamil, clarithromycin, and ciclosporin reduce efflux and raise systemic and central exposure; inducers such as rifampicin and St John's wort lower it. P-gp substrate and inhibitor profiles overlap substantially with CYP3A4, so the two frequently act together at the enterocyte to shape first-pass exposure.

20.9 UGT and glucuronidation: lamotrigine and valproate

The Phase II axis with its own interactions. The UGT family conjugates lamotrigine, lorazepam, oxazepam, morphine, and many antipsychotics. **The flagship interaction is valproate plus lamotrigine.** Valproate inhibits UGT (specifically the glucuronidation of lamotrigine), roughly doubling lamotrigine levels and prolonging its half-life; this is why the lamotrigine titration schedule is halved when it is co-prescribed with valproate, to reduce the risk of serious rash including Stevens-Johnson syndrome. Conversely, **enzyme-inducing anticonvulsants** (carbamazepine, phenytoin, phenobarbital) induce UGT and roughly halve lamotrigine levels, requiring a higher target dose (Spina 2015). Carbapenem antibiotics induce UGT-mediated glucuronidation and can precipitously drop valproate levels, a well-recognised inpatient interaction. The polymorphism *UGT1A1*28* reduces glucuronidation capacity and is associated with Gilbert syndrome and reduced lamotrigine clearance (Kaplan & Sadock 2024).

CLINICAL ANCHOR

When adding lamotrigine to valproate, start lower and go slower (typically half the usual lamotrigine titration), because valproate's UGT inhibition doubles lamotrigine exposure and the rash risk is dose- and titration-rate-dependent. When adding it to an enzyme inducer such as carbamazepine, expect to need a higher maintenance dose.

RULE **Valproate inhibits UGT and roughly doubles lamotrigine, so halve the lamotrigine titration when they are combined.** The Stevens-Johnson risk is titration-rate-dependent.

20.10 Master inhibitor and inducer table

ISOENZYME	KEY PSYCHIATRIC SUBSTRATES	IMPORTANT INHIBITORS	IMPORTANT INDUCERS
CYP1A2	Clozapine, olanzapine, asenapine, duloxetine, caffeine, theophylline	**Fluvoxamine (potent), ciprofloxacin, oral contraceptives, cimetidine**	**Tobacco smoke (PAHs), carbamazepine, phenytoin, charcoal-grilled meat, modafinil**
CYP2C9	Warfarin (S-isomer), phenytoin, NSAIDs, sulfonylureas	Valproate, fluoxetine, fluconazole, amiodarone	Carbamazepine, rifampicin
CYP2C19	Diazepam, citalopram, escitalopram, clopidogrel (activation), PPIs, amitriptyline	**Fluvoxamine (potent), fluoxetine, omeprazole, cimetidine, ticlopidine**	Carbamazepine, phenytoin, phenobarbital, rifampicin

ISOENZYME	KEY PSYCHIATRIC SUBSTRATES	IMPORTANT INHIBITORS	IMPORTANT INDUCERS
CYP2D6	TCAs, paroxetine, fluoxetine, venlafaxine, duloxetine, risperidone, aripiprazole, haloperidol, codeine and tramadol (activation)	**Bupropion, fluoxetine, paroxetine (all potent), quinidine, terbinafine, duloxetine**	**None (not inducible)**
CYP3A4	Most benzodiazepines, buspirone, statins, quetiapine, ziprasidone, pimozide, lurasidone, carbamazepine	**Ketoconazole, itraconazole, clarithromycin, ritonavir, grapefruit juice, fluvoxamine, nefazodone**	**Carbamazepine, phenytoin, phenobarbital, rifampicin, St John's wort**
UGT (Phase II)	Lamotrigine, lorazepam, oxazepam, morphine, many antipsychotics	Valproate (raises lamotrigine)	Carbamazepine, phenytoin, phenobarbital (lower lamotrigine); carbapenems (lower valproate)
P-glycoprotein (ABCB1)	Digoxin, TCAs, SSRIs, atypical antipsychotics, carbamazepine, lamotrigine	Verapamil, clarithromycin, ciclosporin, itraconazole	Rifampicin, St John's wort, phenytoin

High-yield inhibitor and inducer map for the five psychiatric CYP isoenzymes plus the UGT and P-glycoprotein axes; discriminators highlighted are the facts most often tested (fluvoxamine as pan-inhibitor, smoking as the 1A2 inducer, 2D6 as non-inducible).

HOLD THIS

Tobacco smoke (not nicotine) induces CYP1A2, so quitting raises clozapine and olanzapine levels toward toxicity. Inhibition is immediate; induction and its reversal take one to two weeks.

MNEMONIC

SICKFACES.COM (inhibitors) and CRAP GPS (inducers)

For broad-spectrum CYP inhibitors: **S**odium valproate, **I**soniazid, **C**imetidine, **K**etoconazole, **F**luconazole/fluvoxamine, **A**miodarone, **C**iprofloxacin, **E**rythromycin/clarithromycin, **S**ulfonamides, **C**hloramphenicol, **O**meprazole, **M**etronidazole/grapefruit. For inducers: **C**arbamazepine, **R**ifampicin, **A**lcohol (chronic), **P**henytoin/phenobarbital, **G**riseofulvin, **P**henobarbital, **S**t John's wort/smoking. In psychiatry the four you must never forget are fluvoxamine (inhibits everything, especially 1A2 and 3A4), fluoxetine and paroxetine (2D6), and smoking plus carbamazepine (inducers).

INDIA

Two interactions recur in Indian practice. First, rifampicin from antitubercular therapy is a powerful pan-inducer (3A4, 2C9, 2C19, P-gp) and will lower levels of most psychotropics, so a patient started on ATT may need upward dose adjustment and closer monitoring. Second, the high prevalence of smoking and bidi use in male psychiatric inpatients makes the clozapine/olanzapine-smoking interaction a frequent real-world problem on admission to smoke-restricted wards.

21 · Receptor up/down-regulation, tolerance and sensitisation

Receptors are not fixed hardware. When a receptor is chronically over-stimulated or chronically blocked, the neuron re-tunes itself to defend a set-point, altering the *number*, *affinity*, and *coupling efficiency* of its receptors over hours to weeks. This **adaptive receptor regulation** is the single unifying concept behind four apparently separate clinical phenomena: the delayed onset of antidepressants, the tolerance and withdrawal that define substance dependence, the sensitisation that drives stimulant addiction, and the tardive movement disorders and supersensitivity psychosis that follow long-term antipsychotic exposure (Kaplan and Sadock 2024). The rule of thumb is homeostatic and directional: chronic agonism (or a chronic surplus of transmitter) tends to **down-regulate** and desensitise receptors, while chronic antagonism (or a chronic deficit of transmitter) tends to **up-regulate** and supersensitise them.

Why it recurs. Almost every long-latency or long-term drug effect in the paper resolves at this level. A candidate who can state that antidepressants occupy their transporter within hours but take two to three weeks to change receptor density, and can extend the same adaptive logic to why benzodiazepines cause dependence, why cocaine sensitises, and why stopping a high-potency antipsychotic can precipitate rebound movements or psychosis, has one mechanism that answers a dozen questions. The examiner is testing whether you can distinguish the immediate pharmacology of a drug from the slow neuroadaptation the brain mounts against it.

21.1 Up-regulation and down-regulation: the homeostatic direction rule

The core principle. Receptor sensitivity is under continuous regulatory and homeostatic control, so that the same drug concentration can produce a greater or lesser response depending on the receptor state (Companion to Psychiatric Studies). Two directions matter. **Down-regulation and desensitisation** follow prolonged agonist stimulation: the cell becomes refractory, receptor number falls, and coupling to G proteins weakens. **Up-regulation and supersensitivity** follow prolonged loss of stimulation, whether from denervation, transmitter depletion, or chronic antagonist blockade, and the cell responds by increasing receptor number and affinity.

Fast versus slow mechanisms. The earliest change is **homologous desensitisation**: the agonist-occupied receptor is phosphorylated by a G-protein-coupled receptor kinase (GRK), which recruits **beta-arrestin** to uncouple the receptor from its G protein within seconds to minutes, then to internalise it into endosomes (Kaplan and Sadock 2024). Internalised receptors may be recycled back (resensitisation) or trafficked to lysosomes for degradation, the latter producing true **down-regulation** (a fall in total receptor number) over hours. The slowest limb is **altered synthesis**: long-term negative feedback suppresses new receptor transcription, or induces a structurally modified receptor, changing receptor density over days to weeks (Companion to Psychiatric Studies). This three-tier timescale, phosphorylation to internalisation to transcription, is why some drug adaptations are minutes-fast and others take weeks.

Homologous desensitisation

Loss of response confined to the receptor that was occupied by agonist; mediated by GRK phosphorylation and arrestin recruitment at that receptor specifically.

Heterologous desensitisation

Loss of response spreading to other, unoccupied receptors sharing a downstream pathway; mediated by second-messenger kinases (PKA, PKC) phosphorylating receptors or shared effectors.

Down-regulation

A true reduction in receptor *number* (not just coupling), from lysosomal degradation or reduced synthesis; the slow structural correlate of chronic agonism.

Up-regulation (supersensitivity)

An increase in receptor number or affinity after chronic understimulation or antagonism; the substrate of denervation supersensitivity, withdrawal, and tardive phenomena.

HOLD THIS

Chronic agonism down-regulates and desensitises; chronic antagonism up-regulates and supersensitises. One homeostatic direction rule answers antidepressant latency, tolerance, tardive dyskinesia and supersensitivity psychosis.

21.2 Tolerance defined: the rightward shift of the dose-response curve

The operational definition. **Tolerance** is a reduced effect from a given dose after repeated exposure, so that a higher dose is needed to reproduce the original effect. Graphically it is a **parallel rightward shift of the dose-response curve** (Goodman and Gilman 2018). It is a normal, expected adaptation of the nervous system to a drug and is not in itself evidence of addiction; DSM-5-TR is explicit that tolerance and withdrawal to a prescribed CNS medication taken as directed are normal physiological responses and do not by themselves indicate a substance use disorder (DSM-5-TR 2022).

Tolerance is effect-specific, not drug-specific. A single drug develops tolerance to its different effects at different rates, a fact that is clinically lethal with opioids. Tolerance to euphoria and analgesia develops rapidly, but tolerance to respiratory depression develops slowly; a dependent user chasing the fading high can therefore reach a dose that stops their breathing, which is the pharmacological basis of the opioid overdose epidemic (Goodman and Gilman 2018). By contrast, with opioids there is minimal tolerance to constipation and miosis, so pinpoint pupils and constipation persist even in a heavily tolerant user, a useful examination discriminator.

COMMON TRAP

Tolerance, dependence, and addiction are three separate axes and must not be conflated. **Tolerance** is a shifted dose-response curve. **Physical dependence** is the emergence of a withdrawal syndrome on cessation. **Addiction (substance use disorder)** is a behavioural syndrome of compulsive use despite harm. A patient on chronic morphine for cancer pain is tolerant and physically dependent but is not addicted; a binge stimulant user can be addicted while showing sensitisation rather than tolerance and little physical withdrawal.

21.3 Pharmacokinetic versus pharmacodynamic tolerance (and tachyphylaxis)

The mechanisms of tolerance divide into two families that examiners routinely ask to be contrasted. **Pharmacokinetic (dispositional) tolerance** is a reduction in the *concentration* of drug

reaching the target, most often through **induction of metabolising enzymes.** Chronic alcohol, barbiturates, and carbamazepine induce hepatic cytochrome P450 enzymes so the drug is cleared faster and less reaches the brain; the dose-response curve shifts right because less drug arrives, not because the receptor has changed (Goodman and Gilman 2018). **Pharmacodynamic (functional) tolerance** is an adaptation at or beyond the receptor despite unchanged drug concentration: receptor down-regulation, desensitisation, or compensatory changes in downstream signalling and opposing circuits. Most tolerance of psychiatric interest, and most cross-tolerance, is pharmacodynamic.

Special forms. **Tachyphylaxis** is very rapid tolerance developing over minutes to hours with closely spaced doses, classically to indirectly acting sympathomimetics such as ephedrine and tyramine, which act by displacing stored noradrenaline: once the readily releasable vesicular pool is exhausted, further doses have little effect (Goodman and Gilman 2018). **Acute tolerance** is tolerance developing within a single episode of use, such as declining effect across a cocaine binge. **Cross-tolerance** is tolerance to one drug conferring tolerance to a pharmacologically related drug, which is exploited therapeutically: heroin-dependent patients can be detoxified with any mu-opioid agonist such as methadone or buprenorphine, and alcohol withdrawal is managed with cross-tolerant benzodiazepines (Goodman and Gilman 2018). **Learned or conditioned tolerance** adds a behavioural layer, in which environmental cues that reliably precede the drug trigger anticipatory compensatory responses; loss of those cues in a novel setting can unmask the drug's full effect and precipitate overdose at a previously tolerated dose.

TYPE	LOCUS / MECHANISM	PROTOTYPE EXAMPLE
Pharmacokinetic	**Faster clearance (enzyme induction); drug level falls**	Barbiturates, carbamazepine, alcohol inducing P450
Pharmacodynamic	**Receptor down-regulation / desensitisation; level unchanged**	Benzodiazepine, opioid receptor adaptation
Tachyphylaxis	Depletion of a releasable transmitter pool over minutes	**Ephedrine, tyramine (indirect sympathomimetics)**
Acute tolerance	Within a single exposure / binge	Cocaine across a binge
Cross-tolerance	Shared receptor or pathway	**Alcohol to benzodiazepines; heroin to methadone**
Learned / conditioned	Cue-triggered compensatory response	Setting-dependent opioid tolerance

The discriminating question is always whether less drug is reaching the target (pharmacokinetic) or the target has adapted to the same amount of drug (pharmacodynamic); tachyphylaxis is distinguished by its speed and its mechanism of transmitter-pool depletion.

21.4 Sensitisation (reverse tolerance): when repetition amplifies

The opposite adaptation. **Sensitisation**, also called **reverse tolerance**, is the progressive *increase* in a drug effect with repeated intermittent dosing, a leftward shift of the dose-response curve (Goodman and Gilman 2018). It is characteristically seen with **psychostimulants** (amphetamine, cocaine) and depends critically on an **intermittent, spaced dosing schedule**;

continuous exposure tends instead to produce tolerance. The behavioural readout in animal models is escalating locomotor activation and stereotypy to a fixed dose, and the neural substrate is progressive enhancement of dopamine release and responsiveness in the mesolimbic pathway, particularly the nucleus accumbens and ventral tegmental area, with lasting changes in glutamatergic synaptic strength.

Why it matters clinically. Sensitisation is the leading neurobiological account of the **incentive-salience** theory of addiction (Robinson and Berridge): repeated drug use sensitises the "wanting" system so that drug cues acquire escalating motivational pull even as the drug's pleasurable "liking" effect wanes, dissociating craving from enjoyment. It is also invoked to explain **stimulant-induced psychosis** and its tendency to recur faster and at lower doses on re-exposure, and it offers a candidate mechanism for the **kindling** model, in which repeated affective episodes or repeated withdrawals become progressively easier to trigger. The exam-critical contrast is that the *same* drug can produce tolerance to some effects and sensitisation to others depending on the dosing schedule.

PEARL

Schedule is the switch. **Continuous or closely-spaced dosing favours tolerance; intermittent, spaced dosing favours sensitisation.** This is why a steady therapeutic infusion behaves differently from binge use of the same stimulant, and why the behavioural sensitisation paradigm in the lab is deliberately built on spaced injections. Whenever a question pairs a stimulant with "reverse tolerance" or "increasing response," sensitisation is the answer.

21.5 Dependence and withdrawal: the opponent-process and allostasis model

Withdrawal is adaptation unmasked. Physical dependence is the state in which the brain's compensatory adaptations have grown to oppose the drug so completely that removing the drug leaves those adaptations unopposed, producing a **withdrawal syndrome** that is characteristically the mirror image of the drug's acute effects. Thus opioid withdrawal (a CNS depressant) produces autonomic arousal, insomnia, anxiety, mydriasis, piloerection, cramps and rhinorrhoea, and alcohol or benzodiazepine withdrawal (also depressants) produces hyperarousal, tremor, and seizures (Companion to Psychiatric Studies; Goodman and Gilman 2018). Withdrawal proves dependence, but dependence and withdrawal alone cannot explain the compulsive relapse that defines addiction (Companion to Psychiatric Studies).

The theoretical frame. Solomon's **opponent-process theory** formalises this: every drug-induced hedonic state (the a-process) recruits an opposing b-process that grows with repetition, so that with chronic use the opponent process comes to dominate and defines both tolerance and the negative-affect withdrawal state. Koob and Le Moal extended this to an **allostatic** model in which repeated cycles reset the hedonic set-point downward, recruiting anti-reward systems (CRF and dynorphin in the extended amygdala) and driving negatively-reinforced compulsive use. At the cellular level, opioid tolerance is now understood to involve not only classical receptor desensitisation and down-regulation but wider **allostatic and opponent processes**, including a compensatory up-regulation of the cAMP pathway (superactivation of adenylyl cyclase) in locus

coeruleus neurons that becomes overtly hyperactive on drug removal, and pass-forward adaptations propagated to downstream circuitry and glia (Cahill et al 2016).

21.6 The delayed antidepressant onset and the beta-adrenoceptor down-regulation story

The classic paradox, and its resolution. Monoamine reuptake inhibitors and MAO inhibitors raise synaptic noradrenaline and serotonin within hours, yet clinical antidepressant benefit takes two to three weeks. Acute pharmacology cannot explain a two-week latency, so the effect must be a slow adaptation, and the historically pivotal observation was that chronic (not acute) antidepressant treatment, and electroconvulsive therapy, **down-regulate postsynaptic beta-adrenoceptors** and their coupled cAMP response in cortex, on a timescale that matches the therapeutic lag (Kaplan and Sadock 2024; Companion to Psychiatric Studies). This **beta-adrenoceptor down-regulation hypothesis** reframed the therapeutic action as a receptor adaptation to sustained excess transmitter rather than the acute rise in transmitter itself, and became the textbook answer to "why do antidepressants take weeks to work."

The modern extension. The receptor-adaptation story now sits within a broader plasticity account. Alongside beta-adrenoceptor down-regulation, chronic antidepressants **desensitise inhibitory 5-HT1A and 5-HT1B/1D autoreceptors**, which initially restrain firing; over one to two weeks these autoreceptors desensitise, disinhibiting raphe firing and increasing forebrain serotonin transmission, again on a timescale matching onset (Stahl 2021). Both threads feed downstream into the CREB and BDNF plasticity cascade (subtopic on second messengers), so the fully current answer is that antidepressant latency reflects a sequence of adaptive receptor changes, autoreceptor desensitisation and postsynaptic beta down-regulation, that translate a fast transmitter change into slow synaptic remodelling.

> **COMMON TRAP**
>
> Do not present the raw monoamine hypothesis as the explanation for antidepressant onset. A simple deficit-of-monoamines model predicts an *immediate* response once reuptake is blocked, which is exactly what does not happen. The examinable point is that the **delay is itself the evidence against the naive monoamine theory** and in favour of an adaptive receptor and plasticity mechanism.

21.7 Antipsychotic dopamine supersensitivity, tardive dyskinesia and supersensitivity psychosis

Chronic blockade breeds supersensitivity. The mirror-image case is chronic *antagonism*. Sustained D2 receptor blockade by antipsychotics drives a compensatory **up-regulation and supersensitivity of striatal D2 receptors**, demonstrable as increased D2 density after chronic antipsychotic exposure (Kaplan and Sadock 2024). Two clinical consequences follow. **Tardive dyskinesia** is the classic late motor syndrome of involuntary orofacial and limb movements, attributed in the traditional model to nigrostriatal D2 supersensitivity, and it is characteristically worsened transiently by dose reduction or withdrawal (which further disinhibits the supersensitive receptors) and masked by dose increase; it is more associated with prolonged first-generation antipsychotic use and can be irreversible (Maudsley Prescribing Guidelines). The current disease-specific treatments are the **VMAT2 inhibitors valbenazine and**

deutetrabenazine, which deplete presynaptic dopamine rather than blocking the supersensitive postsynaptic receptor.

TRAP Tardive dyskinesia is transiently *worsened* by dose reduction and masked by a dose increase, because withdrawal disinhibits the supersensitive D2 receptors; raising the dose is not a treatment.

Supersensitivity in the mesolimbic system. The same adaptation in the mesolimbic pathway underlies **dopamine supersensitivity psychosis** (Chouinard's neuroleptic-induced supersensitivity psychosis): tolerance to the antipsychotic effect, rebound or breakthrough psychosis on dose reduction or switching, and an association with tardive dyskinesia are its features (Chouinard and Jones 1980; Yin et al 2017). This is the mechanistic caution behind never stopping a high-potency antipsychotic abruptly, and behind the observation that apparent "relapse" immediately after discontinuation may in part be a supersensitivity rebound rather than the natural course of illness.

CLINICAL ANCHOR

The supersensitivity concept has a practical corollary in polydipsia and hyponatraemia: one proposed mechanism is that chronic postsynaptic D2 blockade produces receptor supersensitivity with increased presynaptic dopamine release, driving hypothalamic thirst, and reducing the number and dose of antipsychotics can lessen dopamine supersensitivity and its adverse effects (Maudsley Prescribing Guidelines). It is the same adaptive up-regulation, read out in a different circuit.

21.8 Discontinuation and withdrawal syndromes across psychotropic classes

A shared logic, class-specific faces. Every discontinuation syndrome is the unmasking of an adaptation that opposed the drug, so its features are broadly the reverse of the drug's action and its severity tracks the drug's **half-life** (shorter half-life means faster fall in level and more abrupt, more severe withdrawal). **Antidepressants.** The SSRI/SNRI **discontinuation syndrome** is captured by the mnemonic **FINISH** (Flu-like symptoms, Insomnia, Nausea, Imbalance, Sensory disturbances including the characteristic "electric shock" or brain-zap sensations, and Hyperarousal). It is worst with short-half-life, high-potency agents such as paroxetine and venlafaxine, minimal with long-half-life fluoxetine, typically begins within days of stopping, and is distinguished from relapse by its early onset, physical symptom profile, and rapid resolution on reinstatement (Maudsley Prescribing Guidelines). It is now emphasised that a subset of patients experience severe and protracted withdrawal, mandating slow, often hyperbolic, tapering (Maudsley Deprescribing Guidelines).

Sedative-hypnotics and others. **Benzodiazepine withdrawal** reflects GABA-A down-regulation and glutamatergic up-regulation and can produce anxiety, insomnia, perceptual disturbance, and, dangerously, seizures and delirium, again worse with short-acting agents such as alprazolam; management is a gradual taper, often after switching to a long-acting agent such as diazepam. Tolerance to benzodiazepines and z-drugs is well recognised and is itself a reason the initial

benefit fades (Maudsley Deprescribing Guidelines). **Lithium** discontinuation, especially if abrupt, carries a rebound risk of mania and is associated with loss of prophylactic efficacy. **Antipsychotic** discontinuation can produce cholinergic rebound (nausea, insomnia, agitation) from muscarinic receptor up-regulation, plus the dopaminergic supersensitivity phenomena of subtopic 21.7.

MNEMONIC

FINISH

Flu-like, **I**nsomnia, **N**ausea, **I**mbalance (dizziness), **S**ensory disturbance (paraesthesiae, brain zaps), **H**yperarousal (anxiety, agitation). The six-domain picture of SSRI/SNRI discontinuation; onset within days of stopping, tied to short half-life, resolves on reinstatement, which is what separates it from a depressive relapse.

21.9 Exam integration: one adaptation, four syndromes

The reward for this topic is a single decision tree. Ask first whether the drug is a chronic *agonist*/transmitter-surplus (expect down-regulation, tolerance, and a hyperactive withdrawal) or a chronic *antagonist*/transmitter-deficit (expect up-regulation, supersensitivity, and rebound on removal). Then ask whether the schedule is continuous (favours tolerance) or intermittent (favours sensitisation). This maps every case: antidepressants down-regulate beta-adrenoceptors and desensitise autoreceptors, explaining their two-to-three-week latency; benzodiazepines and opioids down-regulate their inhibitory systems, explaining tolerance and mirror-image withdrawal; intermittent stimulants sensitise mesolimbic dopamine, explaining reverse tolerance and craving; and chronic antipsychotics up-regulate D2 receptors, explaining tardive dyskinesia and supersensitivity psychosis. Current agents fit the same frame: the muscarinic antipsychotic **xanomeline-trospium** acts through M1/M4 GPCRs subject to the same desensitisation biology, and rapid-acting antidepressants (esketamine, zuranolone) bypass the slow receptor-adaptation route by driving plasticity directly.

INDIA

In settings where laboratory monitoring and continuity of supply can be intermittent, the adaptive-receptor concepts translate into concrete safety rules worth voicing in a viva. Abrupt stoppage of a high-potency antipsychotic or lithium, whether through non-adherence or a supply gap, risks rebound psychosis, cholinergic rebound, or rebound mania, not merely "relapse." Short-half-life SSRIs such as paroxetine and short-acting benzodiazepines such as alprazolam, both widely prescribed, carry the sharpest discontinuation and dependence profiles and warrant deliberate tapering and patient counselling about missed doses.

Apply and consolidate

22 · Apply: four mechanism-to-bedside vignettes

The whole chapter converges here. Neurochemistry earns its place in the exam only when a receptor, an enzyme or a pathway is made to *predict* a clinical event and then a first move. These four vignettes are deliberately drawn from four different systems, so the discriminator in each is a different piece of machinery: a dopamine pathway, a serotonergic toxidrome, a cytochrome P450 isoenzyme, and a glutamate receptor cascade. Each runs to the same three-beat rhythm the examiners reward: the **presentation**, then the **mechanism** that alone explains it, then the **first drug choice or interpretation** that the mechanism forces. Where a management step belongs to clinical practice rather than basic science, the pointer is to the clinical psychiatry chapters (Paper II), not a full protocol here.

Read each as a reasoning drill, not a fact to memorise. If you can name the pathway, isoenzyme or receptor the moment the stem lands, the answer is already written; the drug simply follows from the biology. Numbers that carry weight are given only where a canonical source verifies them, and any figure you should confirm against a current formulary before quoting is flagged (Stahl 2021; Kaplan & Sadock 2024; Meyer & Stahl 2019; Taylor 2021).

HOLD THIS

Name the mechanism first and the answer writes itself: presentation, then the one mechanism that explains it, then the first move it forces. Galactorrhoea to tuberoinfundibular D2; clonus to 5-HT2A; smoking-cessation sedation to lost CYP1A2 induction; rapid antidepressant response to NMDA-to-AMPA-to-BDNF.

22.1 Vignette 1: galactorrhoea on a D2 antagonist, and the tuberoinfundibular logic

CLINICAL ANCHOR

A young man with a first episode of psychosis (ICD-11 6A20 schizophrenia; DSM-5-TR schizophrenia) is started on risperidone and responds well over three weeks. He then returns distressed, reporting breast tenderness and a milky nipple discharge; a woman on the same drug might present with galactorrhoea, amenorrhoea or loss of libido. Serum prolactin is raised.

Reasoning. Dopamine tonically *inhibits* prolactin release: it is the prolactin-inhibiting factor, travelling from the hypothalamus down the **tuberoinfundibular pathway** to act on D2 receptors on the lactotrophs of the anterior pituitary. A D2 antagonist blocks that brake, so prolactin rises unopposed, producing hyperprolactinaemia and its downstream galactorrhoea, menstrual disturbance and hypogonadism. This is the one classic dopamine pathway that lies largely *outside* the blood-brain barrier, which is why even a drug that raises prolactin need not be the most sedating or extrapyramidal-prone one: risperidone, amisulpride and the typical antipsychotics are the notable prolactin-raisers because they occupy pituitary D2 heavily and, unlike quetiapine or olanzapine, bind tightly without the offsetting rapid dissociation from D2 (Stahl 2021; Kaplan & Sadock 2024).

Management pointer. After excluding other causes of a raised prolactin (pregnancy, a prolactinoma, hypothyroidism), the mechanistically clean move is to switch to an agent that does not lock the tuberoinfundibular D2 receptor. **Aripiprazole** is the archetype: a D2 *partial agonist*, it supplies enough intrinsic dopamine tone at the lactotroph to hold prolactin down while still antagonising the overactive mesolimbic signal, which is why aripiprazole is described as prolactin-sparing and is used both as a switch target and as an add-on to lower antipsychotic-induced hyperprolactinaemia. The full switching and monitoring protocol belongs to the clinical psychiatry chapters (Paper II).

COMMON TRAP

Do not reach for a dopamine agonist such as bromocriptine or cabergoline as the reflex answer in a psychotic patient: adding a dopaminergic drug can destabilise the psychosis it is meant to sit alongside. The receptor-level fix is a partial agonist that raises tone *at the pituitary* without flooding the mesolimbic system, which is exactly the aripiprazole solution.

22.2 Vignette 2: agitation, hyperreflexia and fever on SSRI plus tramadol, the serotonin toxidrome

CLINICAL ANCHOR

A woman on a stable dose of an SSRI for depression (ICD-11 6A70 single episode depressive disorder; DSM-5-TR major depressive disorder) is prescribed tramadol for back pain. Within hours she becomes agitated and restless, then develops tremor, brisk lower-limb reflexes with inducible clonus, sweating, a rising temperature and a racing pulse.

Reasoning. This is **serotonin syndrome (serotonin toxicity)**, an excess-serotonin state that evolves over hours rather than days, driven here by a two-drug additive load on serotonergic transmission. The SSRI blocks the serotonin transporter (SERT), raising synaptic 5-HT; tramadol adds to the same pool by *two* routes, weak SERT inhibition and, importantly, an examinable pharmacokinetic twist, so the combination pushes serotonergic tone past threshold. The clinical picture is the Hunter triad and maps directly onto over-stimulation of postsynaptic serotonin receptors, chiefly **5-HT2A** (and 5-HT1A): *neuromuscular excitation* (clonus, hyperreflexia, tremor, rigidity, with a lower-limb predominance), *autonomic instability* (hyperthermia, diaphoresis, tachycardia, mydriasis, diarrhoea) and *altered mental state* (agitation, delirium). Spontaneous or inducible clonus, especially ocular and lower-limb, is the single most useful discriminator (Kaplan & Sadock 2024).

Management pointer. The mechanism dictates the moves: stop every serotonergic agent, then supportive care with cooling and benzodiazepines for agitation and rigidity, escalating to the 5-HT2A antagonist **cyproheptadine** in more severe cases; hyperthermia above roughly 41 degrees Celsius with rigidity is the critical-care threshold and mandates aggressive cooling, sedation and consideration of paralysis (confirm the exact figure and dosing on the clinical psychiatry chapters (Paper II)). The take-home for the science paper is that naming the receptor (5-HT2A) tells you the antidote (a 5-HT2A blocker).

COMMON TRAP

Serotonin syndrome versus neuroleptic malignant syndrome. Both give hyperthermia and altered mental state, but serotonin toxicity is *hyperkinetic* (clonus, hyperreflexia, rapid onset over hours, a serotonergic drug or combination) whereas NMS is *hypokinetic* (lead-pipe rigidity *without* clonus, bradyreflexia, slower onset over days, a dopamine antagonist or dopaminergic withdrawal). If the stem gives clonus, it is serotonin syndrome; tramadol added to an SSRI is a stock precipitant, alongside MAOIs, linezolid and triptans.

22.3 Vignette 3: a stabilised clozapine patient quits smoking and turns toxic, the 1A2 induction story

CLINICAL ANCHOR

A man with treatment-resistant schizophrenia (ICD-11 6A20; DSM-5-TR schizophrenia) has been stable for a year on a fixed dose of clozapine. He is a heavy smoker. He is admitted for an unrelated reason, the ward is smoke-free, and he stops smoking abruptly. Over the next several days he becomes increasingly sedated and drowsy, with hypersalivation and, in the worst case, myoclonic jerks or a seizure.

Reasoning. Clozapine is metabolised predominantly by the hepatic isoenzyme **CYP1A2**. It is the *polycyclic aromatic hydrocarbons* in tobacco smoke, not the nicotine, that are the relevant **CYP1A2 inducers**, so a chronic smoker runs an up-regulated enzyme and clears clozapine faster; his stable dose is in fact a dose calibrated to induced metabolism. When smoking stops, induction fades over roughly a week to ten days, CYP1A2 activity falls back to baseline, clearance drops, and plasma clozapine climbs into the toxic range at an unchanged dose, producing dose-dependent sedation, hypersalivation, and a seizure risk that is itself concentration-dependent. The magnitude is examinable: for any given dose, nonsmokers reach plasma clozapine levels around 50 percent higher than smokers (Meyer & Stahl 2019). Nicotine replacement does *not* prevent this, because nicotine is not the inducer, a favourite distractor.

Management pointer (TDM/dose logic). This is the paradigm case for **therapeutic drug monitoring**: check a clozapine level and pre-emptively reduce the dose on cessation, guided by the level rather than by symptoms alone, and warn every clozapine patient at initiation to tell the prescriber before they start, stop or change smoking. The reciprocal trap is the patient who *resumes* smoking and loses efficacy as levels fall. Target-range figures and the reduction schedule sit on the clinical psychiatry chapters (Paper II); verify the current recommended plasma range against your formulary (Taylor 2021).

MNEMONIC

SMOKE INDUCES 1A2; STOP AND YOU RISE

Smoke (the tar, not the nicotine) *induces* CYP1A2, so smokers need *more* clozapine (or theophylline, olanzapine, caffeine, all 1A2 substrates). Stopping removes the inducer, levels rise, toxicity follows. The direction is the whole point: induction lowers levels, so losing the inducer raises them.

TRAP Nicotine replacement does not prevent the clozapine surge on quitting: the polycyclic aromatic hydrocarbons in smoke, not the nicotine, are the CYP1A2 inducer.

22.4 Vignette 4: IV ketamine in treatment-resistant depression, the NMDA to BDNF to mTOR cascade

CLINICAL ANCHOR

A patient with treatment-resistant depression (ICD-11 6A70/6A71; DSM-5-TR major depressive disorder), having failed several adequate antidepressant trials, is given a single sub-anaesthetic intravenous infusion of ketamine at 0.5 mg/kg over about forty minutes. Mood improves within hours, well ahead of any monoamine timeline, with a transient dissociative experience during the infusion (Berman 2000; Zarate 2006).

Reasoning. Ketamine is a non-competitive **NMDA-receptor antagonist**, and its speed is the tell that this is not a monoamine mechanism. The leading account is a disinhibition cascade: by blocking NMDA receptors preferentially on GABAergic inhibitory interneurons, ketamine lifts inhibitory tone on glutamatergic pyramidal neurons, producing a **glutamate surge**. That surge drives postsynaptic **AMPA receptors**, and the downstream signalling, blockade of spontaneous NMDA activation relieving inhibition of eEF2 kinase to permit **BDNF** translation, together with suppression of extrasynaptic-NMDA-driven restraint of **mTOR**, converges on TrkB and the mTOR complex to trigger rapid protein synthesis, synaptogenesis and synaptic potentiation in prefrontal cortex. The active metabolite (2R,6R)-hydroxynorketamine is implicated in the AMPA-dependent, possibly NMDA-independent, limb of the effect (Kaplan & Sadock 2024). The final common path, BDNF and synaptic plasticity, is the same endpoint the delayed monoamine antidepressants reach slowly; ketamine reaches it in hours.

Management pointer (monitoring). The mechanism also frames the risks: the same NMDA antagonism that lifts mood produces the *dissociative and psychotomimetic* effects and a transient rise in blood pressure and heart rate, so infusions are given in a monitored setting with blood-pressure and mental-state observation during and after, and abuse potential is respected. The intranasal S-enantiomer esketamine is the licensed formulation for treatment-resistant depression and is dispensed under a supervised, monitored protocol with post-dose observation. Full monitoring schedules, eligibility and the observation window belong to the clinical psychiatry chapters (Paper II).

PEARL

Keep the three fast-acting mechanisms mechanistically separate, because the exam pairs them. Ketamine and esketamine work at the *glutamate/NMDA* receptor; the neuroactive steroids brexanolone and **zuranolone** are positive allosteric modulators at *GABA-A*; the classical psychedelics (psilocybin) are *5-HT2A* agonists. Three different receptors, one shared clinical promise of rapid antidepressant action, and three different monitoring profiles.

22.5 The four vignettes at a glance: system, discriminator, first move

The consolidating grid. Read the discriminator column first: in each stem it is the single feature that names the mechanism and therefore writes the answer.

VIGNETTE	SYSTEM / MECHANISM	DISCRIMINATOR IN THE STEM	FIRST MOVE
1. Galactorrhoea on a D2 antagonist	Tuberoinfundibular dopamine pathway; loss of the prolactin-inhibiting brake	**Raised prolactin with galactorrhoea, on a prolactin-raising antipsychotic (risperidone, amisulpride, typicals)**	Switch to / add aripiprazole (D2 partial agonist, prolactin-sparing)
2. Agitation, hyperreflexia, fever on SSRI + tramadol	Serotonin excess at 5-HT2A/1A; serotonin toxicity	**Clonus (inducible, ocular, lower-limb) and hyperreflexia, rapid onset over hours**	Stop serotonergics, benzodiazepines, cyproheptadine (5-HT2A antagonist) if severe
3. Sedation and seizure after quitting smoking on clozapine	Loss of CYP1A2 induction; rising clozapine level	**Recent smoking cessation in a previously stable clozapine patient (tar, not nicotine, was the inducer)**	Check level, pre-emptively reduce dose (TDM-guided)
4. Rapid response to IV ketamine in TRD	NMDA antagonism to glutamate surge to AMPA to BDNF/mTOR plasticity	**Antidepressant effect within hours plus transient dissociation, ahead of any monoamine timeline**	Monitored setting: BP, heart rate, mental state during and after

Four systems, four discriminators: a dopamine pathway, a serotonergic toxidrome, a cytochrome P450 isoenzyme, and a glutamate-receptor cascade. In every row the discriminator names the mechanism and the mechanism forces the first move.

23 · Consolidate: mnemonic total, retrieval and synthesis

This closing block is not new material; it is a **consolidation device** for the whole of these notes. This material has run one long circuit, from molecule to syndrome: the transmitter systems and their receptors, the neuropeptides and gasotransmitters, the second-messenger cascades that carry the signal inward, the three neuroendocrine axes, the neurotrophic and neurodevelopmental machinery, and the structural imaging that reads all of it out at the level of the whole brain. **Study by producing, not by re-reading.** Durable learning comes from spaced *active recall* (self-testing from memory) rather than repeated passive review, the testing effect that Roediger and Karpicke (2006) demonstrated directly. The three subtopics below give you the loop to run it: one master mnemonic that chains the smaller topic mnemonics into a single spine, a set of answer-free retrieval prompts, and a one-page synthesis map to redraw from memory.

Use them in that order. Recite the mnemonic spine to confirm the scaffold is intact, close the notes and work the retrieval prompts aloud, then take a blank sheet and rebuild the whole-day circuit from transmitter through receptor to drug to clinical effect. Where a limb of the map will

not come, that gap is the prediction error naming the exact topic to reopen, which is the entire point of the exercise.

HOLD THIS

Learn by producing, not re-reading: spaced active recall beats passive review (the testing effect). Every limb of the map that will not come is the prediction error naming the exact topic to reopen.

System	Receptor	Drug acting here	Clinical read-out
Dopamine	D2	antipsychotic (D2 block)	positive symptoms down; EPS
Serotonin	5-HT2A, SERT	SSRI; atypical antipsychotic	mood up; anxiety down
Noradrenaline	alpha-2, beta	SNRI; alpha-2 agonist	arousal, attention
Glutamate	NMDA	ketamine (open-channel block)	rapid antidepressant
GABA	GABA-A	benzodiazepine	anxiolysis, sedation
Acetylcholine	M, nicotinic	cholinesterase inhibitor	memory (Alzheimer)
HPA axis	CRH, cortisol	dexamethasone (DST probe)	stress; melancholia
Imaging	D2 occupancy	PET, 65 to 80%	antipsychotic window

Cover the right three columns and rebuild each row from the system name alone.

CONCEPT AXIS · SYSTEM TO RECEPTOR TO DRUG TO EFFECT ■ the chapter in one grid

Fig 2.11 The whole synthesis map. Every system here reduces to one line: a transmitter or axis, the receptor that reads it, the drug that acts there, and the clinical effect that follows. This is the retrieval device for the chapter, redraw it from memory and the gaps are your revision list.

23.1 Master mnemonic total: chaining the chemistry into one spine

Every topic today already carries its own mnemonic. The problem at revision is not recalling any single one but retrieving the correct one under time pressure and in the right order. The device below is a *mnemonic of mnemonics*: a spine that indexes the transmitter systems, the three endocrine axes, the imaging rules and the pharmacology principle, so that recalling the spine pulls each sub-mnemonic up with it. Walk it from the outside in, transmitters and their receptors first, then the cascade inside the cell, then the slow endocrine and trophic loops, then the picture the scanner returns.

MNEMONIC

"DA-SANG Signals, Peptides and Gases Whisper, Q Cuts the DIP, CAP the Three Axes, Stress Bends and Treatment Mends, Ventricles Up and Hippocampus Down"

DA-SANG fixes the six classical transmitter systems as an ordered set: *DA* dopamine, then *S*erotonin, *A*cetylcholine, *N*oradrenaline, *G*ABA and glutamate as the paired inhibition-excitation backbone. Each expands to its own device. Dopamine runs on "Limbic Lights up, Cortex Cools, Nigra Numbs, Tubero Talks (prolactin)": the four pathways as mesolimbic (positive symptoms, hyperdopaminergic), mesocortical (negative and cognitive, hypodopaminergic), nigrostriatal (extrapyramidal side effects) and tuberoinfundibular (hyperprolactinaemia). Serotonin runs on "1 is Inhibitory / auto, 2 is Excitatory / cortical, 3 is a Channel": 5-HT1A as the somatodendritic autoreceptor and anxiolytic target, 5-HT2A as the cortical excitatory receptor blocked by atypical antipsychotics, 5-HT3 as the one ionotropic (ligand-gated channel) serotonin receptor, the antiemetic target. Acetylcholine runs on "ACh WAKES you to LEARN and to DREAM": basal-forebrain projections for arousal and memory (the cortex that degenerates in Alzheimer), and brainstem groups driving REM. Noradrenaline runs on "A-VATS": Arousal, Vigilance, Attention, Threat-response, Stress-memory, all from the locus coeruleus. GABA runs on "FRequency vs duRation: Benzos are FRequent, Barbs enduRe": benzodiazepines raise the frequency of GABA-A channel opening, barbiturates prolong its duration, the single fact that explains the wider therapeutic index of the benzodiazepines. Glutamate runs on MEMANTINE = "MEMory, MEek block": the low-affinity uncompetitive NMDA blocker of the hypofunction model, the same receptor whose blockade by ketamine yields the rapid antidepressant effect.

Peptides and Gases Whisper chains the slow and unconventional signals. The opioid peptides run on "END-en-DYN to mu-delta-kappa; Kappa = Krummy": endorphin, enkephalin and dynorphin mapping to their receptors, with kappa activation dysphoric. The gasotransmitters run on "NO-CO-H2S: Not stored, no receptor, just diffuse": nitric oxide, carbon monoxide and hydrogen sulphide, made on demand, not vesicle-packaged, acting through diffusion rather than a membrane receptor. "Whisper" flags the theme: these are modulators layered on top of fast transmission (substance P and neurokinin-1 in pain and mood, CRF driving the stress axis, oxytocin in affiliation), not the fast synaptic signal itself.

Q Cuts the DIP is the second-messenger spine, "Q cuts PIP2 into a DIP": Gq activates phospholipase C, which cuts PIP2 into DAG and IP3 (the DAG-IP3 pair), IP3 releasing intracellular calcium and DAG activating protein kinase C. Hold it beside the Gs-cyclic-AMP-PKA arm and the Gi arm that lowers cyclic AMP, and the whole transduction layer that converts a metabotropic receptor event into a slow intracellular consequence sits in one line. This is where lithium acts, inside the cell on the phosphoinositide cycle, not at a receptor.

CAP the Three Axes encodes the neuroendocrinology. "CAP for the cascade, top to bottom" is the HPA axis: CRF from the hypothalamus, ACTH from the pituitary, and cortisol (the P for the adrenal *p*roduct) from the adrenal cortex, restrained by hippocampal negative feedback. Add the thyroid axis on "T3 to Treat, T4 to the Thinker" (T3 the active augmentation agent, T4 the storage form crossing to the brain) and the gonadal axis as the third HPx loop, and the trio of endocrine cascades is fixed. The exam discriminator for the stress axis is the direction: "Depression is HIGH and escapes; PTSD is LOW and over-suppresses" on the dexamethasone suppression test.

Stress Bends and Treatment Mends is the neurotrophin line, "Stress Bends, Treatment Mends: BDNF": chronic stress and hypercortisolaemia lower BDNF and shrink the hippocampus, while antidepressants, lithium and exercise raise it, the neurotrophic hypothesis of depression. It chains straight into neurodevelopment on "Nervous Programmers Make Dozens, Synapse Away, Myelinate" (proliferation, migration, differentiation, synaptogenesis, apoptosis/pruning, myelination) and the "two hits" model of a first insult in utero and a second trigger in adolescence.

Ventricles Up and Hippocampus Down closes the chapter on the imaging readout: "Ventricles up, hippocampus down, white matter bright, atrophy where the syndrome lives", paired with the sequence rule "T1 = anatomy, fat white; FLAIR = T2 minus water". Ventricular enlargement is the single most replicated structural finding in schizophrenia; hippocampal volume loss tracks depression, PTSD and early Alzheimer; white-matter hyperintensities mark vascular and late-life illness. The toolkit that produces these findings is VBM (where does grey matter differ across the brain), volumetric MRI (how big is this one structure) and DTI or fractional anisotropy (how intact is this tract).

The table restates the spine so you can quiz yourself on any single link. Cover the right two columns and recall the sub-mnemonic and its content from the cue phrase alone.

SPINE LINK	SUB-MNEMONIC	WHAT IT UNLOCKS
DA (dopamine)	Limbic Lights, Cortex Cools, Nigra Numbs, Tubero Talks	**Four pathways: mesolimbic, mesocortical, nigrostriatal, tuberoinfundibular, each to its clinical syndrome**
S (serotonin)	1 inhibitory/auto, 2 excitatory/cortical, 3 a channel	5-HT1A autoreceptor, 5-HT2A cortical, 5-HT3 the one ionotropic receptor
A / N (ACh, NA)	ACh WAKES-LEARN-DREAM; NA is A-VATS	**Cholinergic arousal, memory and REM; noradrenergic arousal, vigilance, threat, stress-memory**
G (GABA / glutamate)	FRequency vs duRation; MEMANTINE MEek block	Benzos raise frequency, barbiturates prolong duration; low-affinity NMDA blockade in hypofunction
Peptides and gases	END-en-DYN to mu-delta-kappa; NO-CO-H2S diffuse	**Opioid peptide-receptor map (kappa dysphoric); gasotransmitters unstored, receptorless, diffusing**
Second messenger	Q cuts PIP2 into a DIP	Gq to PLC to DAG plus IP3 to calcium and PKC, beside the Gs-cAMP-PKA arm; lithium acts here
Three axes (CAP)	CRF-ACTH-cortisol; T3 to Treat, T4 to Thinker	**HPA cascade with hippocampal feedback, HPT and HPG loops; DST direction in depression vs PTSD**

SPINE LINK	SUB-MNEMONIC	WHAT IT UNLOCKS
Trophic and development	Stress Bends, Treatment Mends; N-P-M-D-S-A-M; two hits	BDNF down with stress, up with treatment; developmental sequence; neurodevelopmental model
Imaging	Ventricles up, hippocampus down; T1 anatomy, FLAIR T2 minus water	**Replicated structural findings and the sequence rules; VBM, volumetric MRI, DTI toolkit**

The nine-link master spine for this chapter, each row a cue phrase pointing to a topic mnemonic; recall the middle and right columns from the left cue alone.

23.2 Active-recall prompts: cover the page and answer aloud

These are retrieval questions, not a summary. They are deliberately answer-free, so that they force you to generate the answer from memory, which is where the testing effect does its work; printing a model answer here would defeat the device. Cover everything below the label, answer each aloud in a full sentence, then reopen the relevant topic only for the prompts you could not complete.

RETRIEVAL PRACTICE, COVER THE ANSWERS

1. Name the four dopamine pathways, state whether each is hyper- or hypodopaminergic in schizophrenia, and give the clinical consequence of blocking the tuberoinfundibular pathway.
2. Distinguish 5-HT1A, 5-HT2A and 5-HT3 by location, signalling class and one drug that targets each, and say which is the only ionotropic serotonin receptor.
3. State the single biochemical fact that terminates acetylcholine differently from the monoamines, and explain why that dictates the drug class used to raise it in Alzheimer disease.
4. Give the five functions of the noradrenergic locus coeruleus and name the receptor an alpha-2 agonist acts on to reduce sympathetic outflow.
5. Contrast how benzodiazepines and barbiturates act on the GABA-A channel, and explain from that difference why one has the wider therapeutic index.
6. Explain the NMDA hypofunction model of psychosis, and state why memantine is tolerated as a chronic NMDA blocker while ketamine is not.
7. Map the three opioid peptides to their receptors and say which receptor produces dysphoria; then give the three defining features that separate a gasotransmitter from a classical transmitter.
8. Trace the Gq cascade from receptor to intracellular calcium, naming each intermediate, and state where in this pathway lithium is thought to act.
9. Recite the HPA cascade from hypothalamus to cortisol, name the structure providing negative feedback, and give the opposite dexamethasone-suppression-test directions of depression and PTSD.
10. Explain lithium-induced hypothyroidism, how it is managed, and why a depressive relapse in a euthymic lithium-treated patient should prompt a thyroid test before an antidepressant.
11. State the neurotrophic hypothesis of depression in terms of BDNF and the hippocampus, and name three interventions that raise BDNF.
12. List the developmental sequence from proliferation to myelination, and explain the "two-hit" neurodevelopmental model of schizophrenia.
13. Give the single most replicated structural imaging finding in schizophrenia, the structure that shrinks in depression and PTSD, and what white-matter hyperintensities signify.
14. Distinguish VBM, volumetric MRI and DTI or fractional anisotropy by the exact question each answers about brain structure.
15. State the T1, T2 and FLAIR sequence rules in one line each, and say which sequence nulls cerebrospinal fluid to reveal periventricular disease.
16. Explain the KarXT (xanomeline-trospium) strategy of exploiting the blood-brain barrier for selectivity, and name the analogous older strategy used with levodopa in Parkinson disease.

If more than a third of these will not come cleanly, do not push through the list a second time the same day; space the next attempt, because retrieval spaced across days is what builds durable memory (Roediger and Karpicke 2006).

23.3 Synthesis map: the one page to redraw from memory

The final consolidation step is to build a single **synthesis map** and *redraw from memory* the whole of this chemistry along one axis: **transmitter to receptor to drug to clinical effect**. On a blank sheet, place the six transmitter systems down the left as a column of nuclei of origin, carry each rightward to its principal receptor (ionotropic or metabotropic), then to the drug that acts there, then to the clinical effect that follows, so that dopamine reads across as mesolimbic to D2 to antipsychotic to reduced positive symptoms, serotonin as raphe to 5-HT1A/2A to SSRI or atypical to mood and antipsychotic effect, GABA and glutamate as the inhibition-excitation pair with their channel drugs, and acetylcholine and noradrenaline as the arousal modulators. Below the transmitter block, draw the three neuroendocrine axes as vertical cascades (HPA with its hippocampal feedback loop, HPT and HPG beside it), and to the right of them the trophic and developmental line (stress lowering BDNF, treatment raising it, feeding the neurodevelopmental two-hit model). Across the top, run the imaging readout as a banner: ventricles up, hippocampus down, white matter bright, annotated with the T1, T2 and FLAIR rules and the VBM, volumetric-MRI and DTI toolkit. Redraw it once from memory, then check it against the figures in this chapter and fill only the gaps; the act of reconstructing the map, not admiring a finished one, is what fixes the arc from molecule through receptor and drug to syndrome. The figure to rebuild is a four-column flow, transmitter to receptor to drug to clinical effect, with the three axes and the imaging findings drawn as the endocrine and structural frame around it.

Previously asked

Real long-essay (25-mark) and short-note (10-mark) questions from this territory.

? LONG ESSAYS (25 MARKS)

- Q CSF / Neuropeptide Y / Post ictal psychoses / Prosopagnosia. MUHS 2012
- Q Describe Neuropsychiatric manifestations of Thyroid Disorder. MUHS 2016, 2018
- Q Describe physiological and psychological aspects of stress. MUHS 2017
- Q Describe the anatomy of monoamine neurotransmitter system. MUHS 2011
- Q Difference between neuropeptides and other neurotransmitters. Discuss BDNF and its role in neuroscience. MUHS 2017
- Q Discuss neurotransmitters in detail. MUHS 2011
- Q Merits of available neuroimaging techniques and their application in psychiatry. MUHS 2012, 2014
- Q Neuropeptides / Working memory. MUHS 2012, 2018
- Q Neuropsychiatric Manifestations of thyroid disorder and its management. MUHS 2016
- Q Organic Hallucinosis / Ablative neurosurgery / Circadian sleep wake rhythm. MUHS 2012, 2015
- Q What are the principles of Functional MRI and its use in Psychiatry?. MUHS 2013

SHORT NOTES (10 MARKS)

- Cannabinoid receptors. MUHS 2014
- Cannabinoid receptors / Long term potentiation / Nucleus accumbens. MUHS 2014, 2015
- Describe anatomy of monoamine neurotransmitter system. MUHS 2011
- Difference between neuropeptides and other neurotransmitters - discuss BDNF. MUHS 2017
- Dopamine / Temporal lobe. MUHS 2014
- Dopamine and dopaminergic pathways. MUHS 2013, 2014
- Dopamine receptors. MUHS 2011
- Dopamine receptors / Neurotransmitters. MUHS 2011
- Glutamate. MUHS 2014
- Glutamate / Glutamate Neurotransmission. MUHS 2014, 2016
- Glutamate as neurotransmission. MUHS 2016
- Management of Hyperprolactinemia in Psychiatry. MUHS 2011
- Melatonin. MUHS 2013
- MRI in schizophrenia. MUHS 2015
- Neuropeptide Y. MUHS 2012
- Neuropeptides with special reference to cholecystokinin. MUHS 2013
- Neurotrophic factors. MUHS 2013
- Neurotrophic factors / Implicit Memory / Melatonin. MUHS 2013
- Normal waves in EEG / Functional Magnetic Resonance Imaging / Dopaminergic Pathways. MUHS 2011, 2012, 2013
- Parietal lobe / Acetylcholine. MUHS 2014
- Psychiatric Manifestations of Hypothyroidism / Psychiatric Manifestations of Vitamin B12 deficiency. MUHS 2012
- Quantitative EEG / PET Scan. MUHS 2013
- Serotonin. MUHS 2017
- Serotonin dopamine antagonist. MUHS 2012
- Serotonin syndrome. MUHS 2018
- SPECT. MUHS 2021

Quick review

The whole picture in one table	
CLASSIFYING NEUROTRANSMITTERS	Five axes on one list: chemical class (small-molecule = monoamines / amino-acids / ACh, vs neuropeptide vs gasotransmitter vs lipid); function (glutamate excites, GABA inhibits, monoamines modulate); ionotropic (fast channel) vs metabotropic (slow GPCR); vesicular vs made-on-demand and retrograde (gases, endocannabinoids); Dale's principle and co-transmission.
DOPAMINE	Tyrosine to L-DOPA (TH rate-limiting) to DA; D1-like Gs, D2-like Gi. Four pathways: mesolimbic (positive symptoms), mesocortical (negative and cognitive), nigrostriatal (EPS), tuberoinfundibular (prolactin). Aberrant salience; raised presynaptic synthesis on FDOPA-PET.
SEROTONIN	Tryptophan to 5-HTP (TPH2) to 5-HT to 5-HIAA (MAO-A). 5-HT1A auto and heteroreceptor, 5-HT2A (hallucinogen and atypical-antipsychotic target), 5-HT3 ionotropic (emesis). SSRI lag = autoreceptor desensitisation. Serotonin syndrome.
NORADRENALINE AND ADRENALINE	DA to NA via DBH, then MHPG; adrenaline made by PNMT in C1 to C3 neurons. Locus coeruleus origin. alpha-1, alpha-2 autoreceptor, beta. Arousal, attention, stress; SNRIs, alpha-2 agonists, atomoxetine.
GLUTAMATE	Glutamate-glutamine cycle; NMDA (GluN1/2, Mg block, glycine/D-serine co-agonist), AMPA, kainate, mGluR. NMDA hypofunction (ketamine, PCP) is the disinhibition model of psychosis. Ketamine to BDNF to mTOR = rapid antidepressant. Excitotoxicity; anti-NMDA-receptor encephalitis.
GABA	GAD synthesis. GABA-A (pentameric Cl- channel; benzodiazepine increases frequency, barbiturate duration, plus neurosteroid, alcohol, picrotoxin block, flumazenil antagonist); GABA-B (Gi, baclofen). Neurosteroids brexanolone and zuranolone.
ACETYLCHOLINE	ChAT synthesis, AChE breakdown; nicotinic (ionotropic) vs muscarinic M1 to M5 (metabotropic). Nucleus basalis of Meynert. Cholinergic hypothesis of Alzheimer disease (ChEIs); anticholinergic delirium; xanomeline-trospium (KarXT).
NEUROPEPTIDES AND NOVEL TRANSMITTERS	Co-transmission; substance P/NK1, CRH, oxytocin and vasopressin, endogenous opioids (endorphins, enkephalins, dynorphins; mu/delta/kappa), NPY, CCK, orexin (DORAs). Novel: endocannabinoids (anandamide, 2-AG, CB1, retrograde), nitric oxide (nNOS, retrograde, LTP), TAAR1 (ulotaront).
SIGNALLING, PLASTICITY, DEVELOPMENT	GPCR: Gs to adenylyl cyclase to cAMP to PKA; Gq to PLC to IP3/DAG to PKC; Gi inhibits; both converge on CREB and gene transcription (the slow layer, hence antidepressant lag). Lithium: IMPase and GSK-3. BDNF-TrkB neurotrophic hypothesis (Val66Met). Neurodevelopment: migration, synaptic

The whole picture in one table	
	pruning (adolescent peak), critical periods, two-hit model.
NEUROENDOCRINE AXES	HPA: CRH to ACTH to cortisol; DST non-suppression in melancholia. HPT: subclinical hypothyroidism and depression, T3 augmentation, lithium and thyroid. HPG: PMDD, perinatal, menopause; prolactin and antipsychotics. Circadian: SCN clock genes (CLOCK, BMAL1, PER, CRY); melatonin from the pineal; agomelatine, ramelteon.
NEUROIMAGING	Structural: CT (bone and acute blood bright, the emergency scan) vs MRI (T1 anatomy, T2 and water bright, FLAIR suppresses CSF, DWI catches acute infarct); ventricular enlargement in schizophrenia. Functional: fMRI BOLD, PET/SPECT; hypofrontality, D2 occupancy 65 to 80%, subgenual ACC in depression, cortico-striato-thalamic loop in OCD, FDG and amyloid PET in dementia.
PHARMACOLOGY	PK (ADME): bioavailability, volume of distribution, half-life, steady state, therapeutic drug monitoring (lithium, valproate, clozapine). PD: agonist / partial / antagonist / inverse agonist; EC50 = potency, plateau = efficacy; aripiprazole partial agonist. CYP450 (2D6, 3A4, 1A2, 2C19): fluoxetine and paroxetine inhibit 2D6, smoking induces 1A2. Tolerance (PK vs PD), dopamine supersensitivity and tardive dyskinesia, discontinuation.

References

This chapter is grounded in the standard texts (the source hierarchy below); landmark and contested claims carry a PubMed-verified journal citation. Every PMID here was checked against PubMed this build.

SOURCE HIERARCHY (TEXTBOOKS)

1. Boland R, Verduin ML. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 11th ed. Philadelphia: Wolters Kluwer; 2024. [neurochemistry, neuroendocrinology, neuroimaging backbone]
2. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 5th ed. Cambridge: Cambridge University Press; 2021. [receptor pharmacology, transmitter systems]
3. Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry. 14th ed. Oxford: Wiley Blackwell; 2021. [drug monitoring, pharmacokinetics]
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-5-TR). Washington, DC: APA; 2022.
5. World Health Organization. ICD-11 Clinical Descriptions and Diagnostic Requirements for Mental, Behavioural and Neurodevelopmental Disorders. Geneva: WHO; 2024.
6. Sharp T. Neurotransmitters and signalling. In: New Oxford Textbook of Psychiatry. 3rd ed. Oxford University Press. Chapter 14. No PMID (textbook chapter).
7. Tasman A, et al. (eds). Tasman's Psychiatry. 5th ed. Springer/Wiley; 2024. (serotonin receptor subtypes as pathophysiological and drug targets; 5-HT1A/2A density findings in schizophrenia; mCPP provocation in OCD)
8. Johnstone EC, Owens DGC, Lawrie SM, McIntosh AM, Sharpe M, eds. Companion to Psychiatric Studies. 8th ed. Churchill Livingstone/Elsevier; 2010. (Nicotinic vs muscarinic receptor classes, septohippocampal cholinergic projection, ChAT reduction and nucleus basalis in AD) - no PMID (textbook)
9. Tasman A, Kay J, Lieberman JA, First MB, Riba MB, eds. Psychiatry. 4th ed. Wiley-Blackwell; 2015. (Correlation of amnesia depth with nucleus basalis of Meynert damage; anticholinergic delirium in geriatric patients) - no PMID

(textbook)

10. Swales MA (ed). The Oxford Handbook of Dialectical Behaviour Therapy. Oxford University Press; 2018. (endogenous opioid system three classes: beta-endorphin, enkephalin, dynorphin; mu/delta/kappa; NSSI)
11. Tasman A, Kay J, Lieberman JA, First MB, Riba M (eds). Psychiatry. 4th ed. Wiley-Blackwell; 2013. (neuropeptide co-localisation; substance P; CRF receptor knockout)
12. Brunton LL, Knollmann BC (eds). Goodman & Gilman's The Pharmacological Basis of Therapeutics, 14th ed. McGraw-Hill, 2022. Purinergic (P1 adenosine A1/A2A/A2B/A3, P2X, P2Y) receptor pharmacology. No PMID (textbook).
13. Johnstone EC, et al (eds). Companion to Psychiatric Studies. 8th ed. Churchill Livingstone/Elsevier; 2010. (Lithium and signal transduction: IP3/DAG/PKC; inositol monophosphatase inhibition and inositol depletion hypothesis; GSK-3 inhibition and substrates Wnt/beta-catenin/tau/AP-1/CREB)
14. Geddes JR, Andreasen NC, Goodwin GM (eds). New Oxford Textbook of Psychiatry. 3rd ed. Oxford University Press; 2020. (Reelin and inside-out cortical layering; Cajal-Retzius cells; LIS1/DCX; tangential interneuron migration from ganglionic eminences)
15. Tasman A, Riba MB, Alarcón RD, et al. (eds). Tasman's Psychiatry. 5th ed. Springer; 2024. (Neurodevelopmental model of schizophrenia; two epochs; absence of gliosis; fetal migration abnormalities)
16. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 13th ed. (Goodman & Gilman 2018) - MR vs GR affinity, 11-beta-HSD2 protection of MR, glucocorticoid pharmacology.
17. Semple D, Smyth R. Oxford Handbook of Psychiatry (structural brain imaging in schizophrenia, mood disorders; Johnstone 1976 CT landmark; Haijma et al. 2013 meta-analysis of >18,000 subjects: ventricular volume +30%, brain volume -2.6%, ICV -2%). Also drawn from Cowen P, Harrison P, Burns T. Shorter Oxford Textbook of Psychiatry, 7th ed, OUP 2018 (schizophrenia Box 11.13; depression WMH and hippocampal volume; bipolar lithium reversal). No single PMID (textbook).
18. Johnstone EC, Owens DC, Lawrie SM, et al. Companion to Psychiatric Studies. 8th ed. Churchill Livingstone/Elsevier; 2010. (hypofrontality of dorsolateral prefrontal cortex in schizophrenia; frontostriatal circuitry)
19. Tasman A, Kay J, Lieberman JA, First MB, Riba MB (eds). Psychiatry. 4th ed. Wiley-Blackwell; 2015. (P-glycoprotein, first-pass metabolism, poor-metaboliser toxicity risk with narrow-index drugs)
20. Johnstone EC, Owens DGC, Lawrie SM, et al (eds). Companion to Psychiatric Studies, 8th ed. Churchill Livingstone/Elsevier; 2010. (receptor sensitivity, desensitisation/down-regulation mechanisms, opioid dependence/withdrawal, ECT and receptor sensitivity)

JOURNAL REFERENCES (PUBMED-VERIFIED)

1. Aizenstein HJ, et al. Vascular depression consensus / white-matter hyperintensity substrate of late-life depression (as cited in Shorter Oxford). Representative: Aizenstein HJ et al. Vascular depression consensus report. Mol Psychiatry. 2016;21(11):1600.
2. Arana GW, Baldessarini RJ, Ornsteen M. The dexamethasone suppression test for diagnosis and prognosis in psychiatry. Arch Gen Psychiatry. 1985;42:1193-1204. PMID: 3000317 - pooled DST performance/prognosis meta-analysis.
3. Arnsten AFT, Rubia K. Neurobiological circuits regulating attention, cognitive control, motivation, and emotion. J Am Acad Child Adolesc Psychiatry. 2012;51(4):356-367. PMID: 22449642.
4. Bamalan OA, Moore MJ, Al Khalili Y. Physiology, Serotonin. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; updated 2023 Jul 30. (pre-cached source: NCBI Bookshelf NBK545168)
5. Barde YA, Edgar D, Thoenen H. Purification of a new neurotrophic factor from mammalian brain. EMBO J. 1982;1(5):549-553. PMID:7188352.
6. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000;47(4):351-354. PMID: 10686270 - first controlled human study, single IV ketamine 0.5 mg/kg
7. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Rev. 1998;28(3):309-369. PMID: 9858756.
8. Berridge MJ, Downes CP, Hanley MR. Lithium amplifies agonist-dependent phosphatidylinositol responses in brain and salivary glands. Biochem J. 1982;206(3):587-595. PMID 7150264 (inositol depletion hypothesis)
9. Bertilsson L, Dahl ML, Dalen P, Al-Shurbaji A. Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. Br J Clin Pharmacol. 2002;53(2):111-122. PMID: 11851634
10. Bunney BG, Li JZ, Walsh DM, et al. Circadian dysregulation of clock genes: clues to rapid treatments in major depressive disorder. Mol Psychiatry. 2015;20(1):48-55. PMID: 25349171.

11. Burris KD, Molski TF, Xu C, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. J Pharmacol Exp Ther. 2002;302(1):381-389. PMID: 12065741.
12. Cahill CM, Walwyn W, Taylor AMW, et al. Allostatic Mechanisms of Opioid Tolerance Beyond Desensitization and Downregulation. Trends Pharmacol Sci. 2016;37(11):963-976. PMID: 27670390. (opponent process, allostasis, cAMP superactivation, pass-forward allostasis)
13. Carroll BJ. A specific laboratory test for the diagnosis of melancholia: standardization, validation, and clinical utility. Arch Gen Psychiatry. 1981;38:15-22. PMID: 7458567 - original DST validation for melancholia.
14. Castren E, Monteggia LM. Brain-derived neurotrophic factor signaling in depression and antidepressant action. Biol Psychiatry. 2021;90(2):128-136.
15. Chen ZY, Jing D, Bath KG, et al. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science. 2006;314(5796):140-143. PMID:17023662.
16. Chouinard G, Jones BD. Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. Am J Psychiatry. 1980;137(1):16-21. PMID: 6101522.
17. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet. 2007;370(9600):1706-1713. PMID 18022033.
18. Contreras F, et al. Contributions of cortisol suppression tests to understanding of psychiatric disorders: a narrative review of literature. Endocrinol Nutr (English ed). 2013 - 1 mg DST 67% sensitivity / 96% specificity for melancholia, 44% sensitivity in general MDD, PTSD low-cortisol paradox, increased lymphocyte GR density/sensitivity, 0.5 mg DST hypersuppression, atypical depression hypocortisolism.
19. Costa T, Herz A. Antagonists with negative intrinsic activity at delta opioid receptors coupled to GTP-binding proteins. Proc Natl Acad Sci USA. 1989;86(19):7321-7325. PMID: 2552439.
20. Currie GM. Pharmacology, Part 2: Introduction to Pharmacokinetics. J Nucl Med Technol. 2018;46(3):221-230. PMID 29599397 (half-life, clearance, steady-state fundamentals corroborating Pharmaceutical Press 2023 summary).
21. Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. Arch Gen Psychiatry. 1997;54(7):597-606. PMID:9236543.
22. Edwards Z, Preuss CV. GABA Receptor Positive Allosteric Modulators. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Feb 28. Bookshelf ID: NBK554443. PMID: 32119330.
23. Faust TE, Gunner G, Schafer DP. Mechanisms governing activity-dependent synaptic pruning in the developing mammalian CNS. Nat Rev Neurosci. 2021;22(11):657-673. PMID: 34545240; PMCID: PMC8541743.
24. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? J Psychiatr Res. 1982-1983;17(4):319-334. PMID: 7187776.
25. Felmingham KL, Dobson-Stone C, Schofield PR, Quirk GJ, Bryant RA. The BDNF Val66Met polymorphism predicts response to exposure therapy in posttraumatic stress disorder. Biol Psychiatry. 2013;73(11):1059-1063. PMID:23312562.
26. Gaedigk A, Sangkuhl K, Whirl-Carrillo M, Klein T, Leeder JS. Prediction of CYP2D6 phenotype from genotype across world populations. Genet Med. 2017;19(1):69-76. PMID: 27388693
27. Gopaldas JA, Padyana M, Rai PP. Practice Patterns in the Diagnosis and Management of Alcohol Withdrawal Syndrome in Indian Intensive Care Units. Indian J Crit Care Med. 2023 Nov;27(11):816-820. PMID: 37936810.
28. Griebel G, Holmes A. 50 years of hurdles and hope in anxiolytic drug discovery. Nat Rev Drug Discov. 2013;12(9):667-687. PMID: 23989795 (V1b antagonist SSR149415 discontinuation; peptide translational failures)
29. Grogan S, Preuss CV. Pharmacokinetics. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; updated 2023. Bookshelf ID NBK557744; PMID 32491676.
30. Haijma SV, Van Haren N, Cahn W, et al. Brain volumes in schizophrenia: a meta-analysis in over 18,000 subjects. Schizophr Bull. 2013;39(5):1129-1138. PMID: 23042112.
31. Hallahan B, et al. Structural MRI in bipolar disorder: an international collaborative mega-analysis (hippocampal volume, lithium effect). Biol Psychiatry. 2011;69(4):326-335. PMID: 21030008.
32. Hensch TK. Critical period plasticity in local cortical circuits. Nat Rev Neurosci. 2005;6(11):877-888. PMID: 16261181.
33. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III - the final common pathway. Schizophr Bull. 2009;35(3):549-562. PMID: 19325164. doi:10.1093/schbul/sbp006
34. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III, the final common pathway. Schizophr Bull. 2009;35(3):549-562. PMID: 19325164. (presynaptic striatal dopamine synthesis capacity on FDOPA-PET)

35. Hussain LS, Reddy V, Maani CV. Physiology, Noradrenergic Synapse. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. (synthesis cascade, DNB/VNB projections, adrenoceptor second messengers, NE degradation to VMA)
36. Johnstone EC, Crow TJ, Frith CD, et al. Cerebral ventricular size and cognitive impairment in chronic schizophrenia (landmark CT study). Lancet. 1976;2(7992):924-926. PMID: 62160.
37. Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D2 occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry. 2000;157(4):514-520. PMID: 10739409. (65-80% striatal D2 occupancy window)
38. 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.
39. Kenakin T, Christopoulos A. Signalling bias in new drug discovery: detection, quantification and therapeutic impact. Nat Rev Drug Discov. 2013;12(3):205-216. PMID: 23411724. (affinity/efficacy, spare receptors, allosteric modulation, functional selectivity).
40. Knudsen EI. Sensitive periods in the development of the brain and behavior. J Cogn Neurosci. 2004;16(8):1412-1425. PMID: 15509387.
41. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010;35(1):217-238. PMID: 19710631. doi:10.1038/npp.2009.110
42. Kormos V, Gaszner B. Role of neuropeptides in anxiety, stress, and depression: from animals to humans. Neuropeptides. 2013;47(6):401-419. PMID: 24210138 (co-transmission, translational review)
43. Kramer MS, Cutler N, Feighner J, et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. Science. 1998;281(5383):1640-1645. PMID: 9733503 (MK-869 / aprepitant depression trial)
44. Le J. Drug Distribution to Tissues / Blood-brain barrier. In: Ernstmeyer K, Christman E (eds). Nursing Pharmacology, 2nd ed. Chippewa Valley Technical College, 2023. Bookshelf ID NBK595006 (no PMID).
45. Liu CY, Zhu J, Zheng XY, Ma C, Wang X. Anti-N-Methyl-D-aspartate Receptor Encephalitis: A Severe, Potentially Reversible Autoimmune Encephalitis. Mediators Inflamm. 2017;2017:6361479. PMID: 28698711; PMCID: PMC5494059
46. Matuszewska A, Kowalski K, Jawien P, et al. The Hypothalamic-Pituitary-Gonadal Axis in Men with Schizophrenia. Int J Mol Sci. 2023;24(7):6492. doi:10.3390/ijms24076492. PMID: 37047464. (Oestrogen-protection hypothesis, testosterone-dopamine interaction, raloxifene/SERM adjunct, menopause incidence peak).
47. Mayberg HS, Brannan SK, Mahurin RK, et al. Cingulate function in depression: a potential predictor of treatment response. Neuroreport. 1997;8(4):1057-1061. PMID: 9141092. (subgenual anterior cingulate / BA25 hyperactivity in depression)
48. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci. 2011;15(10):483-506. PMID: 21908230. (default mode / salience / central executive triple-network model)
49. Molero P, Ramos-Quiroga JA, Martin-Santos R, Calvo-Sanchez E, Gutierrez-Rojas L, Meana JJ. Antidepressant Efficacy and Tolerability of Ketamine and Esketamine: A Critical Review. CNS Drugs. 2018 May;32(5):411-420. PMID: 29736744
50. Paez-Pereda M, Hausch F, Holsboer F. Corticotropin releasing factor receptor antagonists for major depressive disorder. Expert Opin Investig Drugs. 2011;20(4):519-535. PMID: 21395482
51. Perucca E, Bialer M, White HS. New GABA-Targeting Therapies for the Treatment of Seizures and Epilepsy. CNS Drugs. 2023 Sep;37(9):755-779. PMID: 37603262.
52. Petanjek Z, Judaš M, Šimić G, et al. Extraordinary neoteny of synaptic spines in the human prefrontal cortex. Proc Natl Acad Sci U S A. 2011;108(32):13281-13286. PMID: 21788513; PMCID: PMC3156171.
53. Phillips C. Brain-Derived Neurotrophic Factor, Depression, and Physical Activity: Making the Neuroplastic Connection. Neural Plast. 2017;2017:7260130. PMID:28928987.
54. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research, past, present, and future. Biol Psychiatry. 2006;60(4):376-382. PMID: 16919525. (amygdala hyperactivity, ventromedial prefrontal hypoactivity, hippocampal changes in PTSD)
55. Rice D, Barone S Jr. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ Health Perspect. 2000;108(Suppl 3):511-533. PMID: 10852851; PMCID: PMC1637807.
56. Roediger HL, Karpicke JD. Test-enhanced learning: taking memory tests improves long-term retention. Psychol Sci. 2006;17(3):249-255. PMID: 16507066.
57. Sam C, Bordoni B. Physiology, Acetylcholine. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; updated 2023 Apr 10. Bookshelf ID NBK557825. (ACh synthesis via ChAT, choline transporter rate-limiting step,

VAChT, SNARE release, AChE/BuChE hydrolysis, N1/N2 nicotinic subtypes, M1-M5 muscarinic coupling and locations, basal forebrain and mesopontine tegmentum sources, botulinum/black-widow toxins, scopolamine amnesia) - pre-cached source

58. Saxena S, Brody AL, Schwartz JM, Baxter LR. Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. Br J Psychiatry Suppl. 1998;(35):26-37. PMID: 9829024. (hyperactive orbitofrontal-caudate-thalamus CSTC loop, normalising with treatment)
59. Schafer DP, Lehrman EK, Kautzman AG, et al. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron. 2012;74(4):691-705. PMID: 22632727; PMCID: PMC3528177.
60. Schwarz LA, Luo L. Organization of the locus coeruleus-norepinephrine system. Curr Biol. 2015;25(21):R1051-R1056. PMID: 26528750
61. Sekar A, Bialas AR, de Rivera H, et al. Schizophrenia risk from complex variation of complement component 4. Nature. 2016;530(7589):177-183. PMID: 26814963; PMCID: PMC4752392.
62. Shirayama Y, Chen ACH, Nakagawa S, Russell DS, Duman RS. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. J Neurosci. 2002;22(8):3251-3261. PMID:11943826.
63. Smith GW, Aubry JM, Dellu F, et al. Corticotropin releasing factor receptor 1-deficient mice display decreased anxiety, impaired stress response, and aberrant neuroendocrine development. Neuron. 1998;20(6):1093-1102.
64. Spina E, Trifiro G, Caraci F. Clinically significant drug interactions with newer antidepressants. CNS Drugs. 2012;26(1):39-67 (review synthesised via cached PMC4335312; inhibitor/inducer tables, olanzapine clearance +98% with smoking, lurasidone ~10x with ketoconazole, asenapine +29%/-16%, valproate-UGT-lamotrigine, carbapenem-valproate). PMID 22171584
65. Stambolic V, Ruel L, Woodgett JR. Lithium inhibits glycogen synthase kinase-3 activity and mimics wingless signalling in intact cells. Curr Biol. 1996;6(12):1664-1668. PMID: 8994831
66. StatPearls: NMDA Receptor (Bookshelf NBK519495) - memantine as uncompetitive antagonist, excitotoxicity, anti-NMDAR encephalitis with ovarian teratoma association. [Web-mined, no journal PMID]
67. StatPearls: Physiology, GABA (Bookshelf ID: NBK545230). StatPearls Publishing; 2026. (GAD/pyridoxal-phosphate synthesis, GABA-T shunt, SSADH deficiency, GABA-A/B/C receptor subtypes, subunit binding sites, developmental excitation).
68. Stevens B, Allen NJ, Vazquez LE, et al. The classical complement cascade mediates CNS synapse elimination. Cell. 2007;131(6):1164-1178. PMID: 18083105.
69. Tripathi KD. Essentials of Medical Pharmacology (KDT), 8th ed. Jaypee, 2019 (first-pass metabolism, bioavailability; textbook, no PMID).
70. Tripathi KD. Essentials of Medical Pharmacology (KDT). 8th ed. Jaypee. (Co-transmission: the one-neurone-one-transmitter model as oversimplification; fast small-molecule plus slow neuropeptide co-release). No PMID (textbook).
71. Tripathi KD. Essentials of Medical Pharmacology. 8th ed. Jaypee; 2019. (Buprenorphine partial mu agonist; competitive antagonism; flumazenil reversal).
72. Tuplin EW, Holahan MR. Aripiprazole, a drug that displays partial agonism and functional selectivity. Curr Neuropharmacol. 2017;15(8):1192-1207. PMID: 28412910.
73. US FDA. Xanomeline-trospium (KarXT / Cobenfy) approval for schizophrenia, September 2024 (M1/M4 muscarinic agonist antipsychotic, non-D2 mechanism).
74. Varghese FP, Brown ES. The Hypothalamic-Pituitary-Adrenal Axis in Major Depressive Disorder: A Brief Primer for Primary Care Physicians. Prim Care Companion J Clin Psychiatry. 2001;3(4):151-155. PMID: 15014598. doi:10.4088/pcc.v03n0401 - DST non-suppression 43% MDD / 67% psychotic depression, age-dependence 34%-64%, DEX/CRH sensitivity up to 90%, CSF CRH state marker, relapse/suicide prognostic value.
75. Volkow ND, Wang GJ, Newcorn JH, et al. Motivation deficit in ADHD is associated with dysfunction of the dopamine reward pathway. Mol Psychiatry. 2011;16(11):1147-1154. PMID 20856250.
76. Web-cached review (Bioengineering 2023, PMC9952193): neuropeptides in depression and anxiety - substance P, neurotensin, orexin/hypocretin, MCH amino-acid counts and receptor subtypes
77. Westacott LJ, Wilkinson LS. Complement Dependent Synaptic Reorganisation During Critical Periods of Brain Development and Risk for Psychiatric Disorder. Front Neurosci. 2022;16:840266. PMID: 35600620; PMCID: PMC9120629.
78. Wiesel TN, Hubel DH. Single-cell responses in striate cortex of kittens deprived of vision in one eye. J Neurophysiol. 1963;26:1003-1017. PMID: 14084161.
79. Yang T, Nie Z, Shu H, et al. The Role of BDNF on Neural Plasticity in Depression. Front Cell Neurosci. 2020;14:82. doi:10.3389/fncel.2020.00082. PMID:32351365.

80. Yehuda R. Risk and resilience in posttraumatic stress disorder / low-dose (0.5 mg) DST hypersuppression and enhanced GR feedback in PTSD (Yehuda 2004).
81. Yin J, Barr AM, Ramos-Miguel A, Procyshyn RM. Antipsychotic Induced Dopamine Supersensitivity Psychosis: A Comprehensive Review. Curr Neuropharmacol. 2017;15(1):174-183. PMID: 27264948.
82. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006;63(8):856-864. PMID: 16894061 - confirmed rapid antidepressant effect of IV ketamine 0.5 mg/kg in TRD
83. Zhao M, Chen L, Yang J, et al. BDNF Val66Met polymorphism, life stress and depression: a meta-analysis of gene-environment interaction. J Affect Disord. 2018;227:226-235. PMID:29102837.
84. de Bartolomeis A, Tomasetti C, Iasevoli F. Update on the mechanism of action of aripiprazole: translational insights into antipsychotic strategies beyond dopamine receptor antagonism. CNS Drugs. 2015;29(9):773-799. PMID: 26346901.

FIGURE CREDITS

1. Fig 2.6 normal CT brain series: Department of Radiology, Uppsala University Hospital, CC0; normal T2 MRI: Afiller, CC BY-SA 3.0; both via Wikimedia Commons.
2. Fig 2.8 FDG-PET (normal brain): Jens Maus, public domain, via Wikimedia Commons.
3. Fig 2.9 PiB amyloid PET (Alzheimer vs control): Klunkwe, CC BY-SA 3.0, via Wikimedia Commons.
4. Figs 2.1 to 2.5, 2.7, 2.10 and 2.11 are original concept schematics drawn for Weave Sprint.

Index

aberrant salience 14
agomelatine 17
allostatic load 88
aripiprazole 15
BDNF 21
biased agonism 62
buprenorphine 126
cingulate island sign 123
clonidine challenge test 92
clozapine 12
CYP1A2 49
CYP2D6 129
dexamethasone suppression test 53
dim-light melatonin onset 102
esketamine 22
FDOPA-PET 118
flumazenil 37
Hunter triad 22
hypofrontality 116
ketamine 8
lithium 62
maternal immune activation 76
memantine 31
neuroleptic malignant syndrome 22
nucleus basalis of Meynert 46
P-glycoprotein 128
phase-response curve 101
reelin 69
rimonabant 7
serotonin syndrome 17
suprachiasmatic nucleus 87
tardive dyskinesia 11
therapeutic index 43
TRH stimulation test 94
two-hit model 74
ulotaront 57
Val66Met 77
voxel-based morphometry 114
xanomeline-trospium 15
zuranolone 37

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.