Clinical Pharmacokinetics of Psychotropics

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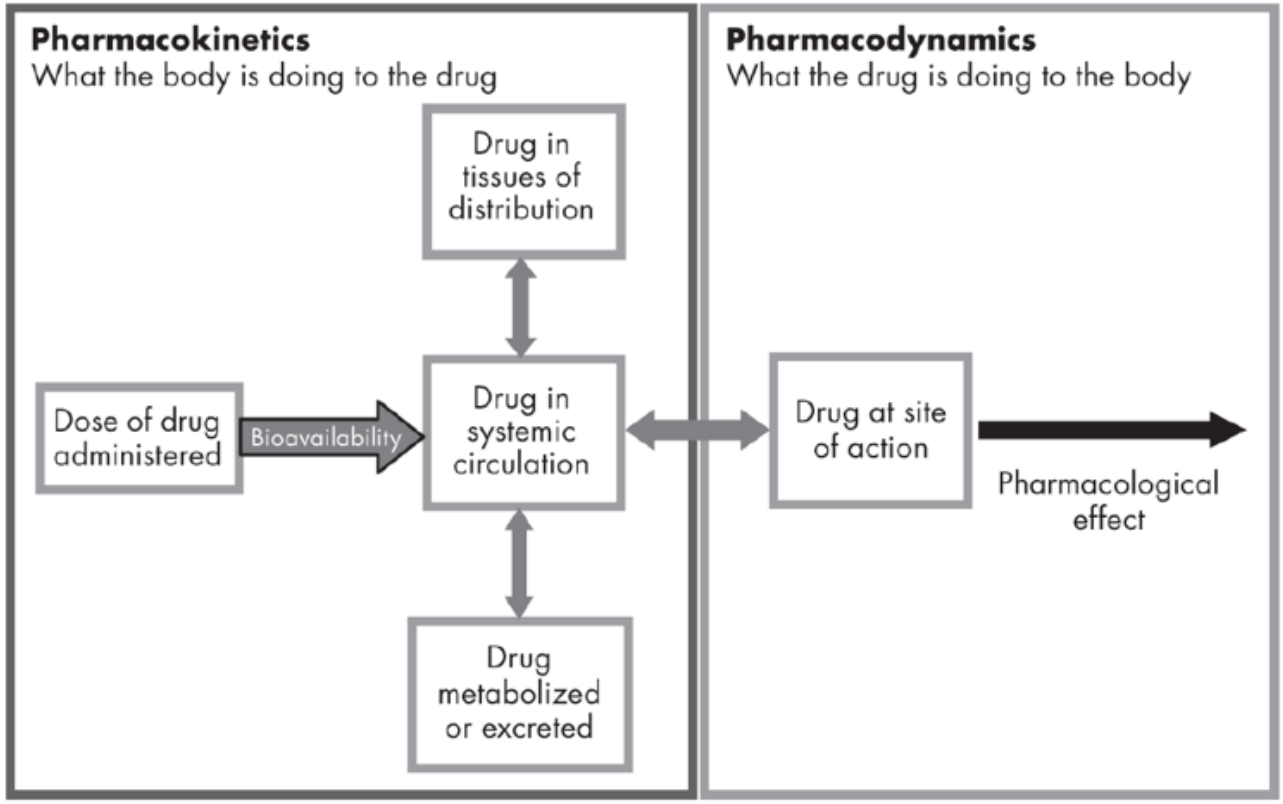
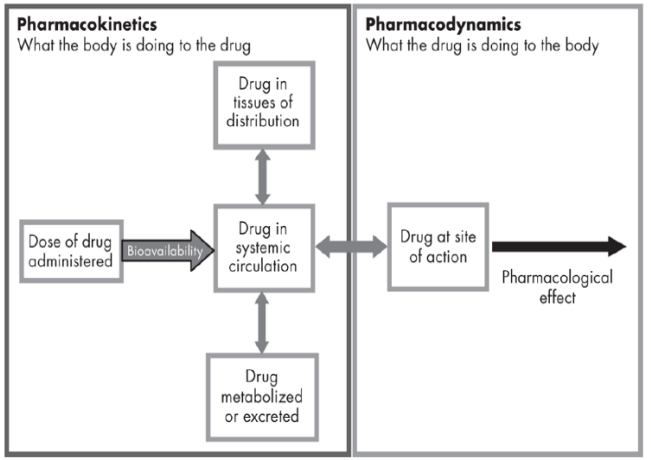
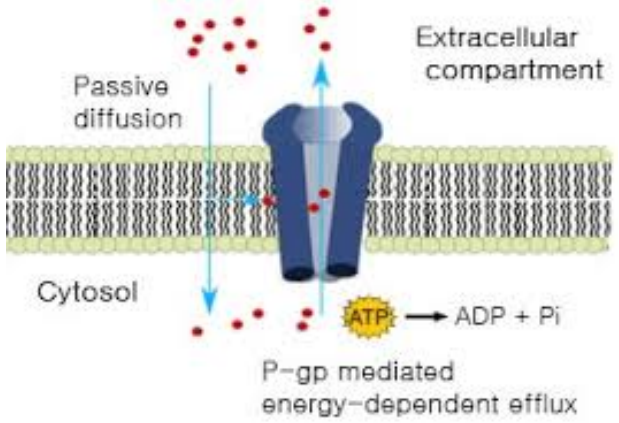

Pharmacokinetics
What the body is doing to the drug
Drug in tissues of distribution
Dose of drug administered
Bioavailability
Drug in systemic circulation
Drug metabolized or excreted
Pharmacodynamics
What the drug is doing to the body
Drug at site of action
Pharmacological effect

Bioavailability (F)

- Bioavailability of a drug formulation describes the extent of drug delivery to the systemic circulation from the formulation. Intravenous or intra-arterial administration.
- Affected by: surface area, pH, mucosal integrity, lipophilicity and hydrophilicity of the drug, particle size, local blood flow, gastric motility, P-glycoprotein (P-gp) efflux transport pump.





How does food affect F?

- Food delays absorption of drugs by delaying gastric emptying and increasing transit time. Some drugs increase F, others decrease F.
- Ziprasidone absorption is increased up to two-fold in the presence of food.
  - Prolonged gastric emptying time: more time for drug dissolution and absorption
  - Increased splanchnic blood flow
  - Enhanced drug solubilization (increase bile)

- Psychotropic drugs that are best taken on an empty stomach include quetiapine XR (as high-fat meals cause the XR capsule to rapidly “dump” its dose, risking oversedation and orthostasis).
- Shift absorption from the colon (where it primarily occurs in the fasted state) to the small intestine (where absorption is more efficient)

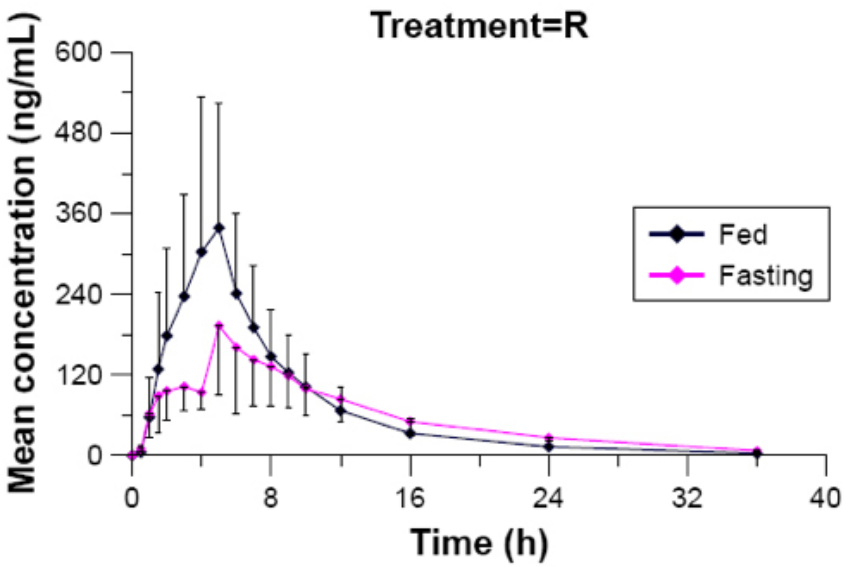
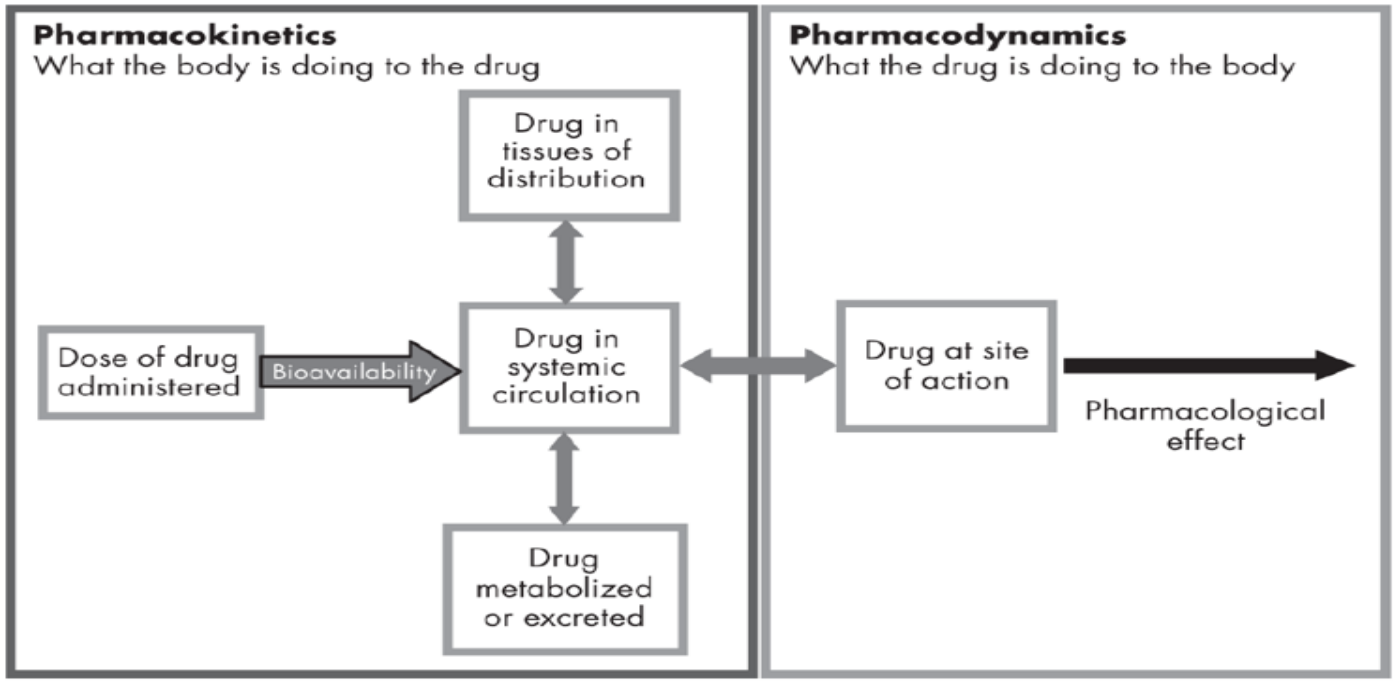


Figure 5 Mean plasma concentration–time curves of Seroquel XR (R) after a single oral dose of 200 mg in 18 healthy subjects under fasting conditions and 20 healthy subjects under fed conditions (mean±SD).
Abbreviations: R, reference preparation; Seroquel XR, Seroquel extended release.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Bariatric Surgery

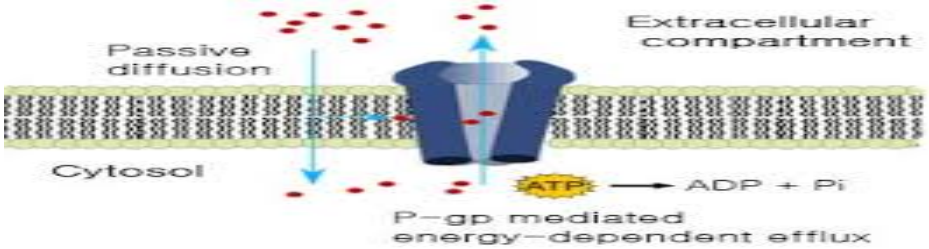


Table 10.16 Antidepressants in bariatric surgery.

Medication	Specific evidence and considerations
SSRIs[4,8,9]	Evidence demonstrates that plasma levels may be significantly reduced following RYGB or sleeve gastrectomy. The concentration of SSRIs may drop initially and then rebound within a few months; dose adjustments occurring in the immediate postoperative period might be temporary. Malabsorption has been implicated in cases of discontinuation symptoms and loss of efficacy. Sertraline and vortioxetine absorption appear to be the most affected and fluoxetine the least.
SNRIs[9–11]	Suggest avoid duloxetine owing to significant reduction in levels and risk of discontinuation syndrome. The absorption of venlafaxine MR capsules seems not to be altered by RYGB

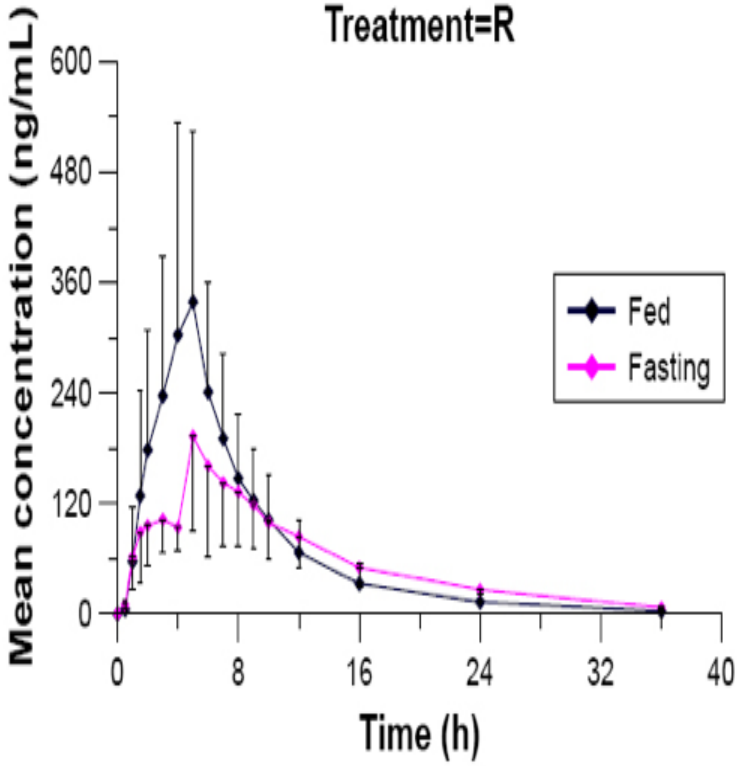


Figure 5 Mean plasma concentration–time curves of Seroquel XR (R) after a single oral dose of 200 mg in 18 healthy subjects under fasting conditions and 20 healthy subjects under fed conditions (mean±SD).
Abbreviations: R, reference preparation; Seroquel XR, Seroquel extended release.

Distribution (Vd)

- Process by which a drug is transferred from the systemic circulation to site-of-action organs.
- Lipophilic drugs (most psychotropic) are sequestered into lipid compartments of the body. High Vd.
- Hydrophilic drugs (e.g., lithium, oxazepam, valproate), being confined mainly to the intravascular volume have a small volume of distribution.
- Most drugs bind, to varying degrees, to the plasma proteins albumin or α1-acid glycoprotein. Acidic drugs (e.g., valproic acid, barbiturates) bind mostly to albumin, and more basic drugs (e.g., phenothiazines, tricyclic antidepressants, amphetamines, most benzodiazepines) bind to globulins.

- Increased free fraction in hypoalbuminemic states (liver disease, renal disease, malnourishment) or protein displacement (drug interaction, uremia) can cause toxicity despite "normal" total levels
- Valproic acid and phenytoin are clinically significant.
- Salicylates, trimethoprim-sulfamethoxazole, dulategravir

Obesity Alters the Distribution of Common Psychoactive Drugs

Miriam E. Tucker

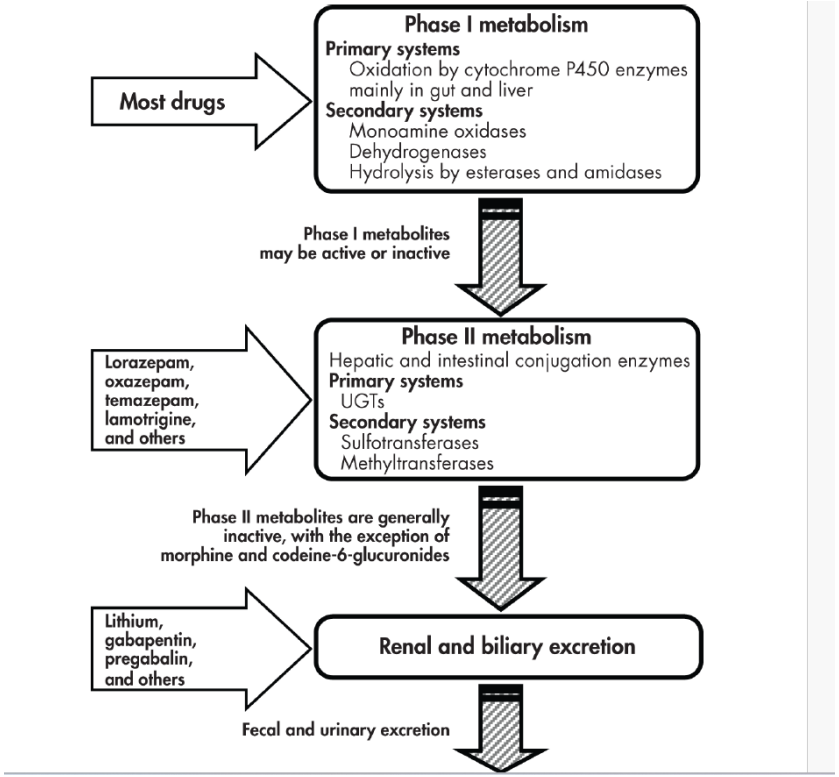
- Obesity alters the pharmacokinetics of several commonly prescribed psychiatric medications in ways that could affect their efficacy and safety, but this information isn't included on most of their product labels.

- For example, obesity increases the half-life of the antipsychotic brexpiprazole (Rexulti) such that it takes longer to reach effective plasma concentrations in heavier people. As a result, said Thomas G. Laughren, M.D., a psychiatrist with Massachusetts General Hospital and former head of the psychiatry drugs division at the Food and Drug Administration (FDA), "clinicians may give up on it. They may move on to something else if the drug appears not to be working when it could work if it's dosed differently."

- The product label for the novel antipsychotic xanomeline and trospium chloride (Cobenfy), just approved in September 2024, mentions that drug exposures are lower in people weighing 120 kg versus 70 kg (although this is not thought to be clinically meaningful).

First Pass Effect (F) and Metabolism (Clearance, CL)

- Biotransformation occurs throughout the body, with the greatest activity in the liver and gut wall.
- First-pass metabolism refers to the transport and metabolism of drugs from the gut lumen to the systemic circulation via the portal vein and liver. Drug passage from the gut lumen to the portal circulation may be limited by two processes: 1) a P-glycoprotein (P-gp) efflux transport pump 2) metabolism within the gut wall by cytochrome P450 (CYP) 3A4



The Maudsley® Prescribing Guidelines in Psychiatry

Table 11.5

Effects of Psychotropics on CYP Function

Bold entries only — predominant metabolic enzyme pathway or predominant enzyme activity

■ **Bold** = Predominant pathway/activity ■ **Bold*** = Minor / not clinically significant ■ Normal font = Significance unclear

Table 11.5 · Maudsley 2025 · Bold Entries Only

CYP1A2

5 Substrates | 2 Inhibitors | 3 Inducers

Substrates	Inhibitors	Inducers
Clozapine	**Asenapine**	**'Barbiturates'**
Duloxetine	**Fluvoxamine**	**Carbamazepine**
Melatonin		**Phenobarbital**
Olanzapine		
Ramelteon		

Table 11.5 · Maudsley 2025 · Bold Entries Only

CYP2B6

1 Substrates | 3 Inhibitors | 4 Inducers

Substrates	Inhibitors	Inducers
Bupropion	**Fluvoxamine**	**Carbamazepine**
	Memantine	**Modafinil**
	Paroxetine	**Phenobarbital**
		Phenytoin

ℹ️ *Inducers shown bold in text extraction; Fluoxetine*, Sertraline* not bold*

Table 11.5 · Maudsley 2025 · Bold Entries Only

CYP2C9

2 Substrates

Substrates	Inhibitors	Inducers
Lamotrigine	**Fluvoxamine**	**Carbamazepine**
Valproate	**Valproate**	**SJW**

Table 11.5 · Maudsley 2025 · Bold Entries Only

CYP2C19

2 Substrates

Substrates	Inhibitors	Inducers
Diazepam	**Fluoxetine**	**Carbamazepine**
Escitalopram	**Fluvoxamine**	**SJW**

CYP2D6 (1/2)

11 Substrates

Substrates	Inhibitors	Inducers
'Amfetamines'	**Amitriptyline**	
Aripiprazole	**Asenapine**	
Atomoxetine	**Bupropion**	
Brexpiprazole	**Duloxetine**	
Clomipramine	**Fluoxetine**	
Deutetrabenazine	**Paroxetine**	
Fluoxetine	**Sertraline>200mg**	
Fluphenazine		
Galantamine		
Iloperidone		
Imipramine		

Inducers: Not known

CYP2D6 (2/2)

10 Substrates

Substrates	Inhibitors	Inducers
Mianserin		
Nortriptyline		
Olanzapine		
Perphenazine		
Risperidone		
Sertindole		
Trimipramine		
Venlafaxine		
Vortioxetine		
Zuclopenthixol		

Table 11.5 · Maudsley 2025 · Bold Entries Only

CYP3A4 (1/2)

18 Substrates | 2 Inhibitors | 6 Inducers

Substrates	Inhibitors	Inducers
Alfentanyl	**Fluoxetine**	**Asenapine?**
Alprazolam	**Paroxetine**	**Carbamazepine**
Aripiprazole		**Modafinil**
Blonaserin		**Phenobarbital**
Brexipiprazole		**Phenytoin**
Buprenorphine		**SJW**
Buspirone		
Carbamazepine		
Cariprazine		
Clonazepam		
Donepezil		
Dosulepin		
Fentanyl		
?Flurazepam		

CYP3A4 (2/2)

18 Substrates | 0 Inducers

Substrates	Inhibitors	Inducers
Lurasidone		
Methadone		
Midazolam		
Mirtazapine		
Nitrazepam		
Pimavanserin		
Pimozide		
Quetiapine		
Reboxetine		
Sertindole		
Suvorexant		
Trazodone		
Valbenazine		
Vilazodone		

Summary · Key Bold Entries Across A

Carbamazepine

Bold inducer for CYP1A2, CYP2C9, CYP2C19, CYP3A4 — major pan-inducer

Fluvoxamine

Bold inhibitor for CYP1A2, CYP2C9, CYP2C19, CYP2D6 — broadest SSRI inhibitor

Fluoxetine

Bold inhibitor for CYP2C19, CYP2D6, CYP3A4

Paroxetine

Bold inhibitor for CYP2D6 and CYP3A4

Phenobarbital / Phenytoin

Bold inducers for CYP1A2, CYP2B6, CYP3A4 — important anticonvulsant interactions

Clozapine

Bold substrate for CYP1A2 — smoking cessation markedly raises levels

SJW (St John's Wort)

Bold inducer for CYP2C9, CYP2C19, CYP3A4 — significant herbal interaction

Valproate

Bold substrate and inhibitor of CYP2C9 — key interaction with lamotrigine

Source: Maudsley Prescribing Guidelines, 15th Ed. 2025, Table 11.5

QTC והארכת מקטע CYP2D6 אינטראקציה על על רקע

מוארך בבסיס QTc: Prolonged QTc (≥440(♂)/460(♀) ms)

לאחר מנת יתר, או כאלה שבהן נצפתה עלייה ממוצעת QTc תרופות בעלות השפעה נמוכה הן תרופות שלגביהן דווח על הארכה משמעותית של מקטע קטנה פחות מ-10 מילישניות במינונים טיפוליים.

ביותר מ-10 מילישניות בממוצע כאשר הן ניתנות במינונים QTc תרופות בעלות השפעה בינונית הן תרופות שנמצא כי הן מאריכות את מקטע טיפוליים.

בדרך כלל מעל 20 מילישניות במינונים טיפוליים QTc תרופות בעלות השפעה גבוהה הן תרופות שלגביהן קיימת הארכה ממוצעת ניכרת של קטע.

טבלה מספר: תרופות פסיכיאטריות מאריכות QTc

High risk	Moderate risk	Low risk
Pimozide	Haloperidol	Aripiprazole
Sertindole	Quetiapine≥300mg	Clozapine
	Amisulpiride	Fluphenazine
	Chlorpromazine	Perphenazine
	Levomepromazine	Zuclopenthixol
	Ziprasidone	Olanzapine
	Citalopram ≥40mg	Risperidone
	Escitalopram ≥20mg	Sulpiride
	Tricyclics	Trazodone
	Lithium	Sertraline >400mg
	Methadone	Venlafaxine

אין השפעה משמעותית על Fluoxetine, bupropion, paroxetine-נא לשים לב שאולם בספרות מדווח כי ל
ושילובם עם אנטיפסיכוטים המתפנים ע"י אותו אנזים CYP2D6 תרופות אלה מעכבות את האנזים QTC
מומלץ אק"ג בסיס, מעקב אק"ג כל 2 -8 שעות לאחר מתן המנה הQTc prolongation מגביר סיכון ל
הראשונה ועד הגעה לשיווי משקל, ולאחר שבוע מתחילת הטיפול או הגעה לשיווי משקל

Valproate-Lamotrigine Interaction

Mechanism and clinical significance: Valproate inhibits glucuronidation, reducing lamotrigine clearance by approximately 60% and doubling its half-life from 25 to 60 hours.

TABLE 41–1. Recommended titration schedule for lamotrigine for patients with bipolar disorder taking valproate

Week	Dosage
Weeks 1 and 2	25 mg every other day
Weeks 3 and 4	25 mg daily
Week 5	50 mg daily
Week 6	100 mg daily
Week 7	100 mg daily

Note. The usual maintenance dosage when lamotrigine is added to valproate is 100 mg/day.
Source. Adapted from GlaxoSmithKline 2023.

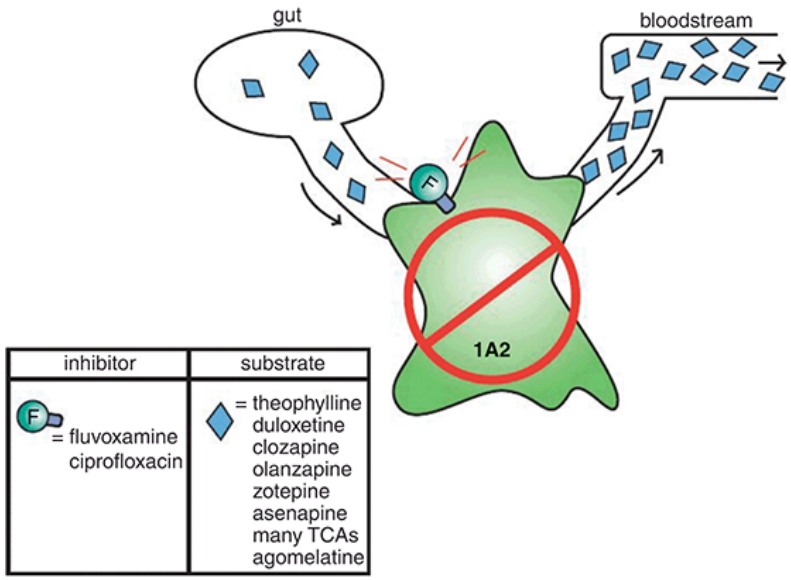
Not all CYP Interactions are bad

- Clomipramine-fluvoxamine OCD: Clomipramine (CMI) undergoes extensive first-pass metabolism in the liver to desmethylclomipramine (DCMI) by CYP1A2, CYP2C19, and CYP3A4. The CMI molecule is a potent serotonin reuptake inhibitor, but DCMI has minimal serotonergic activity and potent noradrenergic activity. CMI+FLV combination mimic CMI IV.
- Dextromethorphan-bupropion: CYP2D6 blockade by bupropion raises dextromethorphan (DXM) exposure and extends its half-life from 4-6 hours to 22 hours.

- Fluvoxamine can increase plasma clozapine levels by 5–10 fold.
- Clozapine is metabolized to norclozapine by CYP1A2

- Fluvoxamine is thought to improve the clozapine (Clozaril) to norclozapine ratio, thereby decreasing adverse effects while boosting clozapine plasma levels for better therapeutic effects

- In theory, a clozapine (Clozaril) to



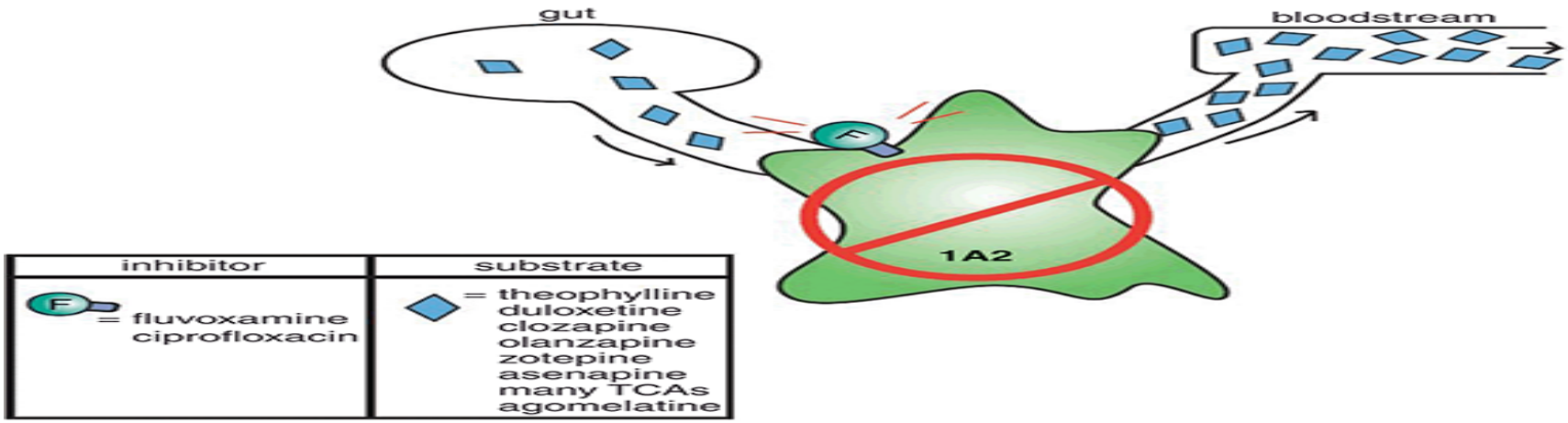
Effect of Metabolites

- Nortriptyline is an active metabolite of amitriptyline with NRI and less anticholinergic adverse events.
- Hydroxybupropion is bupropion's active metabolite that acts as NRI (mean occupancy of approximately 40%, substantially exceeding that of its parent compound, bupropion <5%). PM at CYP2B6, such as slow metabolizers, may have a poor response, while ultra-metabolizers may have noradrenergic adverse events.
- Similarly, quetiapine is converted to norquetiapine by CYP3A4, which has NRI activity and contributes to the antidepressant mechanism.
- Meaningful NET engagement with venlafaxine may occur primarily at higher doses (>150 mg/day) due to accumulation of desmethylvenlafaxine metabolite.

Elimination (renal clearance)

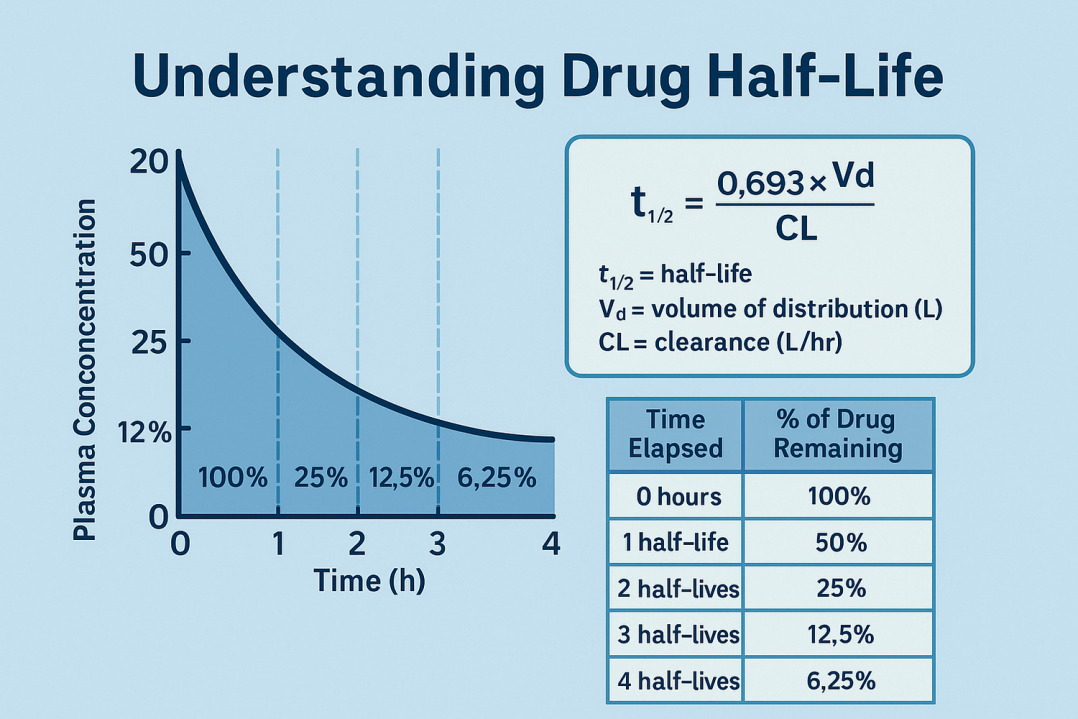
- **G1**: ≥90 mL/min/1.73 m² (normal or high)
- **G2**: 60-89 mL/min/1.73 m² (mildly decreased)
- **G3a**: 45-59 mL/min/1.73 m² (mildly to moderately decreased)
- **G3b**: 30-44 mL/min/1.73 m² (moderately to severely decreased)
- **G4**: 15-29 mL/min/1.73 m² (severely decreased)
- **G5**: <15 mL/min/1.73 m² (kidney failure)

- Many medication recommendations for renal dosage adjustments were based on Cockcroft-Gault estimation of creatinine clearance.



Pregabalin	Cl_{cr} 30–60 mL/min: 50% of usual dosage. Cl_{cr} 15–30 mL/min: 25% of usual dosage. Cl_{cr} < 15 mL/min: 12.5% of usual dosage. Hemodialysis: supplemental dose may be needed after each 4-hour dialysis session. See manufacturer's recommendations.
Lithium	Moderate RI: 50%–75% of usual dosage. Hemodialysis: supplemental dose of 300 mg once after each dialysis session.
Mirtazapine	Moderate RI: clearance decreased by 30%. Severe RI: clearance decreased by 50%.
Venlafaxine	Mild to moderate RI: 75% of usual dosage. Severe RI: 50% of usual dosage. Patients undergoing hemodialysis should have dosage reduced by 50% and receive the dose after dialysis session.

Half-life



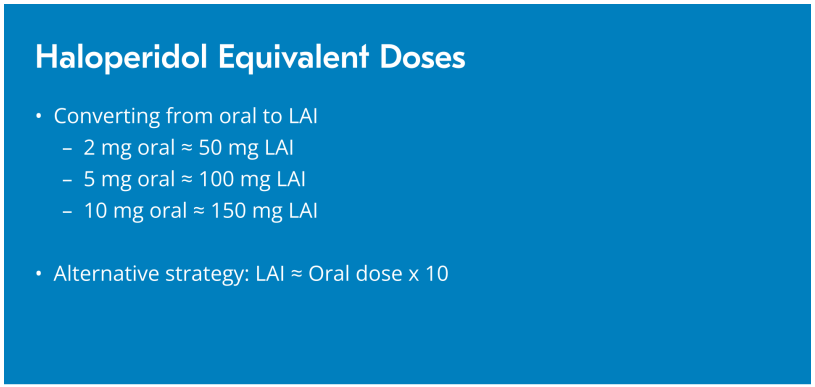
Time Elapsed	% of Drug Remaining
0 hours	100%
1 half-life	50%
2 half-lives	25%
3 half-lives	12,5%
4 half-lives	6,25%

It takes 4-5 half-lives for a drug to be completely eliminated

It takes 4-5 half-lives to reach steady state

A patient treated with haloperidol decanoate 150mg (half-life 21 days) every 28 days. The patient did not receive the last injection. Given that haloperidol's half-life is 21 hours, when do haloperidol plasma levels become negligible?

- 105 hours
- 84 hours
- 28 days
- 105 days



A patient treated with Clopixol Depot 200mg every 14 days, given that the peak concentrations of zuclophentixol occur 4-7 days after injection, and the half-life is 19 days, when is steady-state reached and what strategies could be done to reach peak sooner?

- Steady state reached at 13 weeks (after 4-7 injections).
- Continue Clopixol PO for one week (peak 4-7 days).
- Ratio: Approximately 6.7:1 (depot to daily oral dose). Example: A patient on 30 mg/day oral would convert to approximately 200 mg depot every 2 weeks
- Acuphase could be given until peak concentrations of depot is reached:
  - Acuphase 100 mg every 2-3 days for a week.
  - Give zuclopenthixol decanoate 200 mg IM (standard starting dose)

Plasma drug monitoring

- Valproic acid
- Clozapine
- Lithium
- Lamotrigine
- Carbamazepine

Clozapine Monitoring

- The gold standard is a 12-hour (± 2 h) trough value obtained at steady state (i.e., after 5–7 days) (half-life 8 to 14 hours, range 4-66 hours).
- Many clinicians choose a round number such as 100 mg QHS or 200 mg QHS as the point at which they obtain plasma levels during titration, waiting at least 5–7 days on that dose so clozapine will be at steady state.

	Response threshold	Diminishing tolerability	Point of futility
Level in ng/ml	350	700–1000	> 1000
Level in nmol/l	1070	2140–3057	> 3057

Concentration oral dose relationships

40-year-old male, weight 80 kg:

- Concentration (ng/ml) = 1.08 x oral dose (mg/d) (nonsmoker)

- Concentration (ng/ml) = 0.67 x oral dose (mg/d) (smoker)

40-year-old female, weight 70 kg:

- Concentration (ng/ml) = 1.32 x oral dose (mg/d) (nonsmoker)

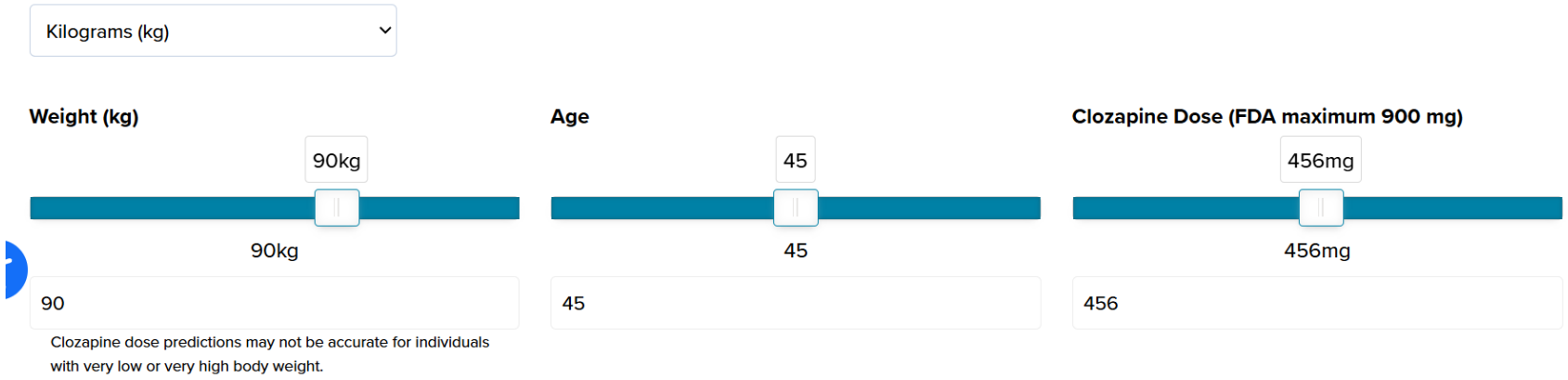
- Concentration (ng/ml) = 0.80 x oral dose (mg/d) (smoker)

Plasma level adverse event relationship

- Seizures > 600 (consider use of anticonvulsant,1000ng/mL add anticonvulsant)
- QTc prolongation> 600
- Obsessive Compulsive Symptoms > 595.1 ± 364.9ng/mL

- 600-1000- reduce dose by 25%
- >1000 reduce dose by 50%

Predicting Plasma Concentration from dose



https://smicaladviser.org/clozapine-dose-planner/

What affects clozapine levels?

- Smoking as few as 7–12 cigarettes/day is sufficient to fully induce CYP 1A2, with a net increase of 1.66-fold in enzyme activity. Aryl hydrocarbons induce CYP 1A2 expression. Nicotine plays no role.
- Upon smoking cessation the CYP 1A2 activity declines with a half-life of 38.6 hours (range 27.4–54.4 h). CYP 1A2 activity will therefore return to baseline after 5 half-lives, or 8 days on average.
- When outpatient smokers treated with clozapine are placed in situations without access to cigarettes for more than 48 hours, doses ought to be lowered by 10% every 48 hours to a maximum reduction of 50%. Plasma levels on days 7 and 14 can be used to guide further dose adjustments.

- Caffeine in large doses may compete with clozapine for CYP 1A2, thereby increasing plasma clozapine levels. In a sample of nonsmoking volunteers who ingested 400–1000 mg/day of caffeine, there was a 19% increase in mean total clozapine exposure ($p = 0.05$).
- Any inflammatory process of sufficient severity to induce marked cytokine release (including COVID-19 infection with systemic symptoms that do not merit hospitalization, and after COVID-19 vaccination) will downregulate CYP 1A2 activity, and this will increase plasma clozapine levels. (reduce dose by 50%)
- one or more nonfunctional CYP 1A2 alleles

Guidelines for Interpreting the Metabolic Ratio (MR)

- MR = 1.32: The expected mean value for nonsmokers who are CYP 1A2 extensive metabolizers.

- MR << 1.32: Trough values of 1.00 or less reflect exposure to an inducer (e.g. smoking, carbamazepine, omeprazole), or CYP 1A2 ultrarapid metabolizer status.

- MR >> 1.32: Trough values greater than 2.00 reflect exposure to inhibitors of the main CYP enzymes involved in clozapine metabolism: 1A2, 2C19, 2D6 or 3A4, or poor metabolizer status, especially at CYP 1A2 or CYP 2D6. As clozapine is principally metabolized via CYP 1A2, strong CYP 2D6 or 3A4 inhibitors will

Box 4.1 Cholinergic Rebound Symptoms*

Mild: sleep disturbance, vivid dreams, nightmares

Moderate: anxiety, nausea, diarrhea, sweating, urinary urgency

Severe: confusion, delirium, catatonia

* Comment: By its actions at striatal cholinergic interneurons, cholinergic rebound may also induce parkinsonism, akathisia or dystonia if the patient is being exposed to another source of D_2 antagonism. In this context the effect of cholinergic rebound can be thought of as “anti-benztropine” [15].

Lithium PK

- At steady state, the peripheral half-life ($T_{1/2}$) in adults is 20–24 h and in the brain $T_{1/2}$ 28–48 h. There is no efficacy based reason to dose lithium other than once daily at bedtime in adults.
- Steady state for oral medications is reached after 5 half-lives. Trough levels should be obtained 12 h after the bedtime dose at steady state.

Multiple daily dosing is associated with more renal dysfunction

By limiting the number of daily peak exposures, once-daily dosing may reduce the repetitive tubular injury that occurs with each concentration spike.

Calculate lithium dose using target levels

- For adults and pediatric patients over 30 kg, the FDA-approved starting dose is 300 mg three times daily (900 mg/day total). The dose is then adjusted based on therapeutic drug monitoring:
- Check serum lithium level after 3-5 days, drawn 12 hours after the last dose
- Titrate by 300 mg every 3-5 days based on serum levels
- Target serum concentration for

Box 4.1 Cholinergic Rebound Symptoms*

Mild: sleep disturbance, vivid dreams, nightmares

Moderate: anxiety, nausea, diarrhea, sweating, urinary urgency

Severe: confusion, delirium, catatonia

* Comment: By its actions at striatal cholinergic interneurons, cholinergic rebound may also induce parkinsonism, akathisia or dystonia if the patient is being exposed to another source of D_2 antagonism. In this context the effect of cholinergic rebound can be thought of as "anti-benztropine" [15].

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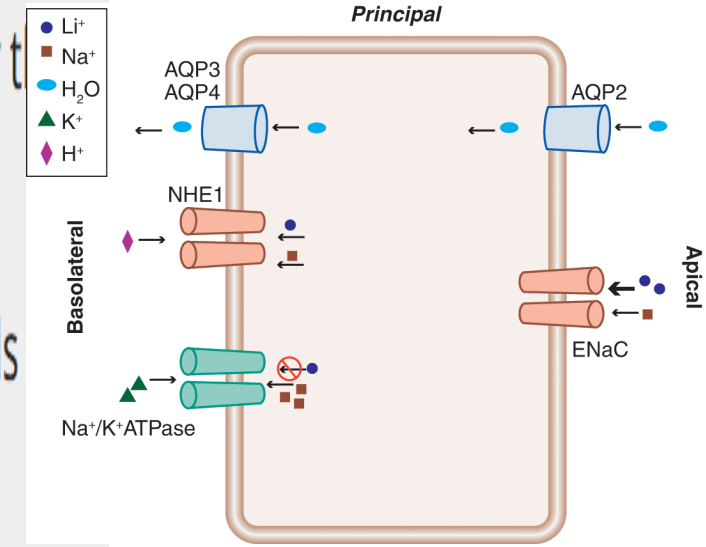


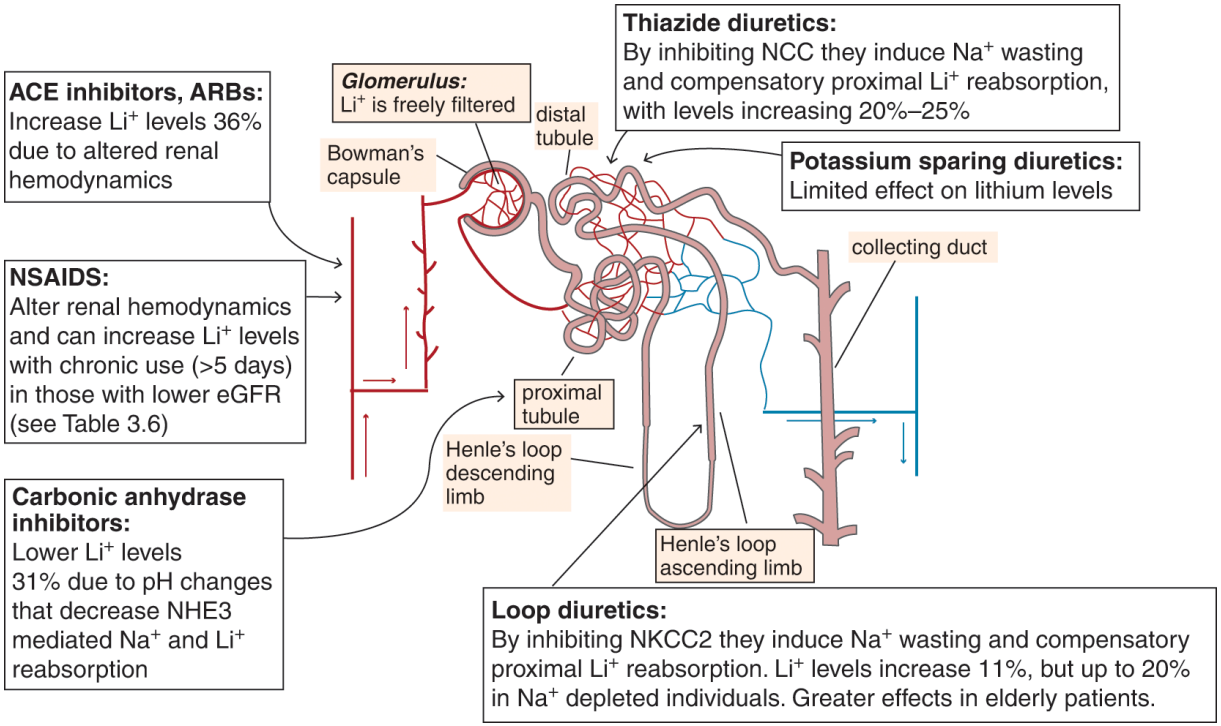
- The prevalence of symptomatic polyuria is under 30% and perhaps < 20%
- Early use of the ENaC inhibitor amiloride may be important to minimize the risk of lithium-related collecting duct pathology when polyuria complaints arise.
- Once daily lithium dosing, use of trough levels < 1.00 mEq/l, and prevention of trough level excursions > 1.20 mEq/l are all associated with lower risk of lithium related renal pathology.

Renal Insufficiency and ESRD

- At steady state, the peripheral half-life ($T_{1/2}$) in adults is 20–24 h and in the brain $T_{1/2}$ 28–48 h. There is no efficacy based reason to dose lithium other than once daily at bedtime in adults.
- Steady state for oral medications is reached after 5 half-lives. Trough levels should be obtained 12 h after the bedtime dose at steady state.

- CKD stage 3-5: 25%
- CKD stage 3: 18%
- ESRD: **absolute risk of approximately 0.5-2%.**

Drug interaction with Lithium



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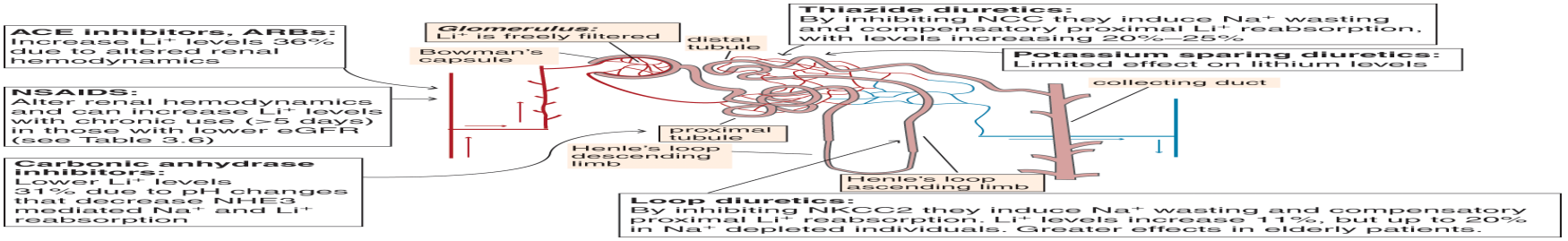

Box 4.1 Cholinergic Rebound Symptoms*

Mild: sleep disturbance, vivid dreams, nightmares

Moderate: anxiety, nausea, diarrhea, sweating, urinary urgency

Severe: confusion, delirium, catatonia

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Prescribing Rationale

Case 1

- A 31-year-old woman with the chief complaint of diagnosed treatment-resistant schizophrenia disorder.
- The patient's first psychotic episode occurred at age 17 after her father died of cancer.
- She was initially started on a second-generation antipsychotic, but her symptoms remained and different antipsychotics were thus trialed over many years.
- The patient was trialed on long-acting injectables in the past when she lived by herself, including paliperidone (Invega) and haloperidol decanoate (Haldol Decanoate)
- Even with appropriate medication compliance, the patient continued to have positive symptoms while on both first- and second-generation

What’s next?

- Approximately 40% to 50% of acute psychoses will experience a remission of positive symptoms or experience only mild symptoms with treatment. The remaining 50% to 60% of patients will improve but will still demonstrate positive symptoms.
- Treatment-resistant schizophrenia (TRS) is defined as persistent moderate symptoms and impairment despite at least 2 sequential trials of different antipsychotic medications at adequate dose, duration (at least 6 weeks at target dose), and adherence.
- TRS affects approximately 20-30% of patients with schizophrenia, with some experiencing primary (early) resistance from illness onset and others developing secondary resistance after initial response.

- The patient eventually tried clozapine (Clozaril) a little over a year ago
- She admitted to manic-like symptoms in the past including episodes of grandiosity, high energy, and little sleep
- She reported multiple past psychiatric medication failures leading to the starting of clozapine roughly 13 months ago
- She denies past suicide attempts
- The patient's biological brother suffers from bipolar disorder, and she

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- The patient admits to current auditory hallucinations, which are command in nature, but not to hurting herself or others as evidenced by the patient's statement, "The FBI tells me to complete my job application for IBM"
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- She reports weight gain since starting clozapine and feels overly sedated some days

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Dopamine supersensitivity hypothesis

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Sodium-glucose cotransporter 2 (SGLT-2) inhibitors	May reduce lithium levels 83% due to increased clearance [103].	Check lithium level after 72 hours and adjust dosage. Recheck level in 1 week.[4]	No adjustments to proposed lithium dose, but may see markedly lower levels than expected due to increased clearance. Check lithium levels after 1 week, 12 weeks.[4]

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- This finding suggests that the medium-dose (9 to <16.5 mg/day) aripiprazole combination with high-dose clozapine treatment is associated with a considerably decreased rate of hospitalization due to a psychotic episode.

Case 2

- At steady state, the peripheral half-life ($T_{1/2}$) in adults is 20–24 h and in the brain $T_{1/2}$ 28–48 h. There is no efficacy based reason to dose lithium other than once daily at bedtime in adults.
- Steady state for oral medications is reached after 5 half-lives. Trough levels

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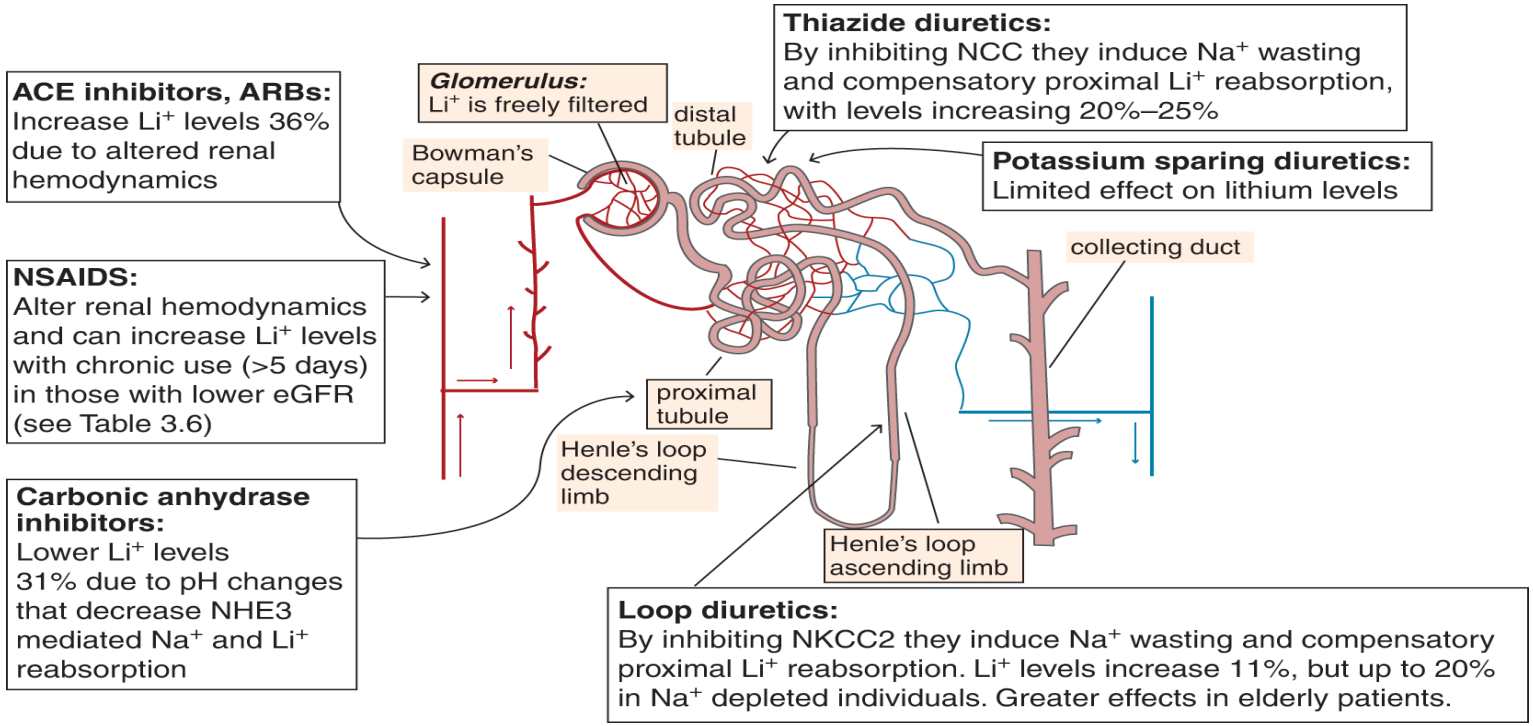
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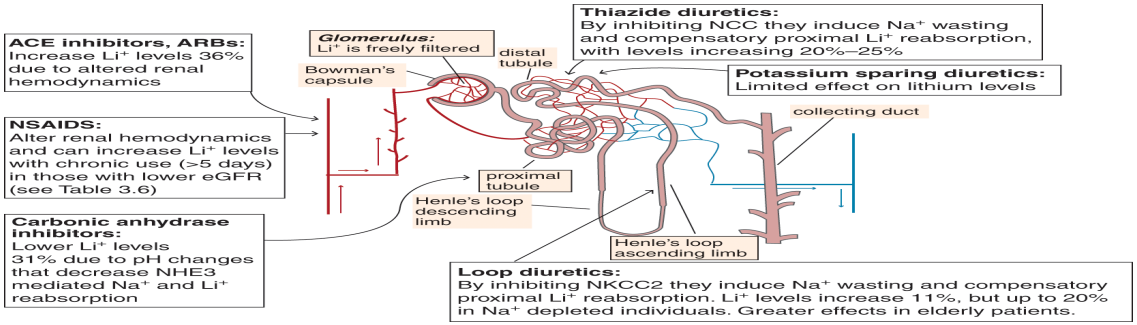

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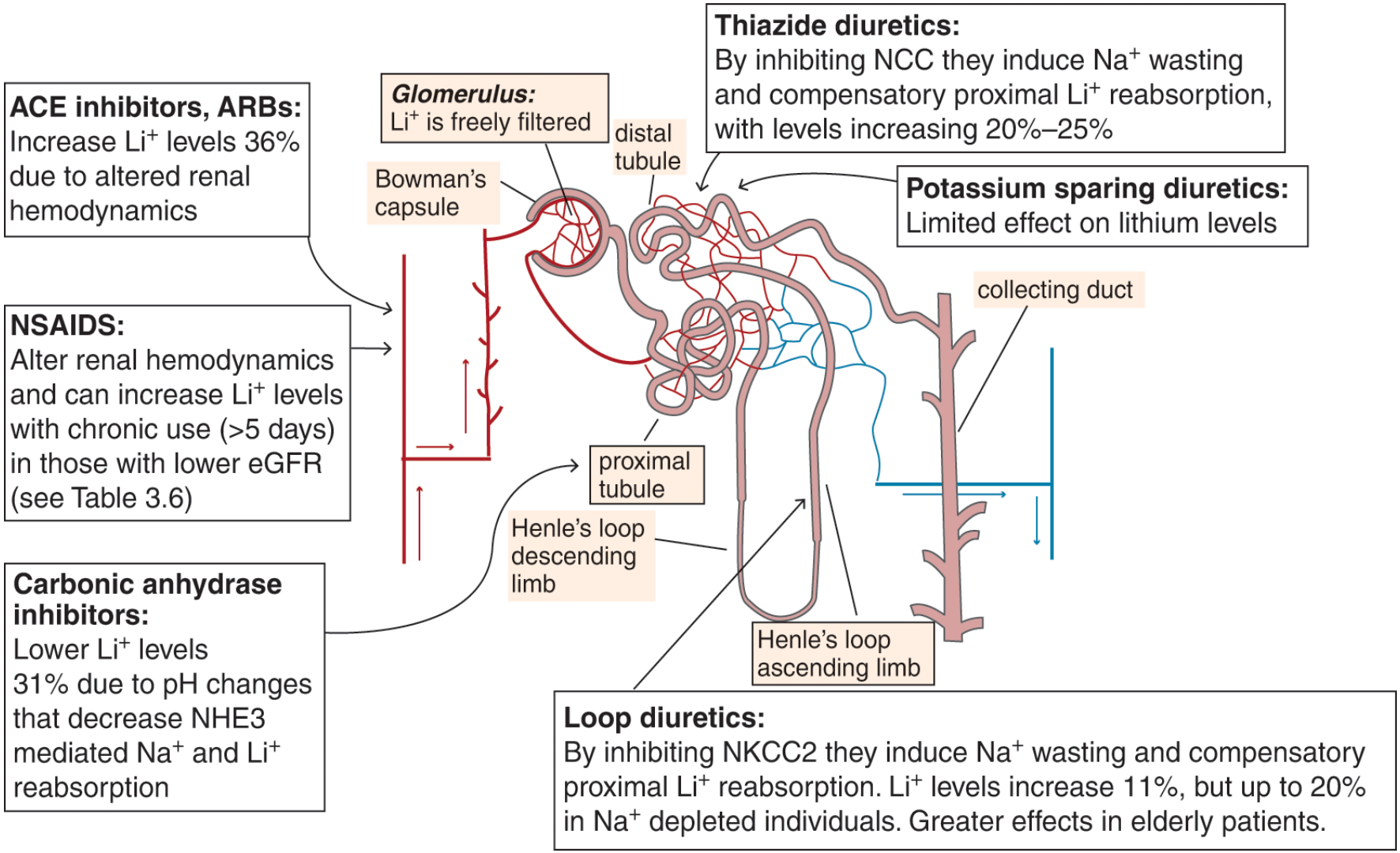
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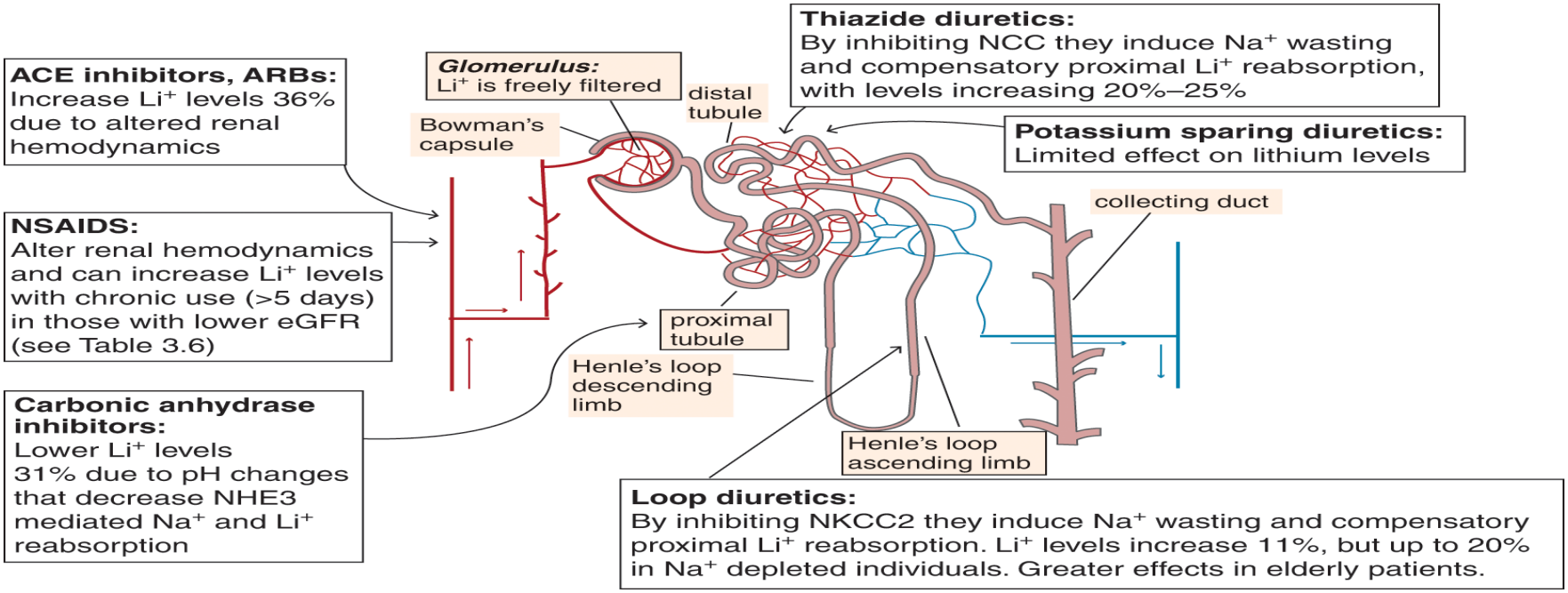
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- She admits to depressive symptoms including depression, low energy, and poor sleep
- She denies suicidal ideation or self-harm thoughts
- She reports weight gain since starting clozapine and feels overly sedated some days

- At steady state, the peripheral half-life ($T_{1/2}$) in adults is 20–24 h and in the brain $T_{1/2}$ 28–48 h. There is no efficacy based reason to dose lithium other than once daily at bedtime in adults.
- Steady state for oral medications is reached after 5 half-lives. Trough levels should be obtained 12 h after the bedtime dose at steady state.