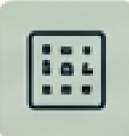
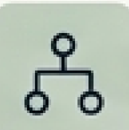
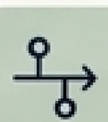
Antidepressant Pharmacotherapy Blueprint

A comprehensive clinical reference across seven decades of pharmacological evolution.

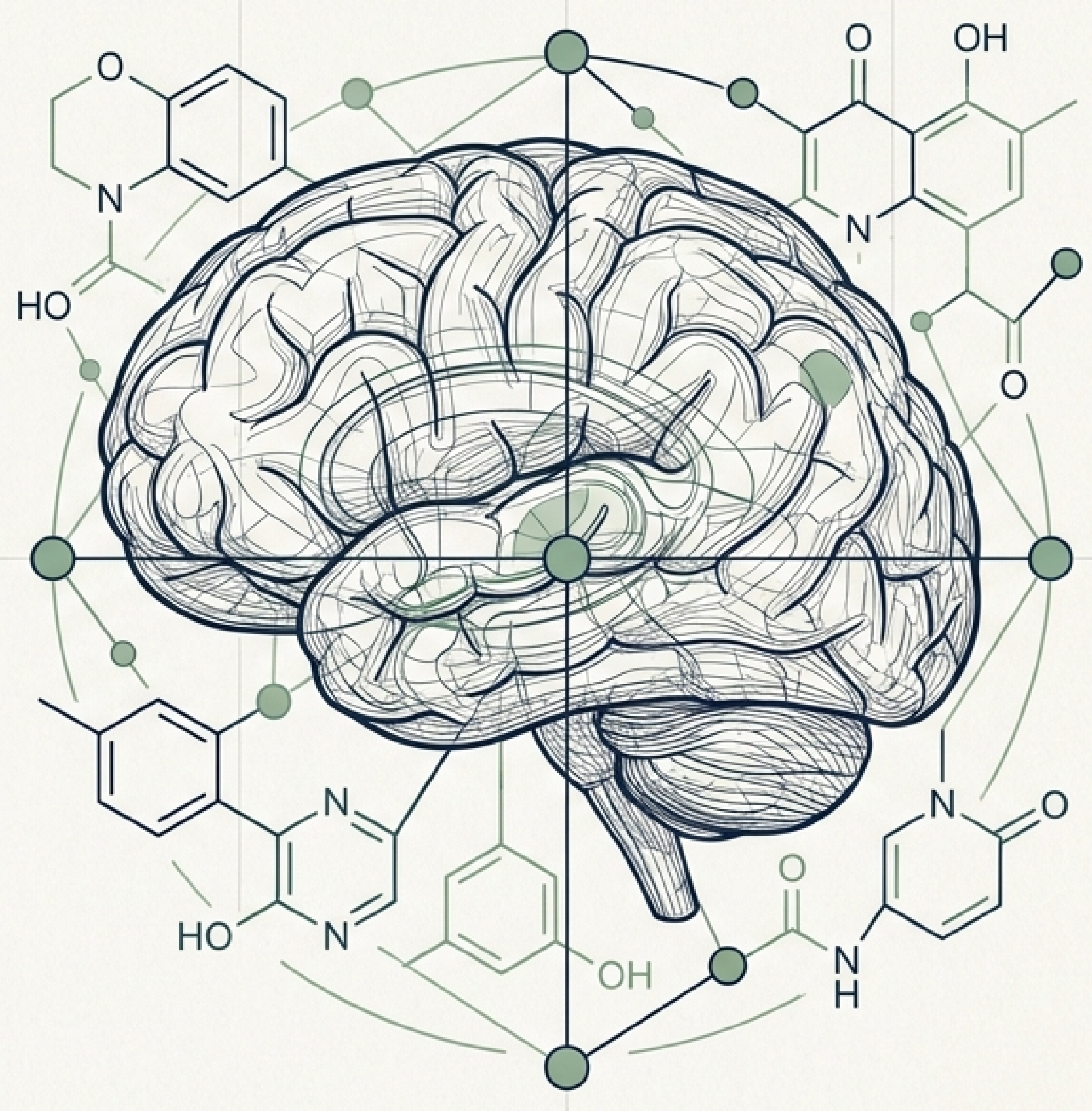
1. Mechanistic Architecture


2. The Tolerability Matrix


3. Clinical Decision Algorithms


4. Longitudinal Safety Frameworks

Data synthesized from current clinical guidelines, STAR*D trials, and the Cipriani efficacy network meta-analysis.



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The Generational Innovation Wave

1952–1980s: The Serendipitous Era

Iproniazid (MAOI) & Imipramine (TCA).

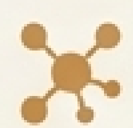
High efficacy but limited by hypertensive crises and cardiotoxicity.

1987: The SSRI Revolution

Fluoxetine (Prozac) approval.

Unprecedented safety profile and lack of lethality in overdose transforms psychiatric practice.

1993–2010s: SNRI & Multimodal



Venlafaxine, Duloxetine, Mirtazapine, Bupropion.

Targeted receptor modulation expands treatment beyond pure serotonin reuptake.

2019–2023: The Paradigm Shift

Esketamine (NMDA) & Zuranolone (GABA-A).

Shatters the delayed-response assumption, delivering rapid efficacy in hours to days.

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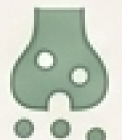
Rethinking the Monoamine Hypothesis

Mechanism Divergence

Depression Pathology

Mechanistic Shift

Traditional Monoamine Modulation



- **Targets:** SERT, NET, DAT.
- **Mechanism:** Blocks reuptake of serotonin, norepinephrine, and dopamine.

- **Timeline:** Weeks to efficacy. Relies on downstream receptor downregulation and structural adaptation.

Rapid Neuroplasticity & GABA Modulation

- **Targets:** NMDA Antagonism & GABA-A PAM.
- **Mechanism:** Bypasses monoamines to directly stimulate BDNF-TrkB signaling, mTOR pathway, and synaptogenesis.

- **Timeline:** Hours to days. Efficacy does not require weeks of adaptation.

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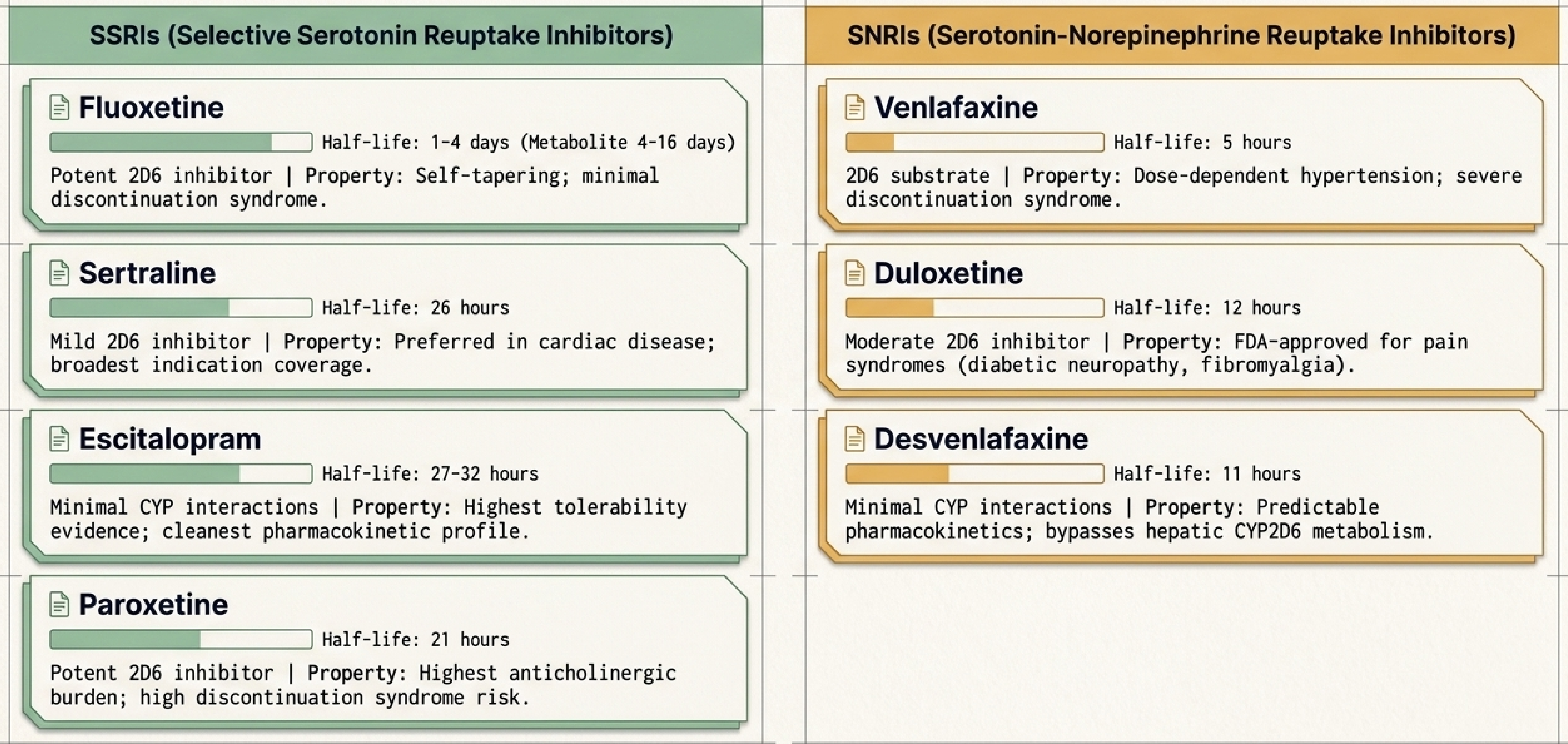
The Core Arsenal: SSRIs and SNRIs



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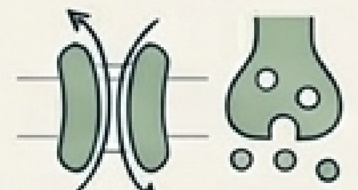
Atypicals and Multimodal Agents

Bupropion (NDRI)

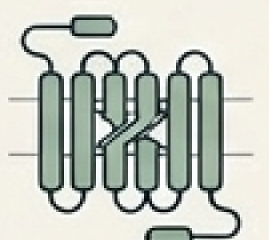


Targets: NET + DAT inhibition.

Profile: Activating; weight neutral or weight loss; strictly no sexual dysfunction.

Warning: Dose-dependent seizure risk (max 450 mg/day). Contraindicated in bulimia/anorexia.

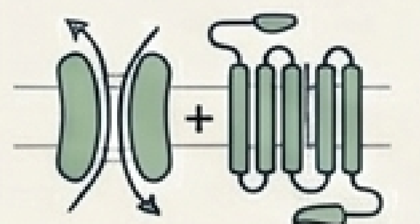
Mirtazapine (NaSSA)



Targets: Alpha-2 antagonism + 5-HT2/3 & H1 blockade.

Profile: Rapid onset of sedation (paradoxically greater at lower doses like 7.5mg due to H1 affinity); highly appetite stimulating. Minimal sexual dysfunction.

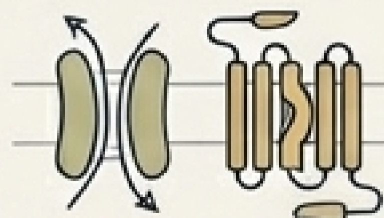
Vortioxetine (Multimodal)



Targets: SERT inhibition + 5-HT1A/1B/3/7 modulation.

Profile: Potential cognitive benefits (processing speed and executive function); statistically lower sexual dysfunction burden than standard SSRIs.

Trazodone (SARI)



Targets: SERT inhibition + 5-HT2A antagonism.

Profile: Heavily utilized off-label for insomnia at sub-antidepressant doses (50-100mg). Rare but severe priapism risk.

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The Rapid-Acting Paradigm Shift

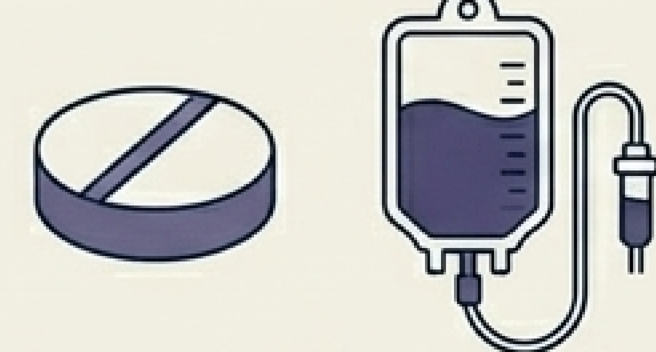
Esketamine (Intranasal NMDA Antagonist)

Mechanism: S-enantiomer of ketamine; stimulates BDNF/mTOR neuroplasticity pathway.

Indications: Treatment-Resistant Depression (TRD) and MDD with acute suicidal ideation/behavior (MDSI).

Clinical Deployment: REMS program required. Administered exclusively in certified settings with 2-hour clinical monitoring for dissociation and blood pressure spikes.

Zuranolone & Brexanolone (Neuroactive Steroids)



Mechanism: Positive allosteric modulation (PAM) of synaptic and extrasynaptic GABA-A receptors.

Brexanolone: 60-hour continuous IV infusion specifically approved for postpartum depression (PPD).

Zuranolone: 14-day oral course for MDD and PPD. Rapid clinical onset observed as early as Day 3.

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Expanding the Indication Footprint

Pain Syndromes

Noradrenergic pathways modulate spinal nociceptive transmission.

Duloxetine is FDA-approved for diabetic neuropathy and fibromyalgia.

TCAs highly effective off-label at sub-MDD doses.

Anxiety & OCD

SSRIs and SNRIs are first-line.

OCD typically requires significantly higher doses (e.g., fluoxetine 80mg, sertraline 200mg) and longer trials (8-12 weeks) than uncomplicated MDD.

Avoid activating agents like bupropion.

PTSD

Sertraline and Paroxetine are FDA-approved; Venlafaxine has strong off-label evidence.

Pharmacotherapy is adjunctive (20-30% symptom reduction); trauma-focused psychotherapy remains equally critical.

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The Clinical Tolerability Heatmap

Drug Class	Sexual Dysfunction	Weight Gain	Sedation	GI Effects	Cardiac Risk	Discontinu-ation
SSRIs	High	Mod	Low	Mod	Low	Mod
SNRIs	High	Mod	Low	Mod	Mod	High
TCAs	High	High	High	Mod	Very High	Mod
MAOIs	High	High	Mod	Low	Very High	Mod
Bupropion	Low	Low	Low	Mod	Low	Low
Mirtazapine	Low	Very High	Very High	Low	Low	Low

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The Legacy Classes: High Efficacy, High Risk

Tricyclic Antidepressants (TCAs) – e.g., Amitriptyline, Nortriptyline

Mechanism: SERT/NET inhibition + heavy off-target M1, H1, and Alpha-1 blockade.

The Danger: Acutely lethal in overdose. Just 10x the therapeutic dose blocks cardiac fast sodium channels, causing QRS widening and fatal ventricular arrhythmia.

Burden: High anticholinergic effects limit use in the elderly (impaired cognition, falls, urinary retention).

Monoamine Oxidase Inhibitors (MAOIs) - e.g., Phenelzine, Tranylcypromine

Mechanism: Irreversible, non-selective MAO-A/B inhibition.

The Danger: The 'Cheese Effect'. Dietary tyramine enters systemic circulation, triggering massive norepinephrine release and hypertensive crisis.

Rule: Requires mandatory dietary restrictions (no aged cheese, cured meats, tap beer) and extreme caution regarding drug interactions (high risk of serotonin syndrome).

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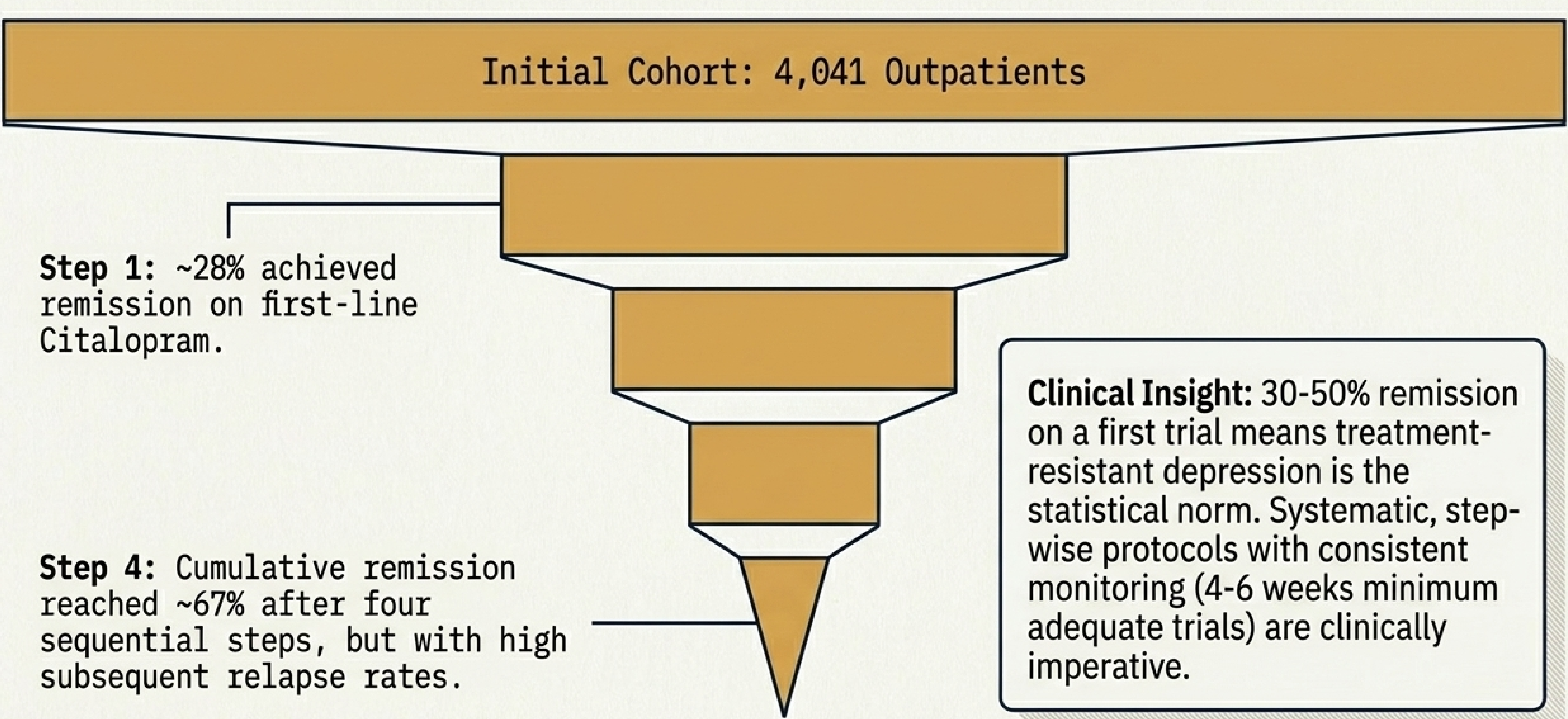
The STAR*D Reality Check



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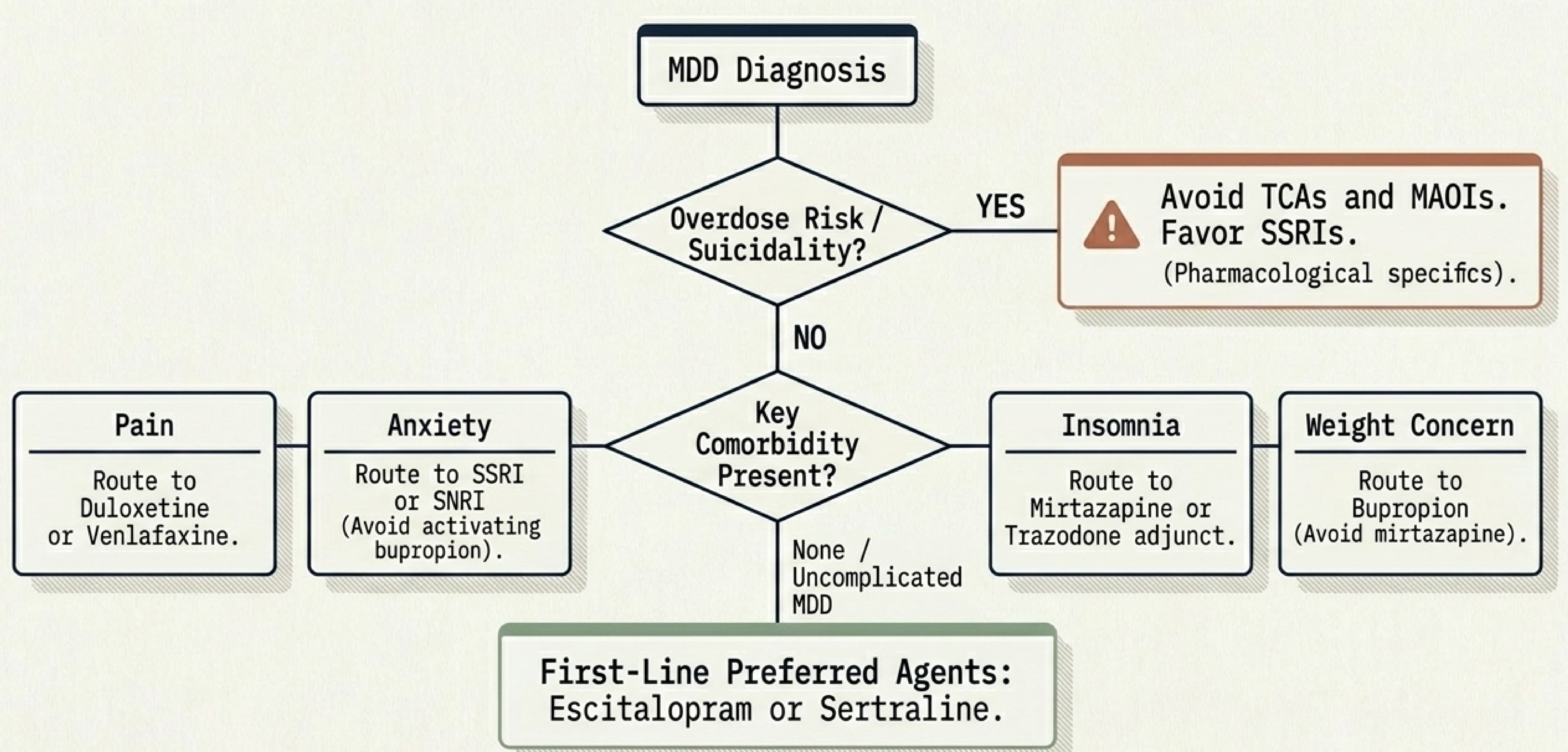
Initial Clinical Decision Algorithm



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Precision Prescribing: Clinical Trade-offs

The Elderly Patient

Preferred: Escitalopram, Sertraline (lowest anticholinergic burden). Must monitor serum Na+ for SIADH.

Avoid: TCAs (falls, cardiac risk), Paroxetine (anticholinergic), Venlafaxine (hypertension).

The Sexual Dysfunction Profile

Preferred: Bupropion, Mirtazapine, Vortioxetine.

Avoid: SSRIs, SNRIs, TCAs (30-40% incidence of delayed orgasm/libido loss).

The Atypical Depression Profile

Preferred: Bupropion (activating properties combat hypersomnia/hyperphagia), MAOIs (historically highly effective).

Avoid: Sedating agents that worsen hypersomnia.

The Treatment-Resistant Profile

Preferred: Augmentation (Lithium, Atypical Antipsychotics, Thyroid), Esketamine, ECT.

Avoid: Endless sequential monotherapy trials of the exact same drug class.

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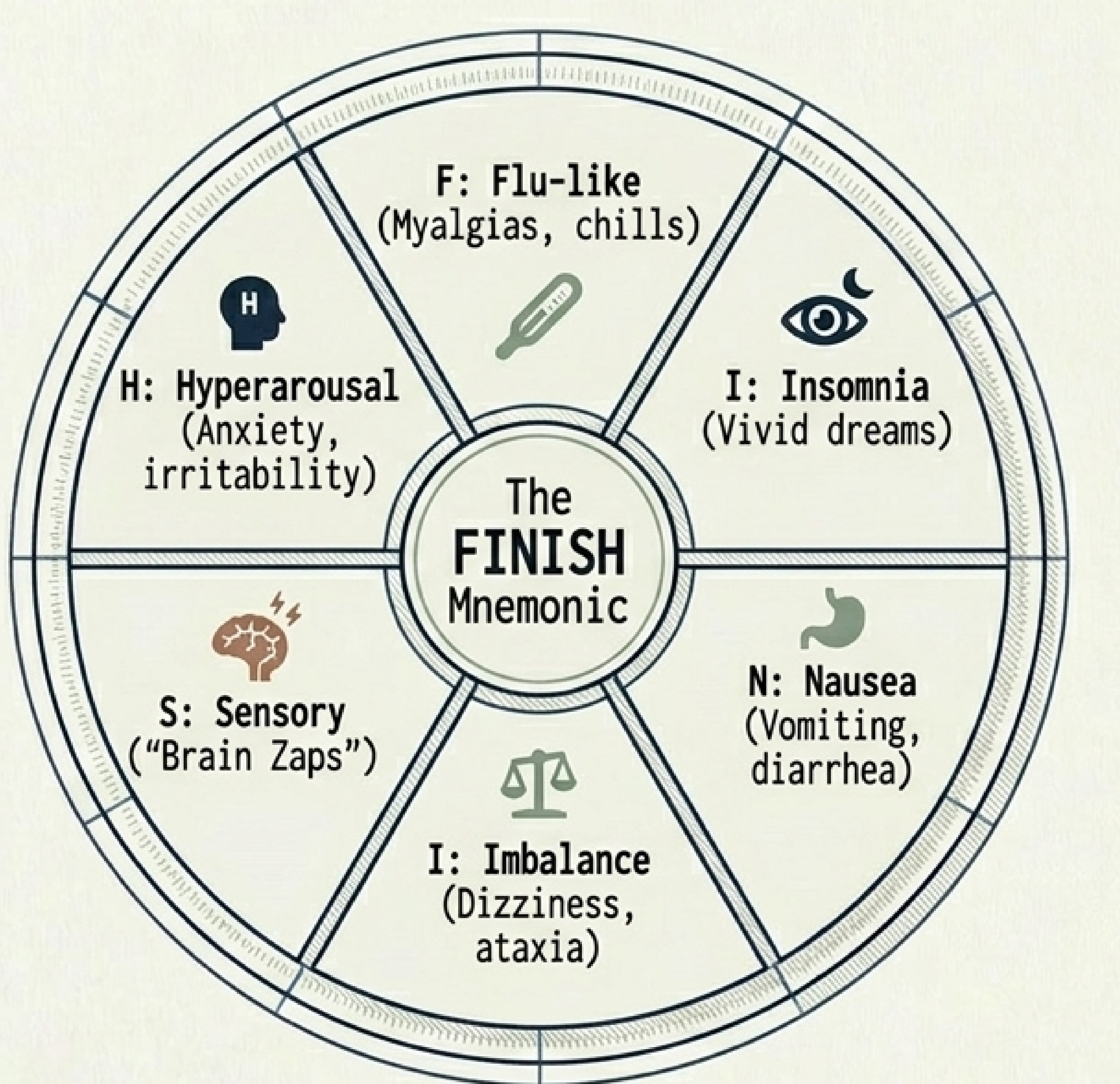
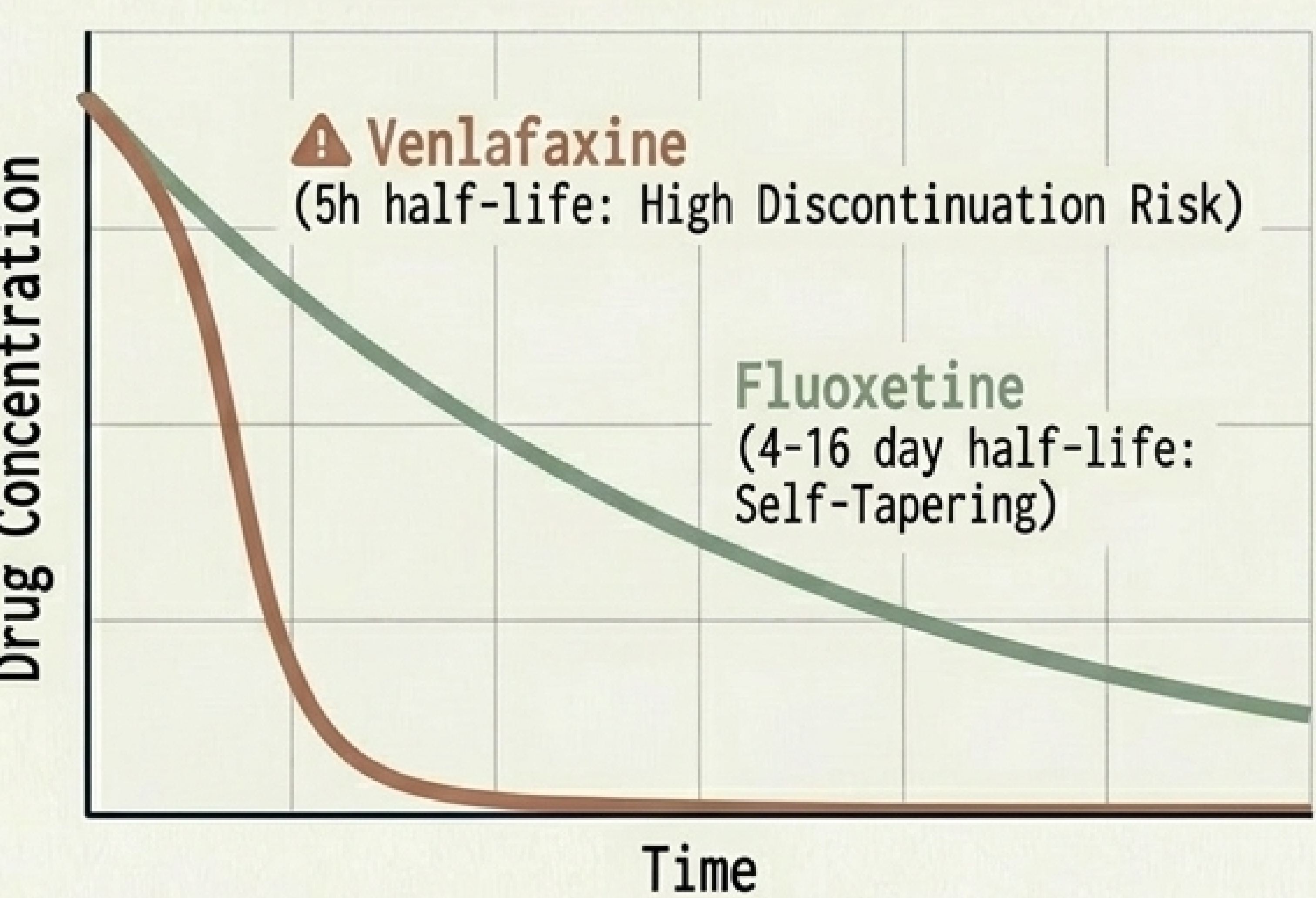
Navigating Discontinuation



The Half-Life Bridge



The Bridge Strategy: Switching a highly symptomatic patient to Fluoxetine exploits its long active metabolite half-life to provide a smooth, natural physiological taper.

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Critical Safety Frameworks

Black Box Warning (<25 Years Old)

Small but statistically significant increase in suicidal ideation (not completion) during the first weeks of treatment. Mandates close weekly follow-up focusing on activation/agitation. Untreated depression carries higher overall risk.

Serotonin Syndrome (Hunter Criteria)

Triggered by SSRI combination with MAOI, Linezolid, or Tramadol. Diagnosed via clonus (inducible/ocular), agitation, diaphoresis, hyperreflexia. Action: Stop agents, administer cyproheptadine, 14-day washout mandatory before MAOI use.

Overdose Lethality

TCAs remain highly lethal in minimal overdose quantities due to cardiac arrhythmia and sodium channel blockade. Strictly avoid prescribing TCAs to acutely suicidal patients; utilize SSRIs or SNRIs.

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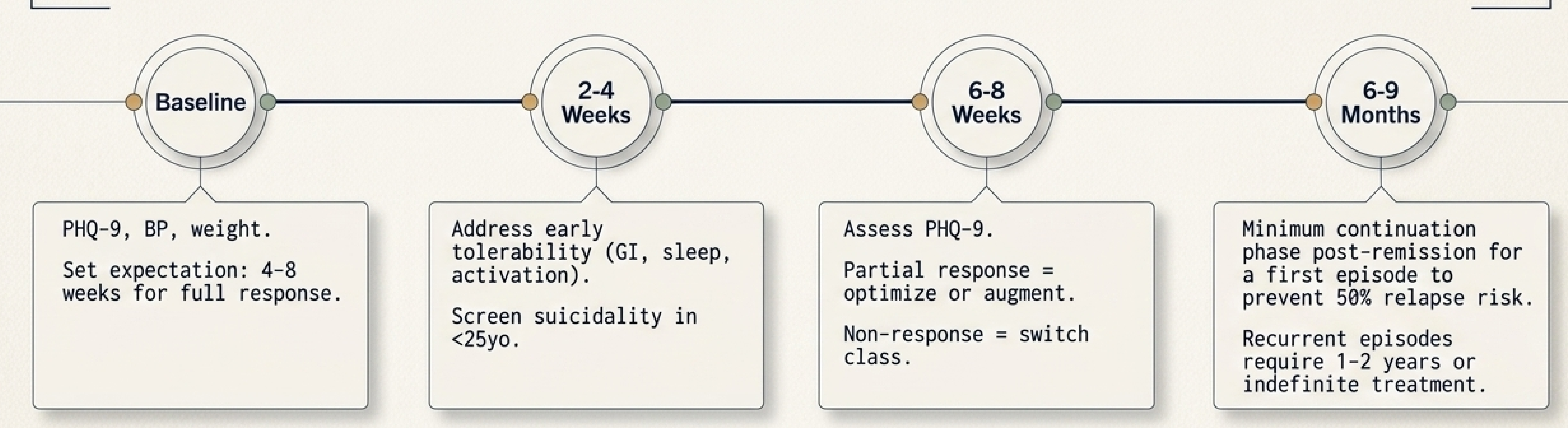
Synthesis: Treating to Remission, Not Response

Response (50% symptom reduction) is an insufficient endpoint. Residual symptoms are the strongest predictor of relapse. Mastering this pharmacological arsenal to achieve full remission (PHQ-9 < 5) is a clinical imperative.



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