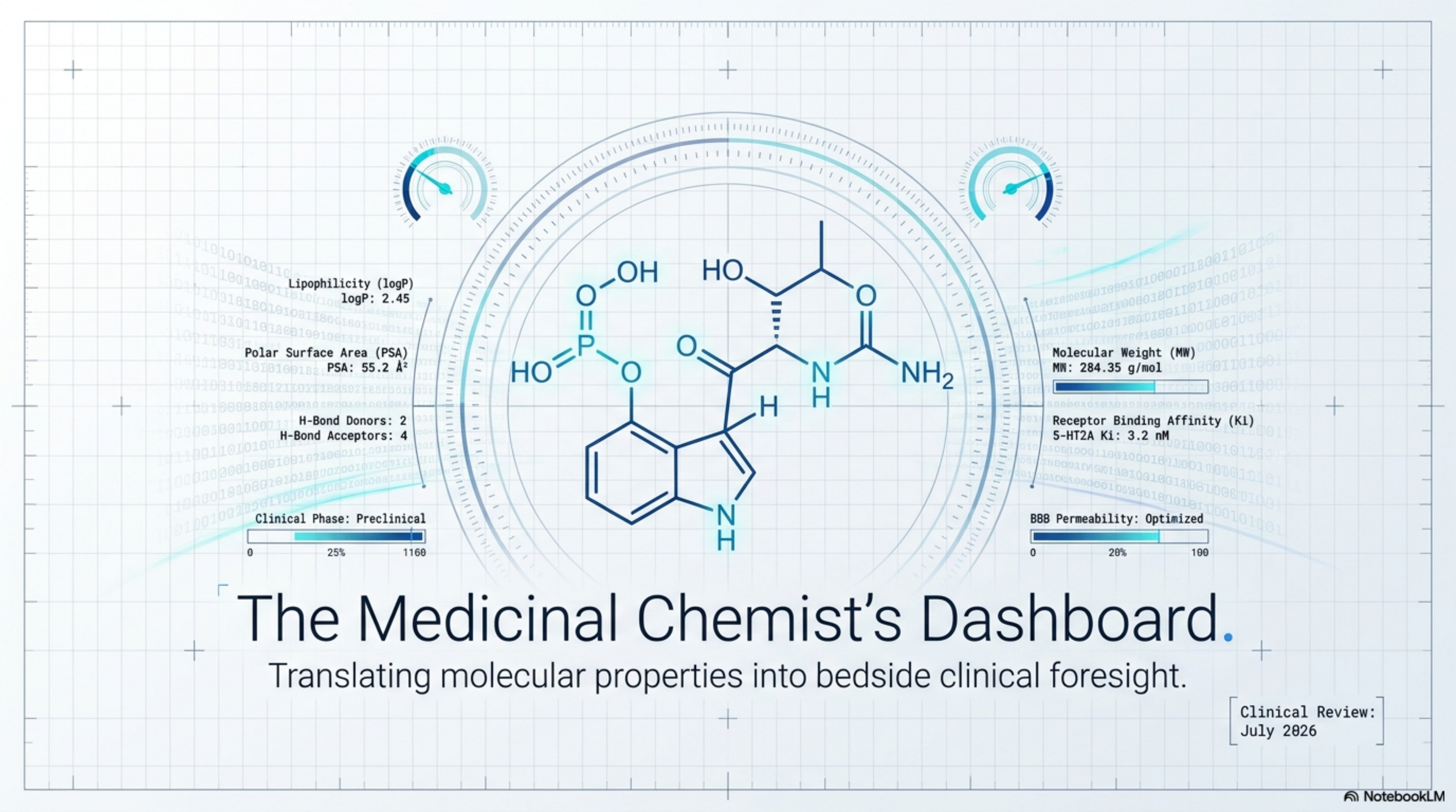


The Medicinal Chemist’s Dashboard.

Translating molecular properties into bedside clinical foresight.

Clinical Review:
July 2026

Every Number is an Intentional Lever

Can it get there?

Molecular Weight 385.4 g/mol

MIN: 150 MAX: 500

cLogP 2.5

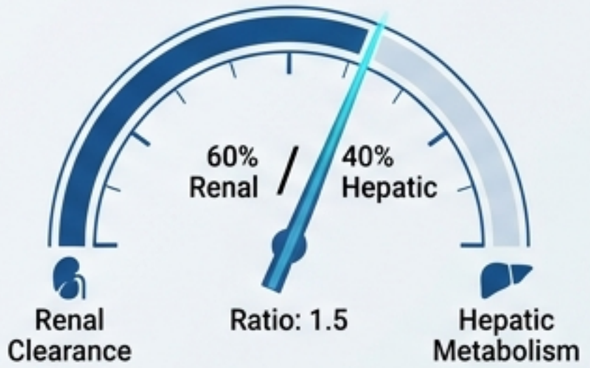
MIN: -2.0 MAX: 5.0

TPSA 80.2 Å²

MIN: 20 MAX: 140

How long does it stay?

Renal vs. Hepatic Profiles



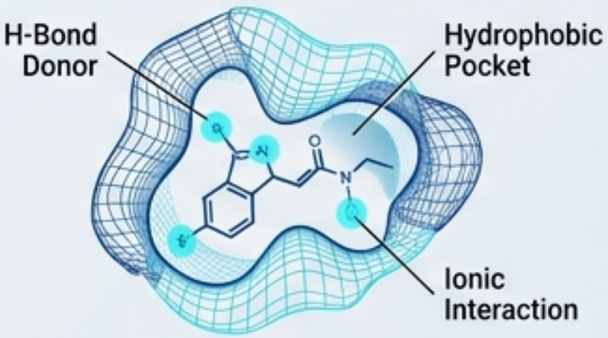
Aqueous Solubility

LOW HIGH

Solubility: High (>100 µg/mL)

What will it collide with?

Protein Binding Region



Binding Affinity: 85%

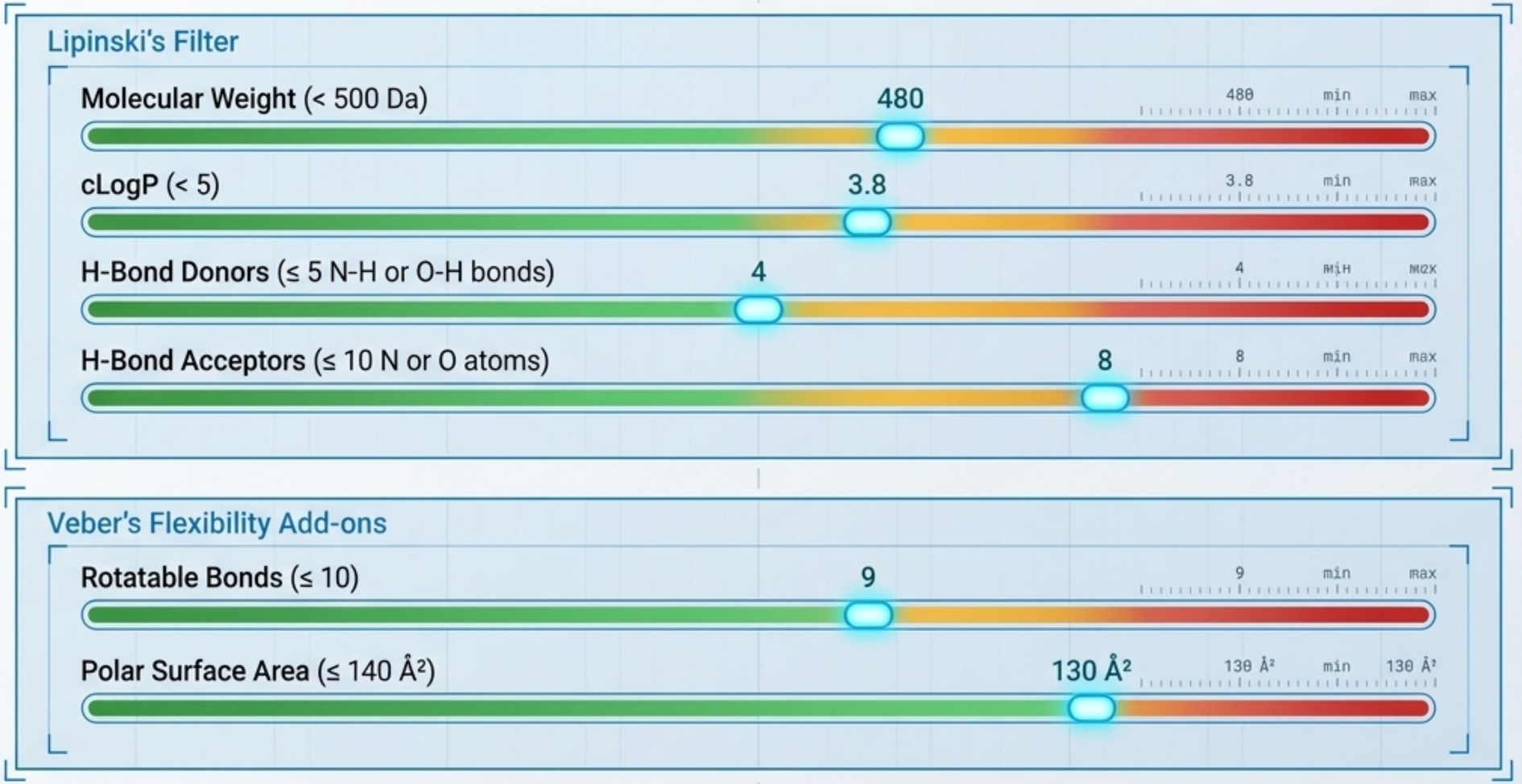
Ionization at pH 7.4

pH 7.4

Acidic (pKa < 7) | pH 7.4 Predominantly Neutral pKa: 6.8 | Basic (pKa > 7)

Medicinal chemists tune these properties to dictate dosing, interactions, and side effects. You can read their intent directly from the structure.

The Oral Bioavailability Gatekeepers



TECH NOTE

Passing these thresholds predicts passive oral absorption of the neutral molecule. Injectables and actively transported drugs bypass this checkpoint.

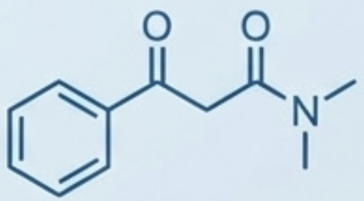
cLogP: The Master Dial for Lipophilicity

Low / Water Soluble
Renal Excretion

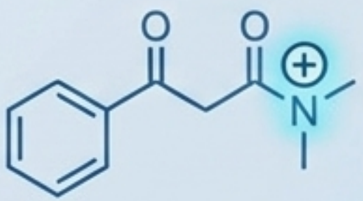
2-4
The CNS Sweet Spot
Rapid passive membrane crossing, deep CNS penetration

High / Fat Accumulation
Sedation, CYP450 Metabolism, Off-Target Promiscuity

logP



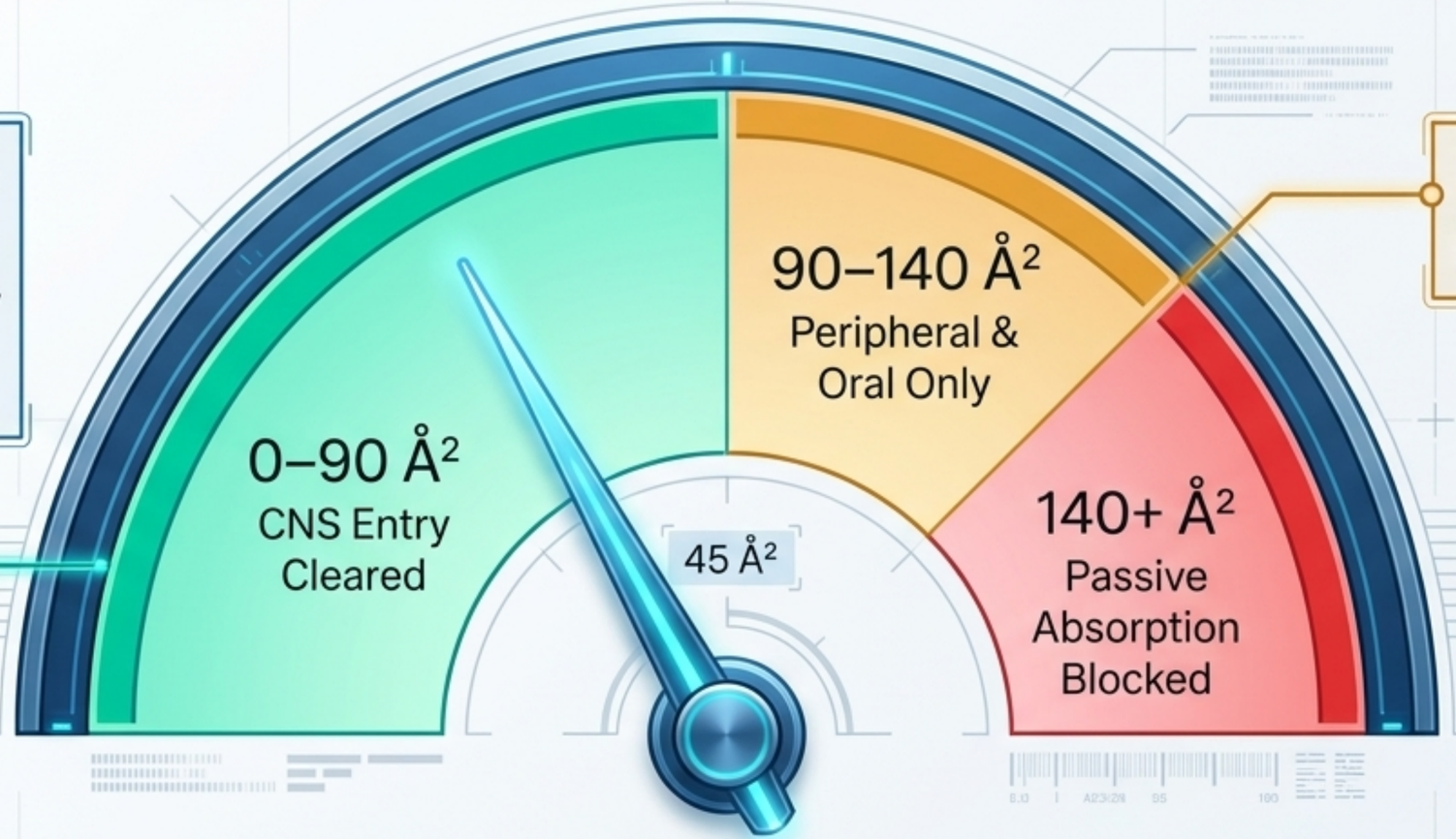
logD



TECH NOTE

logP measures only the neutral species. logD folds in the ionized fraction at pH 7.4. Mentally combine cLogP and ionization for heavily charged drugs.

TPSA: The Blood-Brain Barrier Gate



Most psychotropics (aripiprazole, sertraline, buspirone) are engineered below 90 Å² to guarantee central activity.

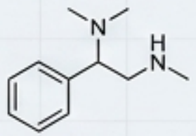
Allows oral absorption but sharply limits brain entry.

Every hydrogen bond a drug makes with water is a tax on membrane crossing.
TPSA measures this exact polarity cost.

Intentional Peripheral Restriction

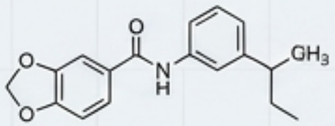
Central Action (Low TPSA)

Diphenhydramine



Slips across BBB → Sedation/Sleep Aid

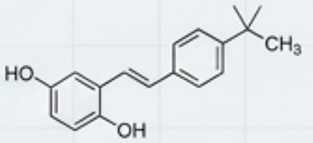
Metoclopramide

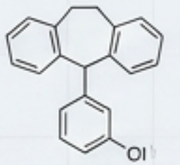


Crosses BBB → EPS, tardive dyskinesia

Peripheral Restriction (High TPSA)

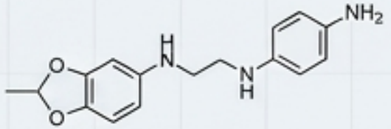
Fexofenadine & Loratadine





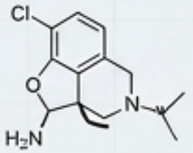
High polarity keeps them in airway/skin → Non-sedating

Domperidone



High TPSA + Efflux → Stays peripheral, targets gut

Loperamide

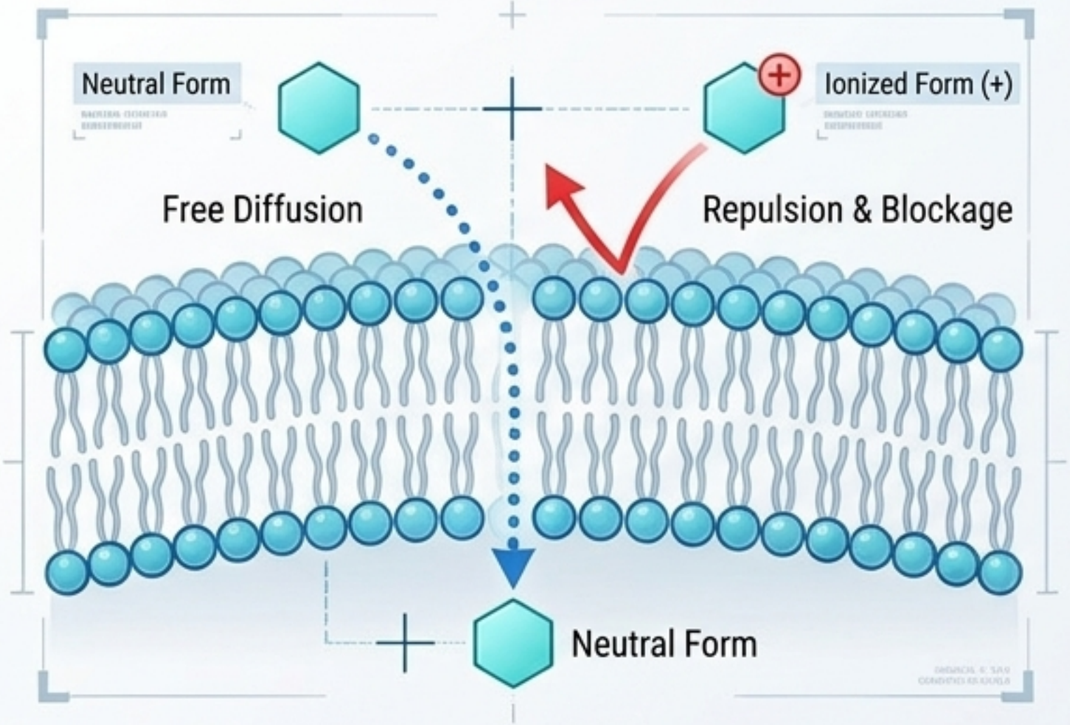


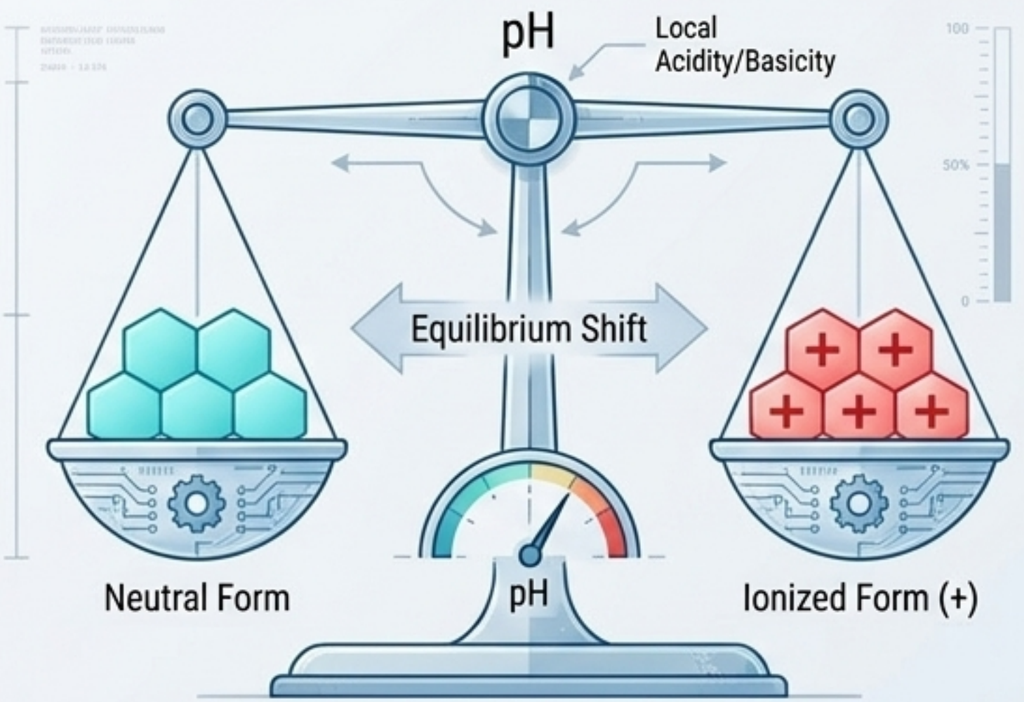
High TPSA + P-gp efflux keeps this potent μ-opioid acting only on gut motility.

⚠ Warning Tag

Massive overdoses overwhelm the P-gp efflux pump, forcing the drug into the heart and brain, causing life-threatening arrhythmies.

Ionization & pKa: Only the Neutral Form Travels





Rule

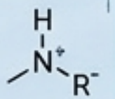
Biological membranes are lipid. Only the uncharged form diffuses across them freely.

Mechanism

The pKa is the pH at which a drug is exactly half-ionized. Local pH dictates the charged fraction.

$$pKa = pH - \log[Neutral]/[Ionized]$$

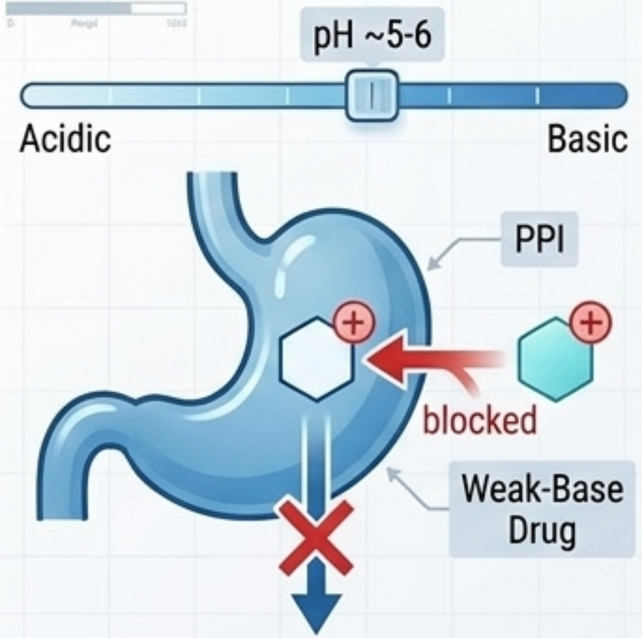
Psychiatric Context



Most psychotropics are weak bases (amine nitrogens). They are substantially protonated and positively charged in plasma, acting as a natural brake on CNS entry.

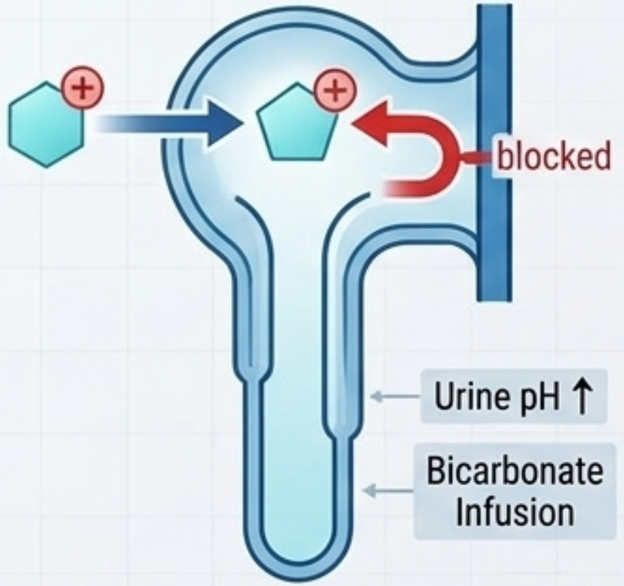
Clinical Ionization: Three Bedside Scenarios

pH-Dependent Absorption



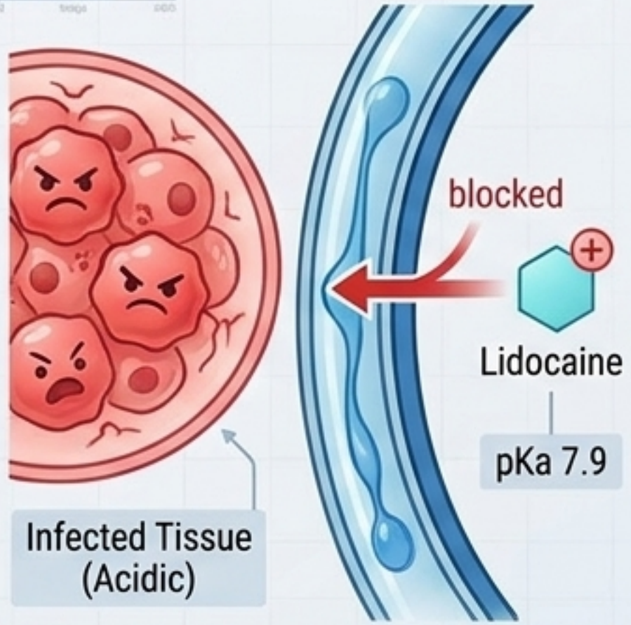
Raising gastric pH with a PPI prevents weak-base drugs (ketoconazole, atazanavir, dasatinib) from dissolving. Efficacy plummets.

Ion Trapping in Overdose



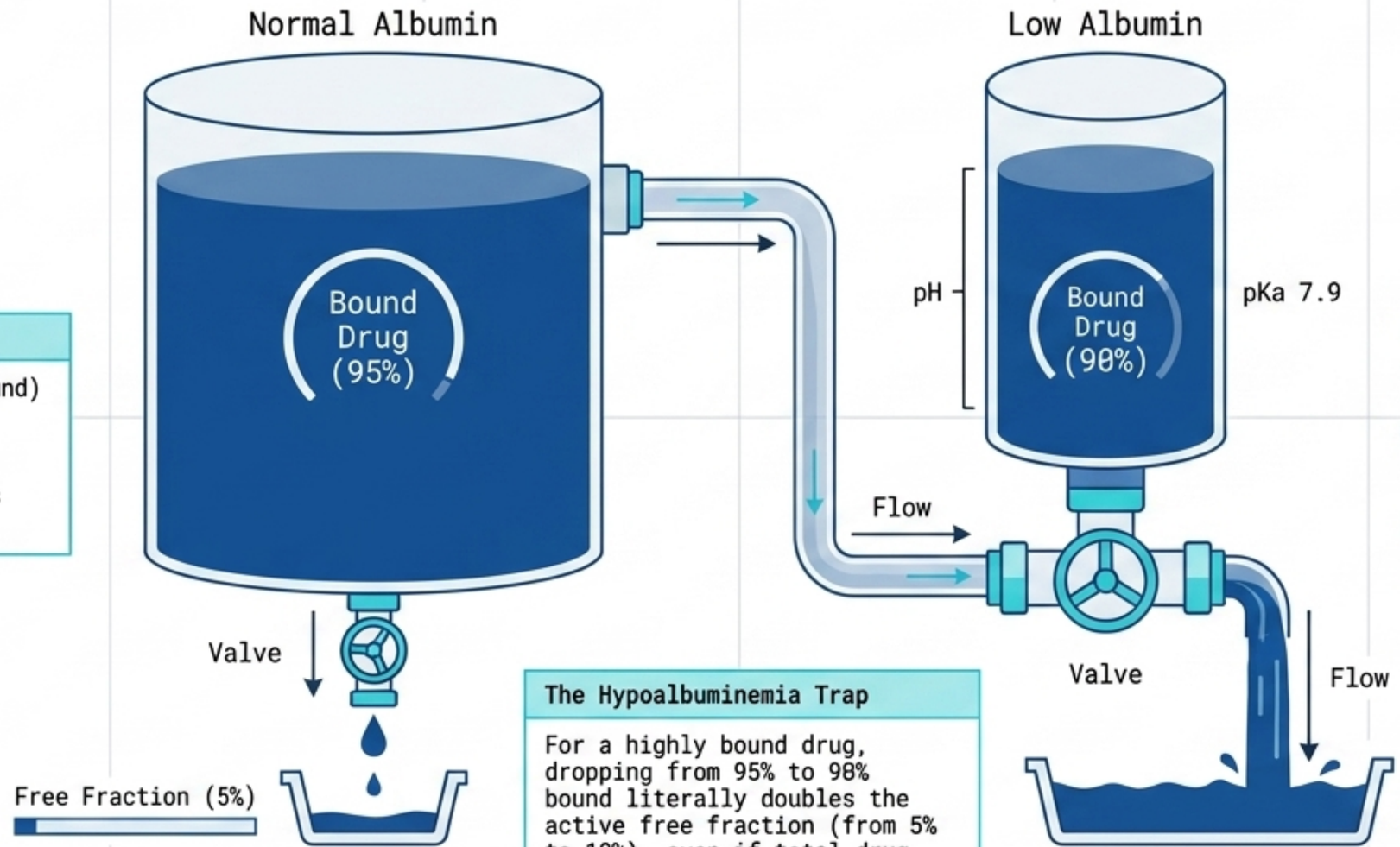
Salicylate and phenobarbital are weak acids. Bicarbonate infusions raise urine pH, converting the drug to a charged anion. It cannot diffuse back and is trapped for excretion.

Local Anesthetic Failure



Lidocaine is a weak base (pKa 7.9). Infected tissue is highly acidic, forcing lidocaine into a charged state outside the nerve. It cannot cross the membrane; the block fails.

The Albumin Reservoir: The Free Fraction Rule



Core Principle

Only the free (unbound) fraction is pharmacologically active, crosses membranes, or causes toxicity.

The Hypoalbuminemia Trap

For a highly bound drug, dropping from 95% to 90% bound literally doubles the active free fraction (from 5% to 10%), even if total drug levels remain unchanged.

Clinical Target

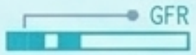
Suspect masked toxicity in low-albumin patients on highly bound, narrow-index drugs like phenytoin and valproate. Always order the free level, not the total.

The Excretion Matrix: Predicting the Exit Route

Renal
Unchanged in Urine

- Hydrophilic (low logP, high TPSA)
- Small molecular weight
- Highly ionized at pH 7.4
- Low protein binding (free to be filtered)

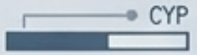
Examples: Lithium, gabapentin, topiramate, paliperidone. Watch GFR and and hydration.



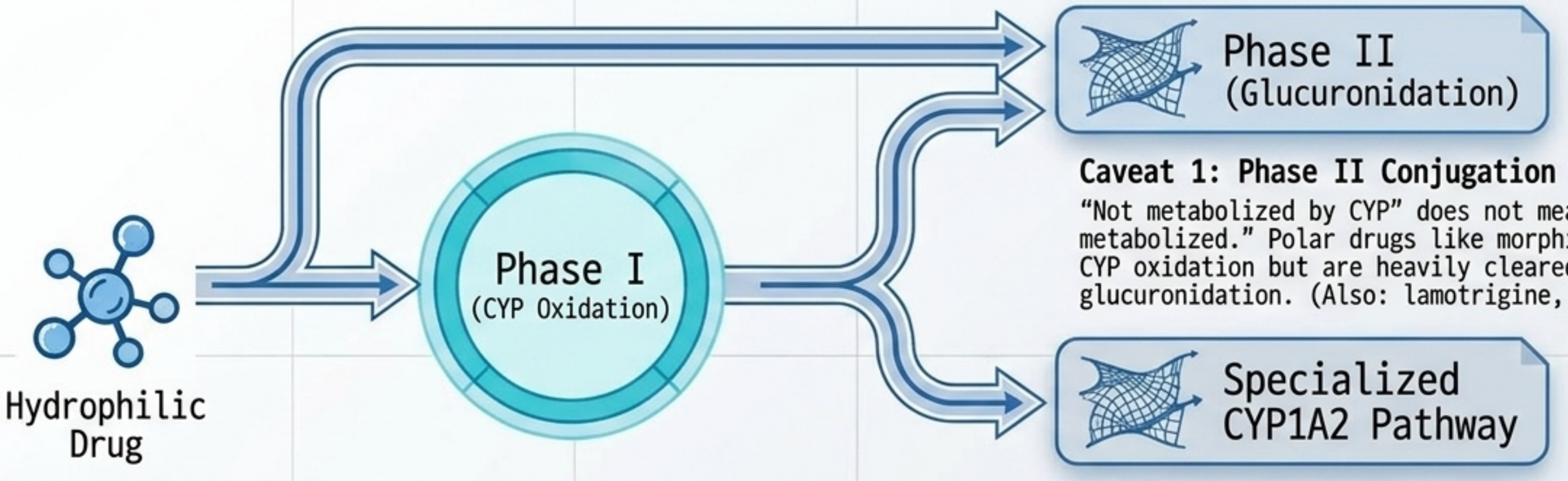
Hepatic
Metabolized First

- Lipophilic (high logP, low TPSA)
- Larger complex structures
- Neutral / weakly ionized
- High protein binding

Examples: Most antidepressants and antipsychotics. Watch CYP interactions and liver function.



When Water-Soluble Drugs Visit the Liver



Caveat 1: Phase II Conjugation

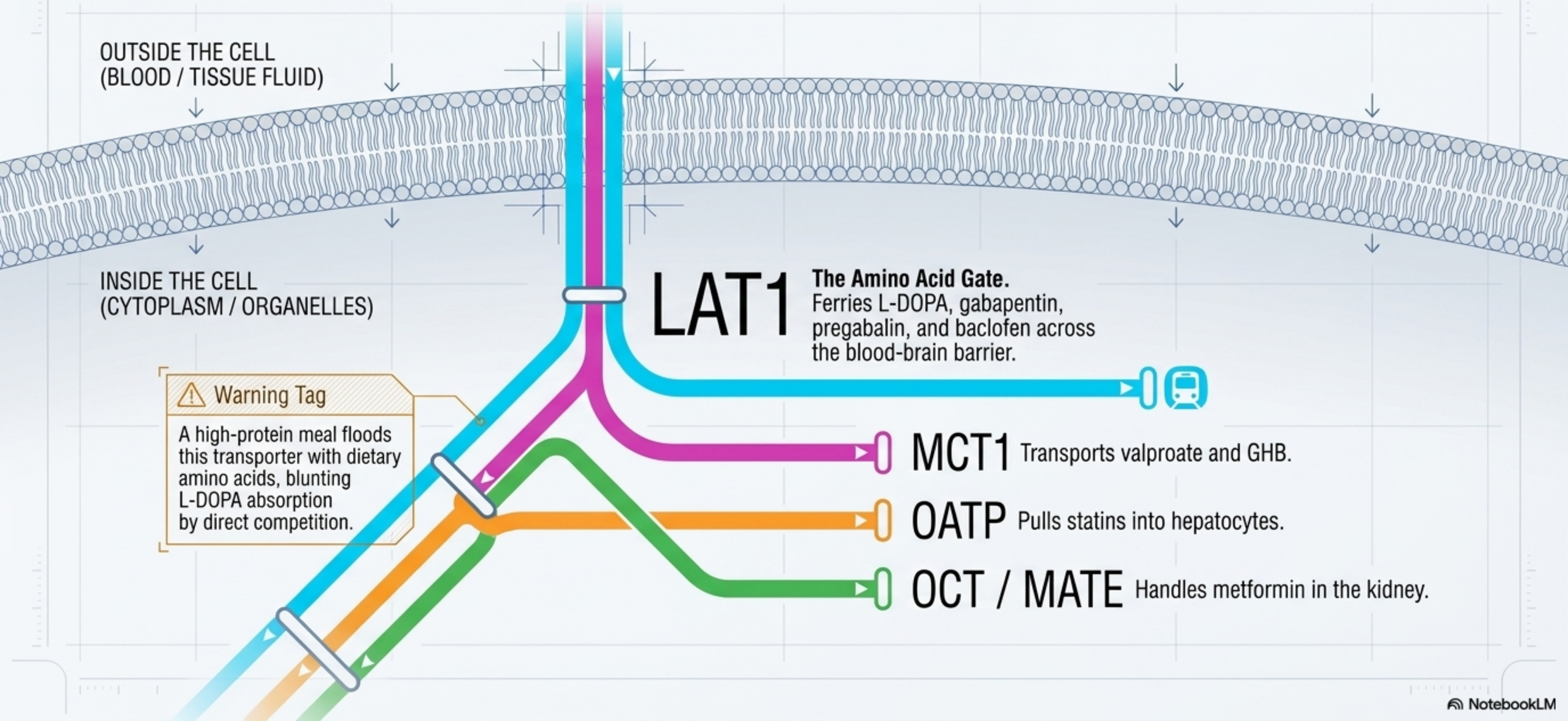
"Not metabolized by CYP" does not mean "not metabolized." Polar drugs like morphine skip CYP oxidation but are heavily cleared by UGT glucuronidation. (Also: lamotrigine, lorazepam).

Caveat 2: The CYP1A2 Outliers

CYP enzymes recognize specific reactive handles, not just overall lipophilicity. The xanthines (caffeine, theophylline) are freely water-soluble but are heavily cleared by CYP1A2.

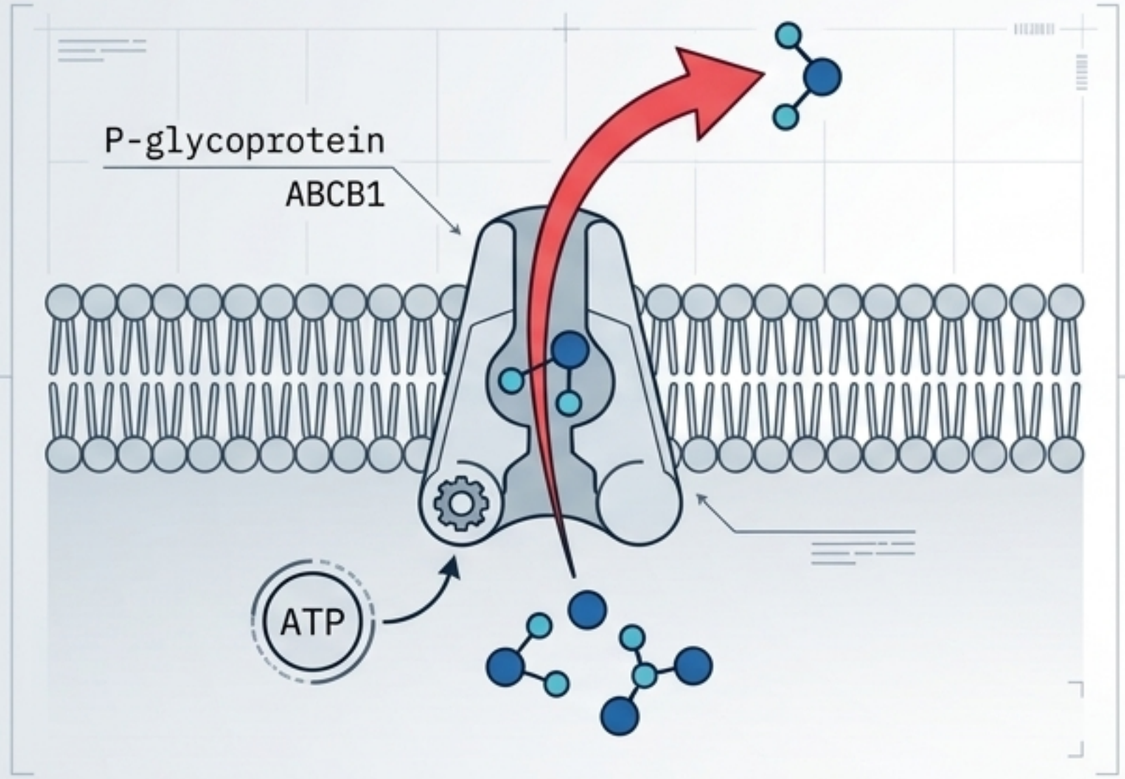
Clinical Impact: This is why smokers (who induce CYP1A2) clear caffeine, clozapine, and olanzapine faster, and why smoking cessation causes clozapine levels to spike dangerously.

The Uptake Lanes: Cheating the Structural Rules



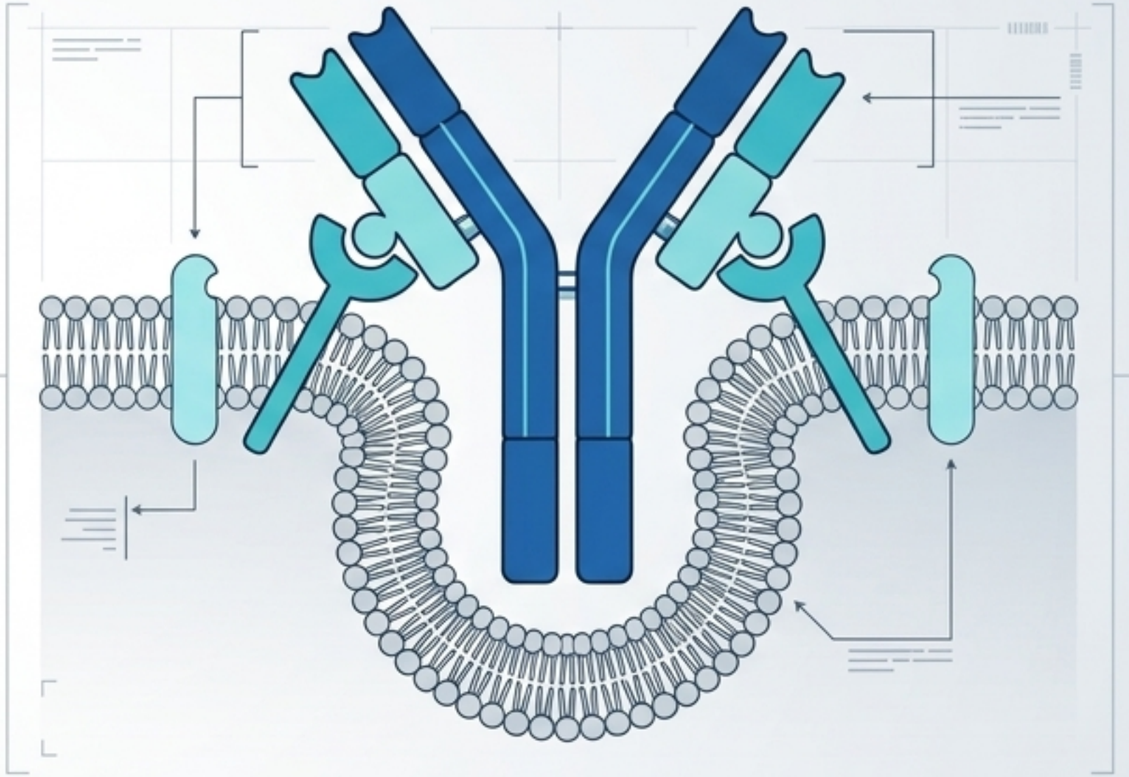
Efflux Bouncers & Molecular Trojan Horses

The ABC Efflux Pumps



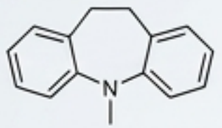
P-glycoprotein (ABCB1) uses ATP to actively pump drugs out of the brain and gut. It actively refluxes risperidone, paliperidone, and aripiprazole. CYP3A4 inhibitors often modulate P-gp simultaneously.

Receptor-Mediated Transcytosis



Passive diffusion cannot move large biologics (antibodies). They must piggy-back on the barrier's own receptors (transferrin or insulin receptors) to be shuttled into the brain.

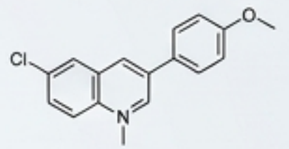
The Architect's Blueprint: Intentional Drug Design



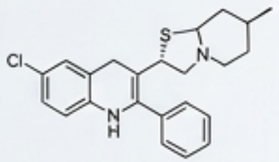
TCA (Base)

Dial Tuned: Strip the Scaffold

TCA to SSRI.
Removing the fused three-ring core sheds off-target H1 and alpha-1 binding. Goal: Overdose safety.



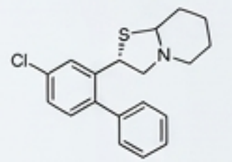
SSRI (Evolved)



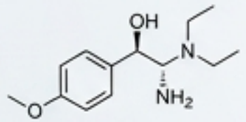
Citalopram (Racemic)

Dial Tuned: The Chiral Switch

Citalopram to Escitalopram.
Purifying to the single S-enantiomer removes the inactive, competing R-form. Goal: Potency and clean dose-response.



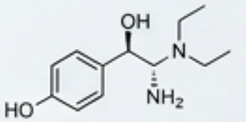
Escitalopram (S-Enantiomer)



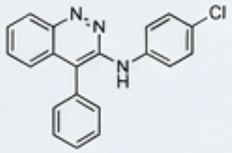
Venlafaxine (Parent)

Dial Tuned: Promote the Metabolite

Venlafaxine to Desvenlafaxine.
Marketing the CYP2D6 active metabolite removes a metabolic step. Goal: Predictable exposure.



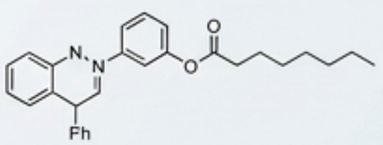
Desvenlafaxine (Active Metabolite)



Fluphenazine (Base)

Dial Tuned: Tune Lipophilicity

Fluphenazine to Fluphenazine Decanoate.
Adding a fatty-acid chain drops water solubility to near zero. Goal: Slow-release depot injections.



Fluphenazine Decanoate (Depot)

The Bedside Cheat Sheet

cLogP

The Lipophilicity Dial. Dictates fat accumulation, sedation risk, and volume of distribution. Sweet spot for CNS: 2 to 4.

TPSA

The Brain Gate.
Measures polarity tax. >90 limits brain entry; >140 limits oral absorption.

Ionization

The Movement Rule. Only the neutral form crosses membranes. Shifts in local pH (stomach, urine, abscess) trap or block the drug.

Protein Binding

The Free Fraction. Only unbound drug is active. Suspect masked toxicity when albumin is low, especially for narrow-index drugs.

Structure is destiny. The clinical future of the molecule is written in its blueprint.