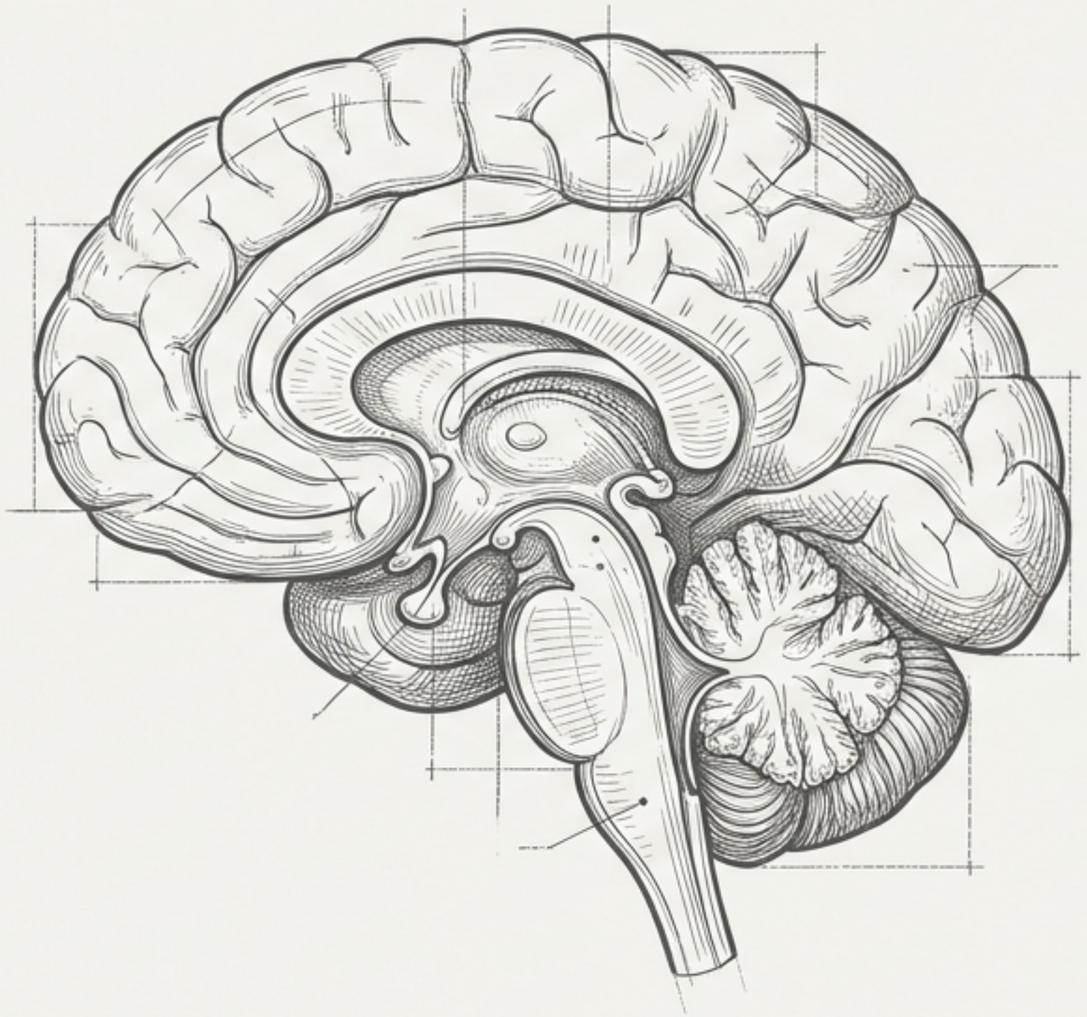
Neuroscience Foundations for Psychiatry

The Clinical Blueprint for Psychopharmacology

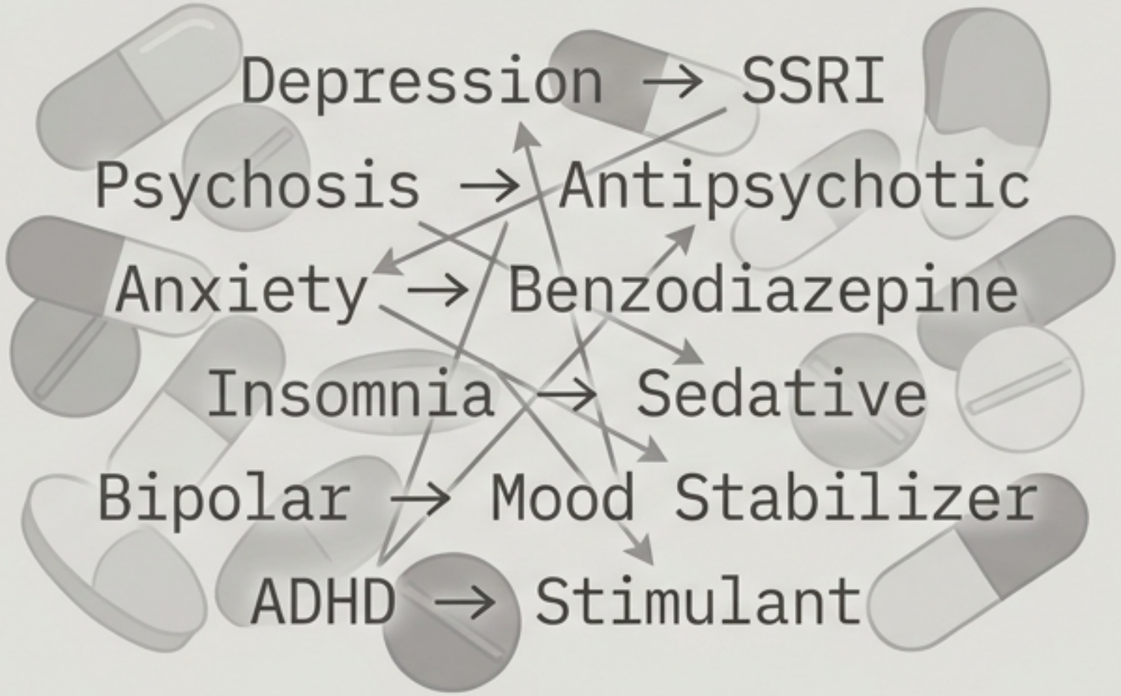


TARGET AUDIENCE: Clinical Prescribers

FRAMEWORK: Mechanism over Memorization

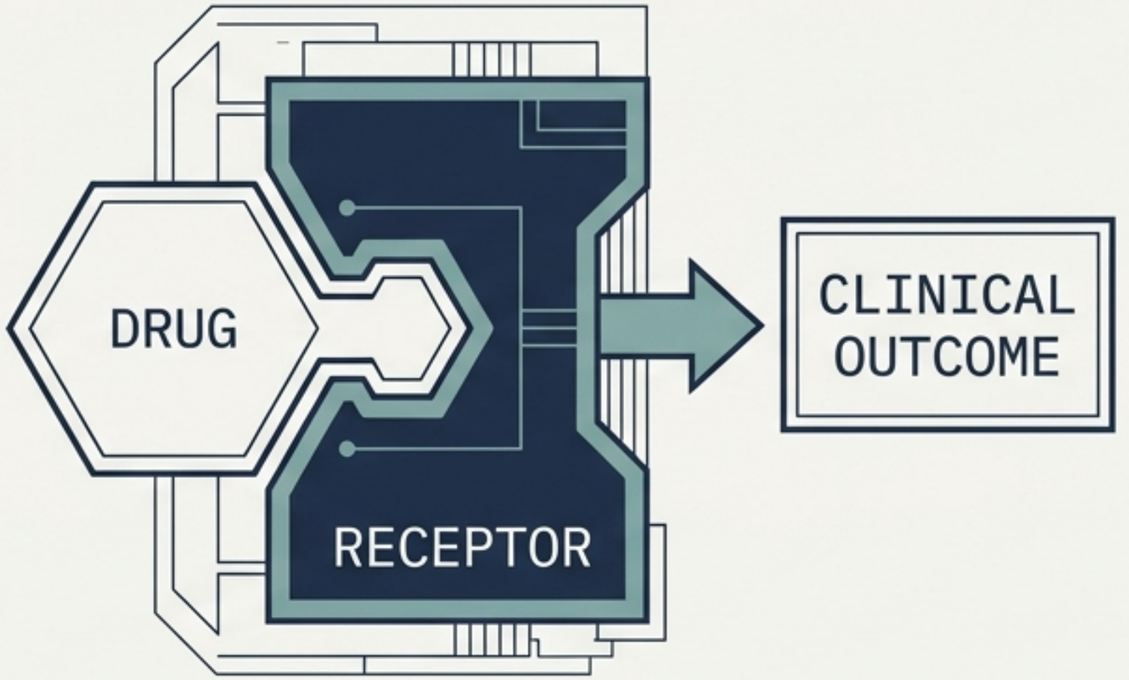
DATA CURRENT AS OF: May 2026

The Legacy Approach



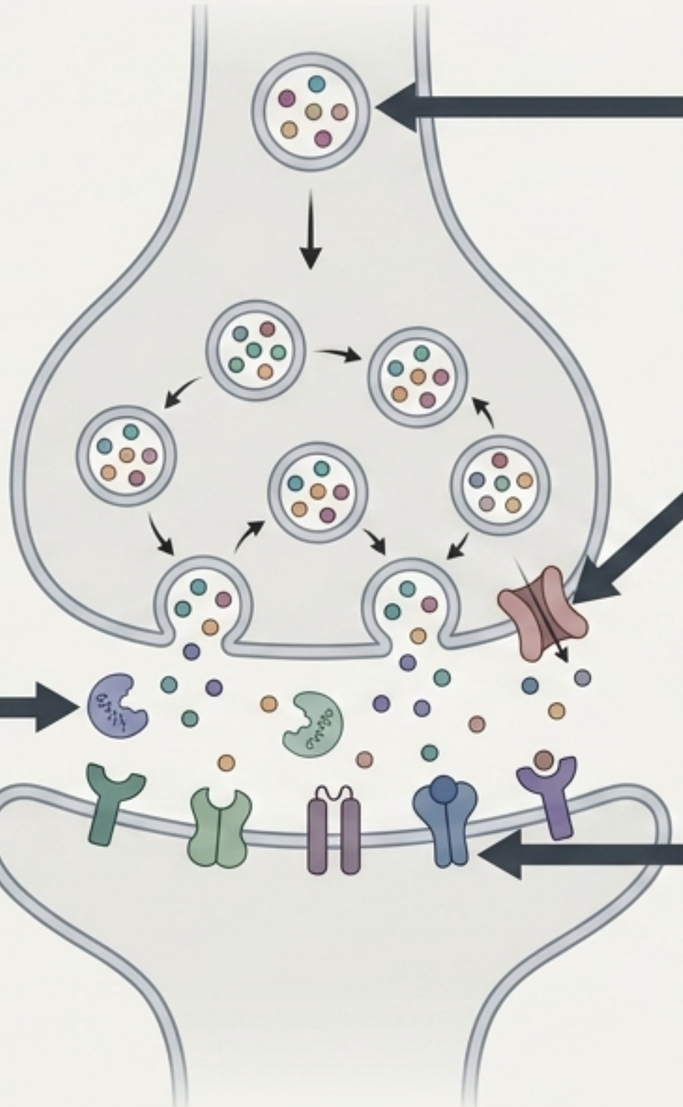
Memorizing symptom-to-drug algorithms fails when patients present with complex, overlapping deficits or intolerable side effects.

The Precision Mechanism Approach



Receptor pharmacology translates symptoms into neural systems. When you know why a drug works—e.g., **mesolimbic D2 blockade** treats psychosis while **nigrostriatal D2 blockade** causes **EPS**—medication selection becomes logical, intuitive, and highly individualized.

All psychiatric interventions target the synaptic engine



Synthesis

Tyrosine hydroxylase inhibitors (rarely used).

Reuptake

Transporter blockade (SSRIs, SNRIs, TCAs).

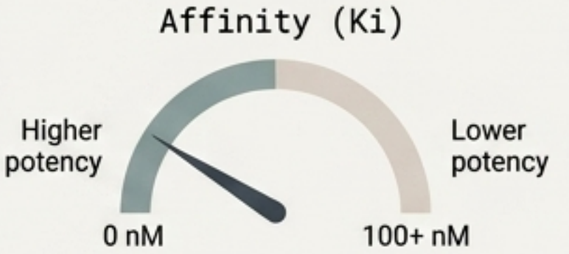
Degradation

Enzyme inhibition (MAOIs).

Receptor Action

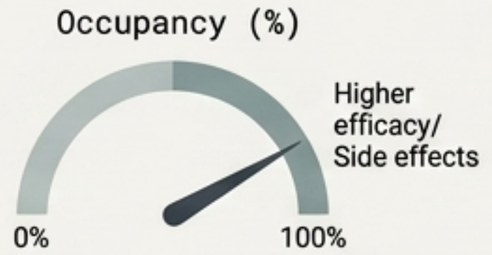
Agonists/Antagonists (Antipsychotics, Buspirone).

Affinity vs. Occupancy

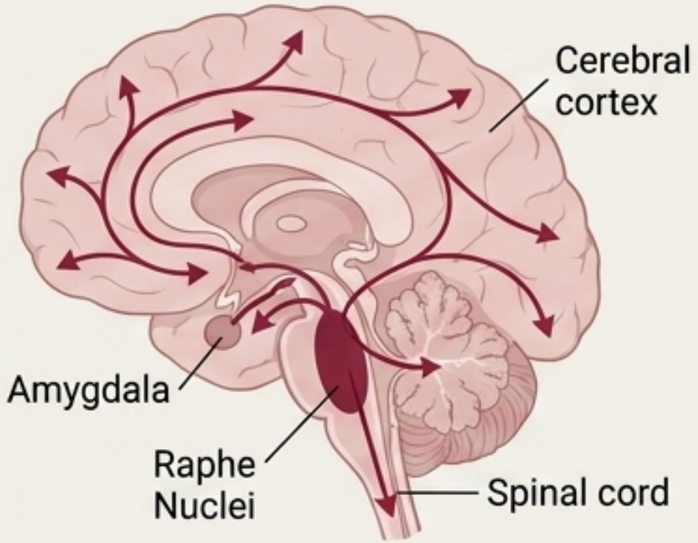


How strongly a drug binds (measured in nanomolar nM). Lower Ki = Higher potency.

Example: Ziprasidone's high affinity for 5-HT2A (Ki ~0.4 nM) vs. low affinity for H1 (Ki ~21 nM) explains its lower sedation compared to olanzapine.



Percentage of receptors bound at a given dose. Drives the threshold of efficacy vs. side effects.



The Serotonin (5-HT) system distributes widely to regulate mood and impulse

5-HT1A (The Anxiety Modulator)

Mechanism: Presynaptic autoreceptor (reduces release) & Postsynaptic (reduces amygdala reactivity).
Clinical: SSRI initial activation (presynaptic) gives way to long-term anxiolytic effect. Buspirone acts as a partial agonist here.

5-HT2A (The Psychosis Pivot)

Mechanism: Cortical receptors. Antagonism is the core mechanism of 2nd-gen antipsychotics.
Clinical: Agonism causes hallucinations (LSD, psilocybin). Blockade balances D2 antagonism.

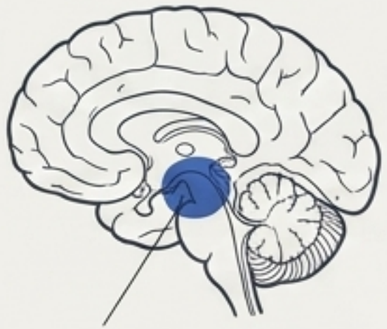
5-HT2C (The Metabolic Trap)

Mechanism: Hypothalamic regulation of appetite and energy.
Clinical: Antagonism (Olanzapine, Mirtazapine) directly drives weight gain and metabolic dysfunction.

5-HT3 (The GI Trigger)

Mechanism: Ionotropic receptors in the chemoreceptor trigger zone/GI tract.
Clinical: SSRI-induced nausea (‘serotonin syndrome lite’). Mitigated by antagonists (Ondansetron).

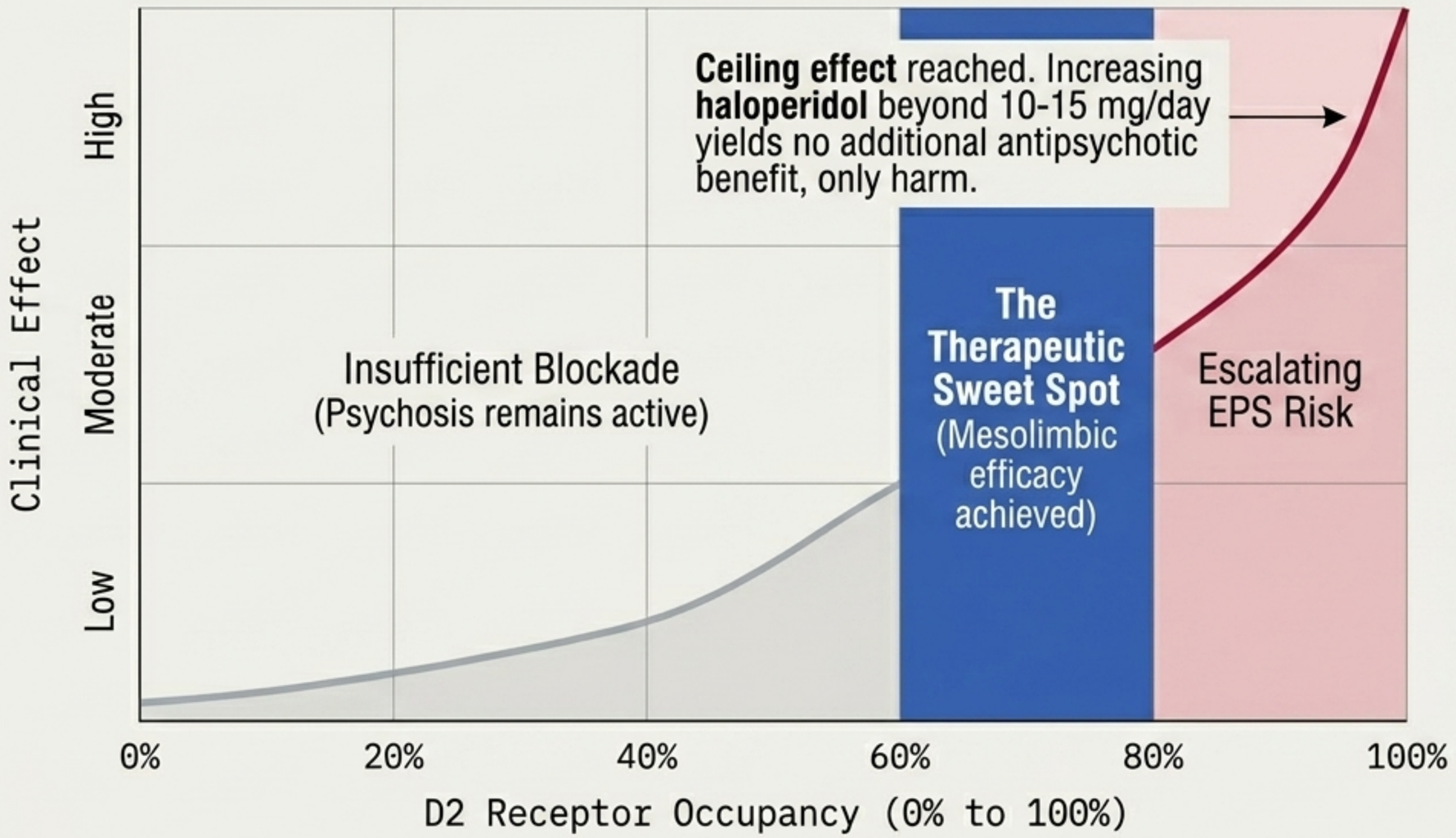
Dopamine blockade acts simultaneously across four distinct neural pathways



VTA / Substantia Nigra

Pathway	Origin/Destination	Normal Function	Clinical Consequence of Blockade
Mesolimbic Pathway	VTA -> Nucleus Accumbens	Reward, motivation, salience	Treats positive symptoms (Psychosis). Blockade here is the primary goal of antipsychotics.
Mesocortical Pathway	VTA -> Prefrontal Cortex	Executive function, working memory	May worsen negative symptoms or cause apathy due to induced hypoactivity.
Nigrostriatal Pathway	Substantia Nigra -> Dorsal Striatum	Motor control	Causes Extrapyramidal Symptoms (EPS) & Tardive Dyskinesia. Degeneration = Parkinson's.
Tuberoinfundibular Pathway	Hypothalamus -> Anterior Pituitary	Inhibits prolactin release	Causes hyperprolactinemia, amenorrhea, and gynecomastia.

Efficacy requires navigating the narrow 60–80% D2 occupancy window



Pharmacological Workarounds

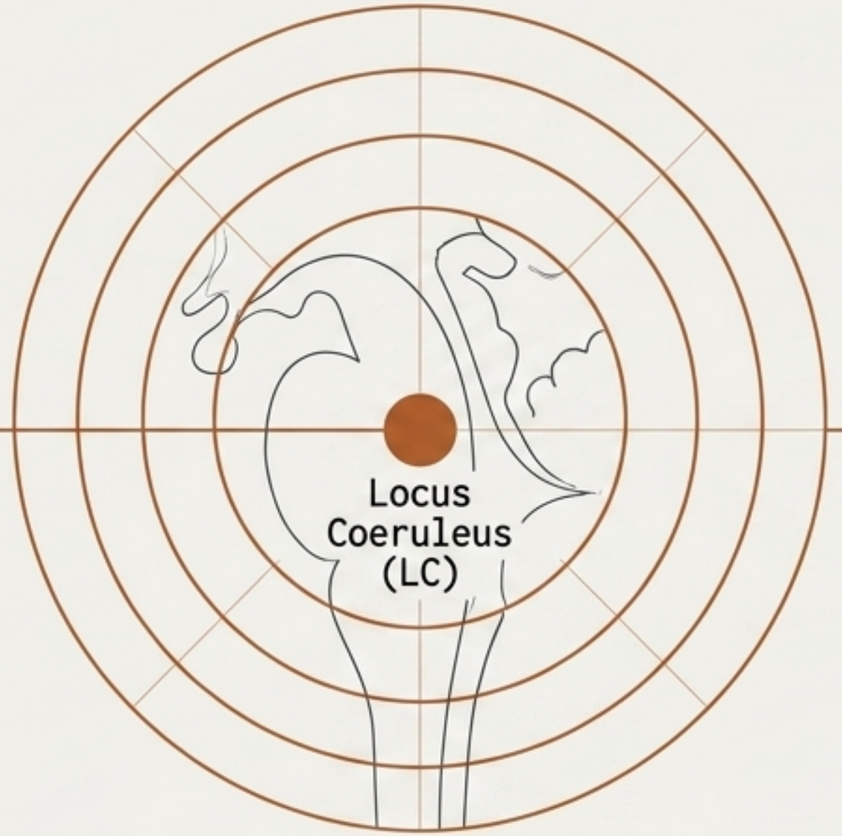
- **Partial Agonism:** `Aripiprazole` occupies D2 but partially partially activates it, keeping the system in a physiologic range to reduce EPS/prolactin.
- **Fast Dissociation:** `Quetiapine` detaches rapidly from D2, leaving receptors unblocked intermittently, lowering EPS risk at therapeutic doses.

The locus coeruleus acts as the brain's exquisitely sensitive alarm system

Alpha-1 (Postsynaptic)

Modulates blood pressure.

Clinical Risk: Antagonism (TCAs, Trazodone, Clozapine) causes orthostatic hypotension and major fall risk in the elderly.



The LC regulates arousal, attention, and sympathetic tone. Chronic stress leads to LC hyperactivity and hyperresponsiveness (a core feature of PTSD and Anxiety).

Alpha-2 (Presynaptic Autoreceptor)

The system's brake pedal.

Clinical Target: Agonists (Clonidine, Guanfacine) suppress LC firing acutely, treating ADHD, PTSD hyperarousal, and opioid withdrawal.

Antagonism (Mirtazapine) increases NE release.

Beta Receptors

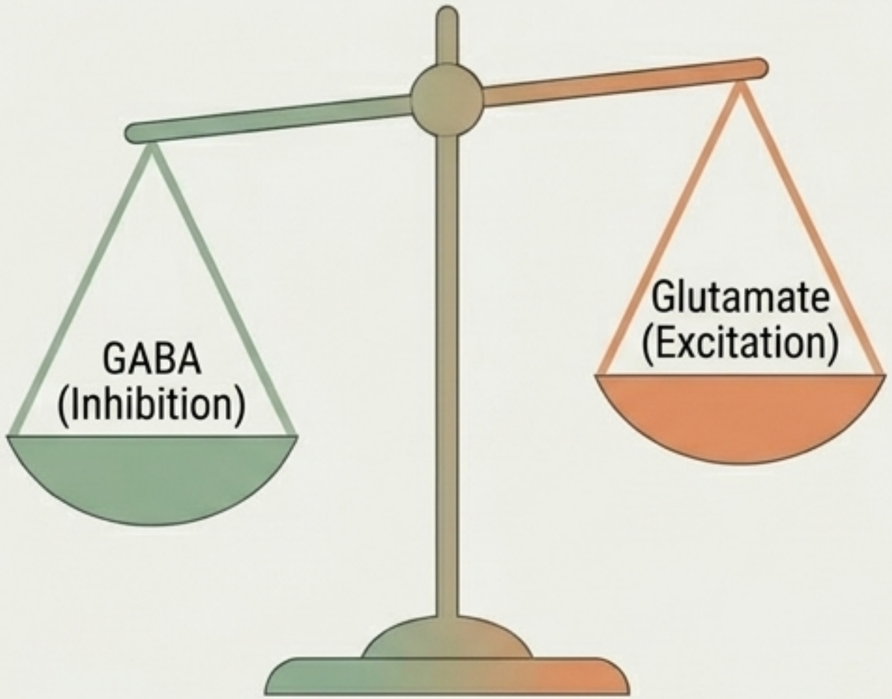
Drives peripheral sympathetic effects.

Clinical Target: Central antagonism (Propranolol) blocks performance anxiety and tremor.

Seizures and neuroplasticity hinge on the GABA and Glutamate fulcrum

GABA – Primary Inhibitor

- **Targets:** GABA-A (Ligand-gated chloride channels. chloride channels).
- **Modulators:** Benzodiazepines, Z-drugs, Alcohol act as allosteric modulators (enhancing inhibition where GABA is present).
- **Clinical:** Highly effective for acute anxiety/panic, but rapid tolerance and dependence limit chronic utility.



Glutamate – Primary Excitator

- **Targets:** NMDA receptors (requires glutamate + depolarization).
- **Clinical:** Ketamine/Esketamine (NMDA antagonists) force rapid neuroplasticity (AMPA/BDNF increases) for Treatment-Resistant Depression. Memantine blocks pathological pathological over-over-stimulation (excitotoxicity) in Alzheimer's.

The Withdrawal Cascade

Chronic alcohol/benzo use → GABA-A downregulation & Glutamate upregulation → Abrupt cessation leaves massive Glutamate excess without GABA brakes leading to seizures, autonomic hyperactivity, and delirium.

Acetylcholine and Histamine blockade dictate the primary side effect burden

Muscarinic (M1) Antagonism

The Threat: The Anticholinergic Burden

Clinical Presentation: Dry mouth, constipation, blurred vistention, blurred vision, urinary retention. In the elderly: Delirium, falls, and cognitive decline.

High-Risk Agents: TCAs (Amitriptyline), 1st-Gen Antipsychotics, Clozapine, Antihistamines, Parkinson's meds (Benztropine).

Note: Cumulative burden across multiple minor agents triggers acute geriatric crises.

Histamine (H1) Antagonism

The Threat: The Metabolic & Sedative Trap

Clinical Presentation: Hypothalamic Hypothalamic disruption leading to profound sedation, appetite stimulation, and subsequent weight gain.

High-Risk Agents: Mirtazapine (potent), Olanzapine, Quetiapine (functions off-label as as an H1-blocking hypnotic at 25-50mg).

Safe Alternatives: Ziprasidone, Aripiprazole, Lurasidone feature minimal H1 antagonism.

Psychiatric symptoms manifest through dysfunction in specific neural architectures

Prefrontal Cortex (PFC)

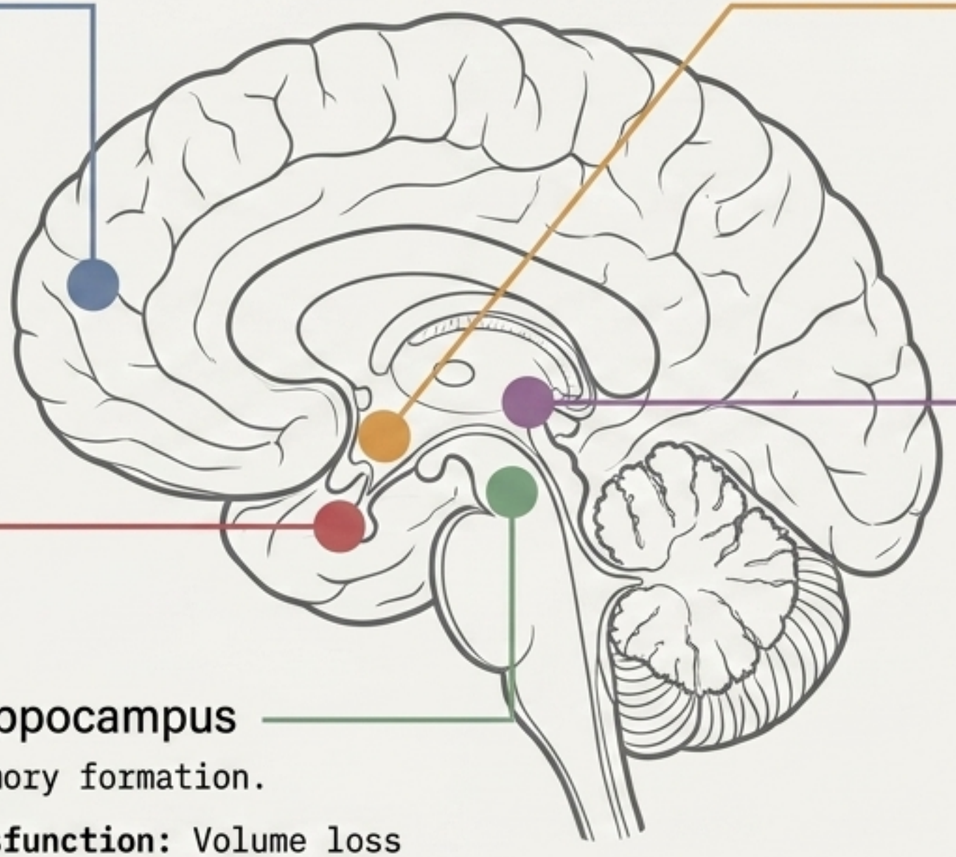
Seat of executive function, planning, impulse control. Rich in DA/NE.

Dysfunction: ADHD (inattention), Schizophrenia (negative symptoms), SUD (impulse failure).

Amygdala

The threat detector.

Dysfunction: Hyperactivity in PTSD/Anxiety. SSRIs/SNRIs reduce reactivity over weeks via PFC connection strengthening.



Hippocampus

Memory formation.

Dysfunction: Volume loss correlates with chronic MDD/PTSD duration. SSRIs promote neurogenesis here.

Hypothalamus

HPA axis command center.

Dysfunction: Hyperactivity drives chronic cortisol in MDD/PTSD. Also controls sleep/weight via histamine/orexin.

Basal Ganglia

CSTC circuits.

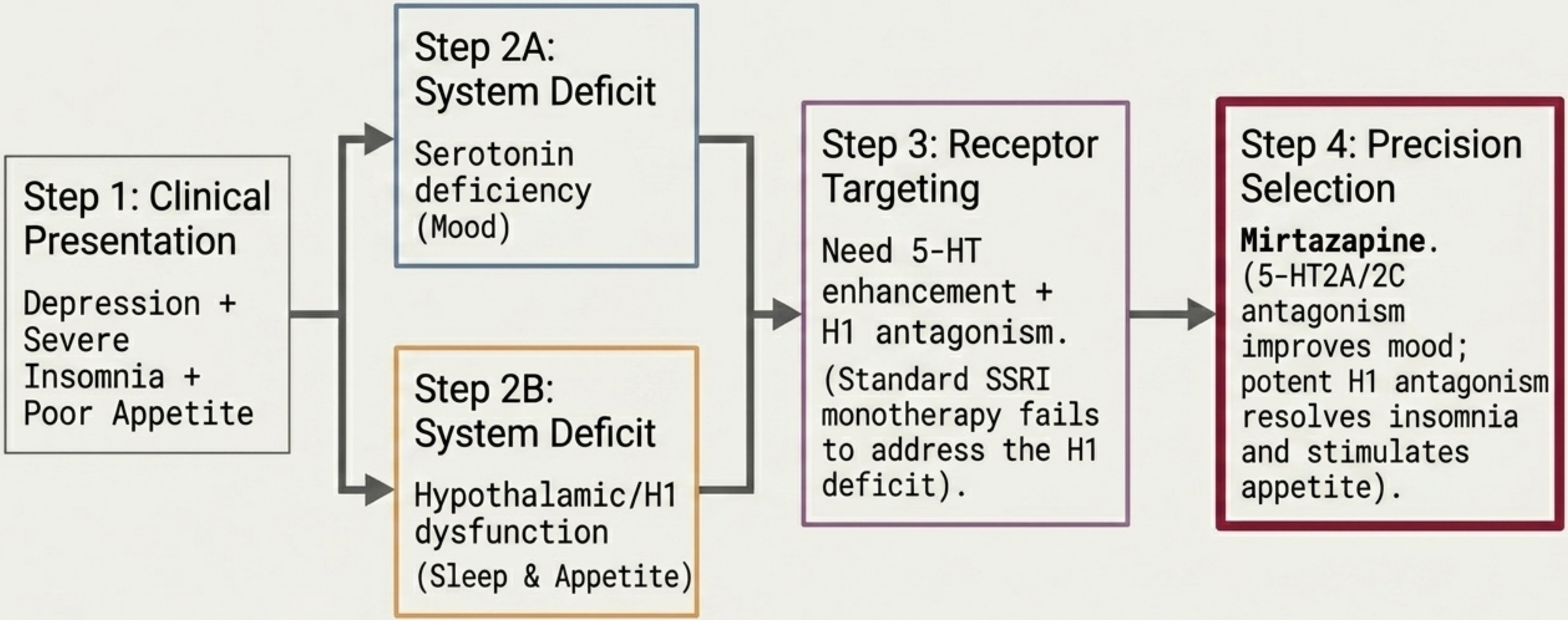
Dysfunction: Hyperactivity drives the obsessive-compulsive loop (OCD). DA blockade or SSRIs dampen this circuit.

The Clinical Liability Matrix: Predicting outcomes via receptor affinity

	M1 (Delirium/ Constipation)	H1 (Sedation/Weight Gain)	Alpha-1 (Orthostasis/ Falls)	5-HT2C (Metabolic Syndrome)	D2 (EPS/Tardive Dyskinesia)
Olanzapine	○	●	◐	●	○
Haloperidol	○	○	○	○	●
Clozapine	●	●	●	●	○
Aripiprazole	○	○	○	○	◐

Key Takeaway: Receptor pharmacology is clinical pharmacology. Understanding this grid transforms prescribing from algorithmic guessing to precision targeting.

Applied Logic: Decoding overlapping symptom clusters



Applied Logic: Targeting anhedonia and obsessive loops

Scenario A: The Dopamine Deficit

Symptom	Logic Path	Resolution
Depression + severe fatigue + lack of motivation (Anhedonia).	Anhedonia indicates Mesolimbic Dopamine deficiency, not just Serotonin. Avoid SSRI (may worsen sexual function). Target: Norepinephrine/Dopamine Reuptake Inhibitor (NDRI).	Bupropion.

Scenario B: The Glutamatergic Loop

Symptom	Logic Path	Resolution
Severe OCD unresponsive to standard SSRI doses.	OCD involves glutamatergic excess in orbitofrontal-anterior cingulate (CSTC) circuits. Standard SSRI doses are insufficient. Require massive indirect glutamate reduction or direct dampening.	Escalate to high-dose SSRI (12+ weeks) **OR** Augment with Glutamate modulators (Memantine) / D2-5HT2A antagonists.

The Neuro-Clinical Reference Architecture

Serotonin (5-HT)	Source: Raphe Nuclei. Key Receptors: 1A (Anxiety), 2A (Psychosis target), 2C (Weight gain), 3 (Nausea).
Dopamine (DA)	Source: VTA / Substantia Nigra. Pathways: Mesolimbic (Treat Psychosis), Mesocortical (Worsen Negative), Nigrostriatal (EPS), Tuberoinfundibular (Prolactin). Rule: 60-80% Occupancy.
Norepinephrine (NE)	Source: Locus Coeruleus. Receptors: Alpha-1 (Orthostasis), Alpha-2 (Autoreceptor/ADHD), Beta (Tremor).
GABA / Glutamate	The Balancing Fulcrum. GABA-A (Benzos/Alcohol), NMDA (Ketamine/Memantine). Withdrawal = Seizure risk.
ACh / Histamine	The Side Effect Drivers. M1 (Delirium, Constipation, Falls), H1 (Sedation, Weight Gain).