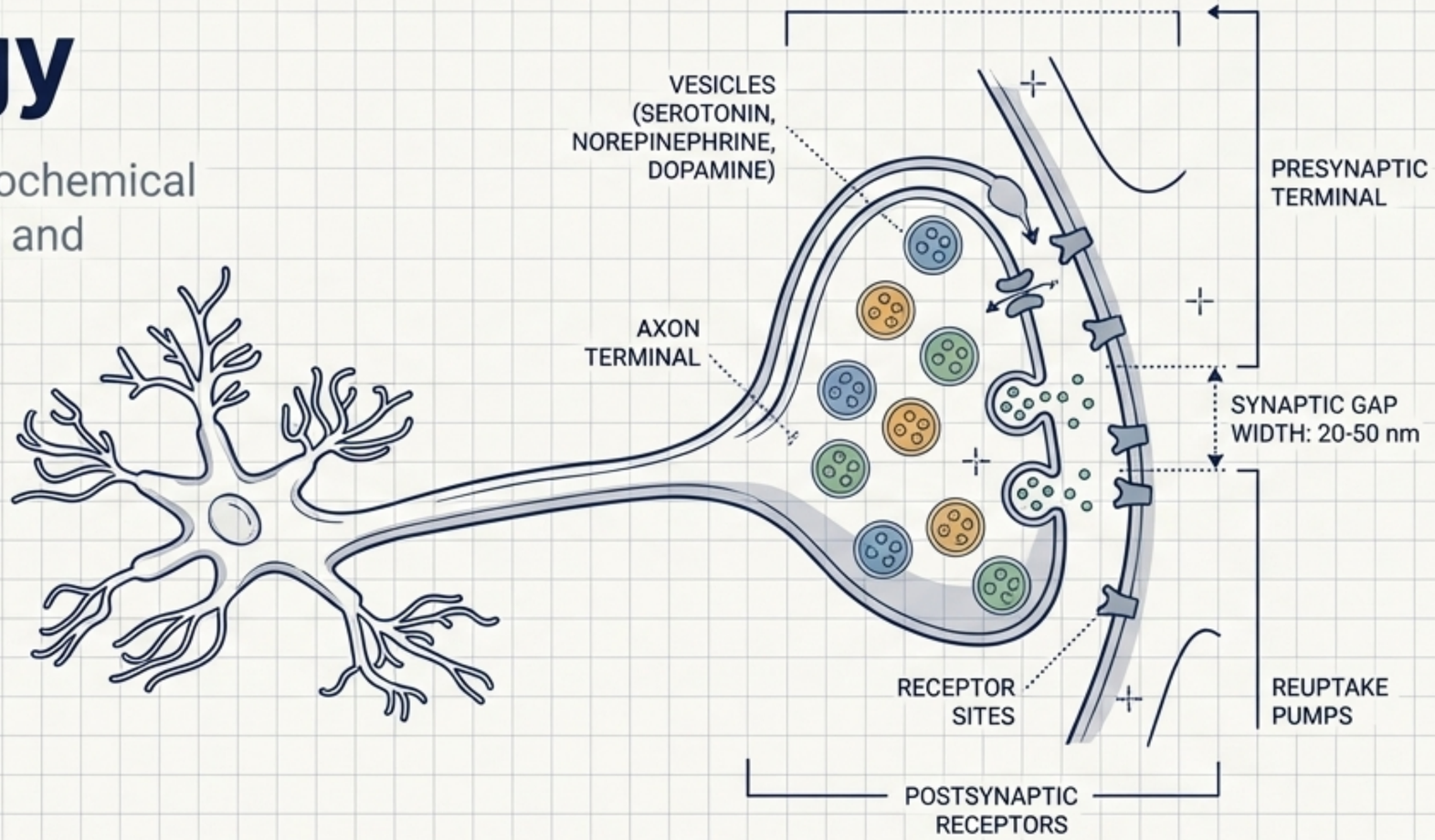
The Synaptic Blueprint of Antidepressant Pharmacology

A structured clinical guide to neurochemical mechanisms, drug classifications, and treatment pathways.



The WHO predicts depression will be the 2nd most debilitating human condition globally.

Cognitive

Thoughts of hopelessness, poor confidence, negative thoughts.

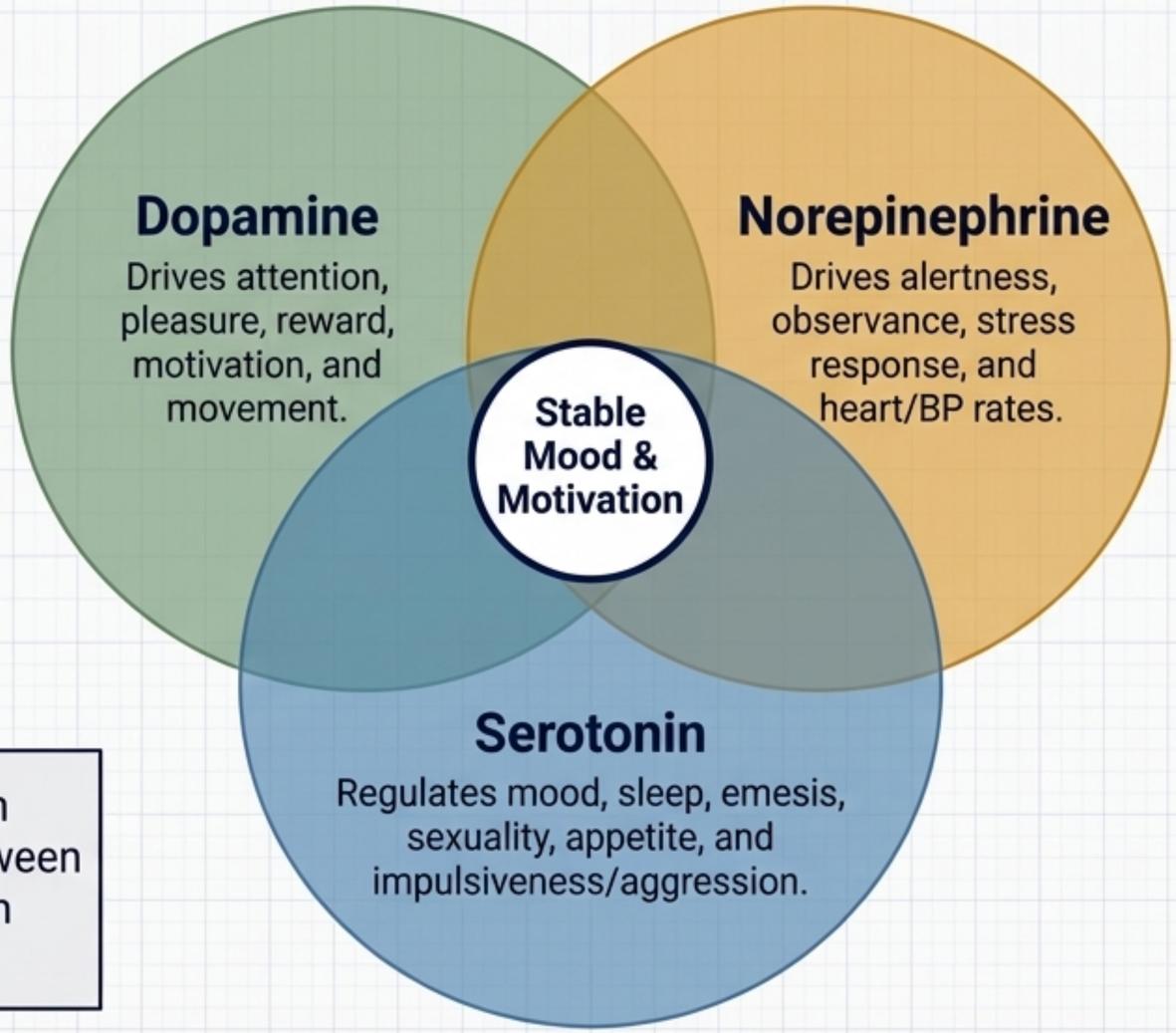
Emotional

Feeling sad, unable to feel pleasure, irritability.

Physical

Decreased libido and energy. Sleep and appetite changes (typically 70% decrease, 30% increase).

The clinical presentation is dictated by an imbalance across three distinct neurochemical systems



Clinical Pearl: Depression is an imbalance and interaction between these neurotransmitters, not an isolated deficit.

Modern pharmacology relies on the Neurotrophic Hypothesis to explain structural brain changes

Monoamine Hypothesis

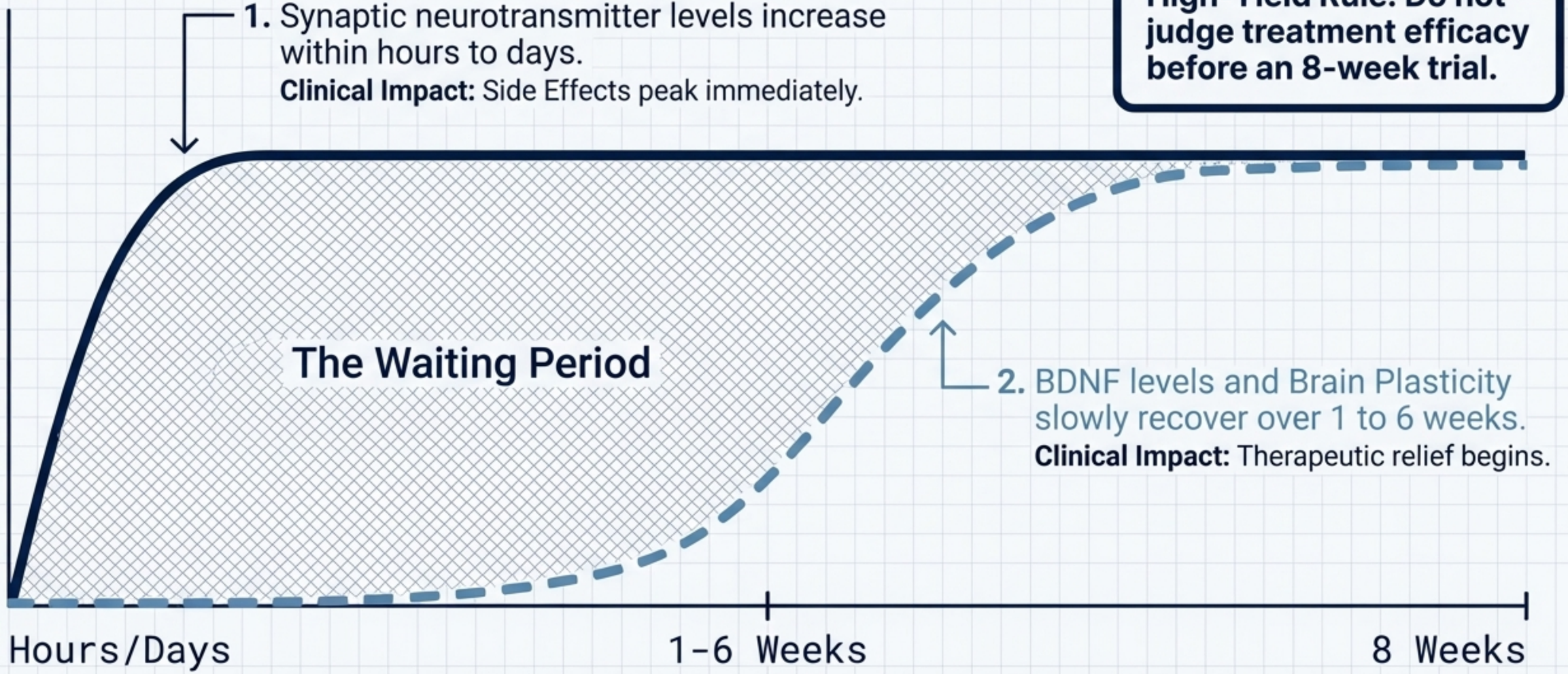
- **Premise:** Depression is a simple deficiency in neurotransmitters.
- **Action:** Drugs increase synaptic levels.
- **Flaw:** Fails to explain why symptom relief takes weeks despite immediate synaptic changes.

Neurotrophic Hypothesis

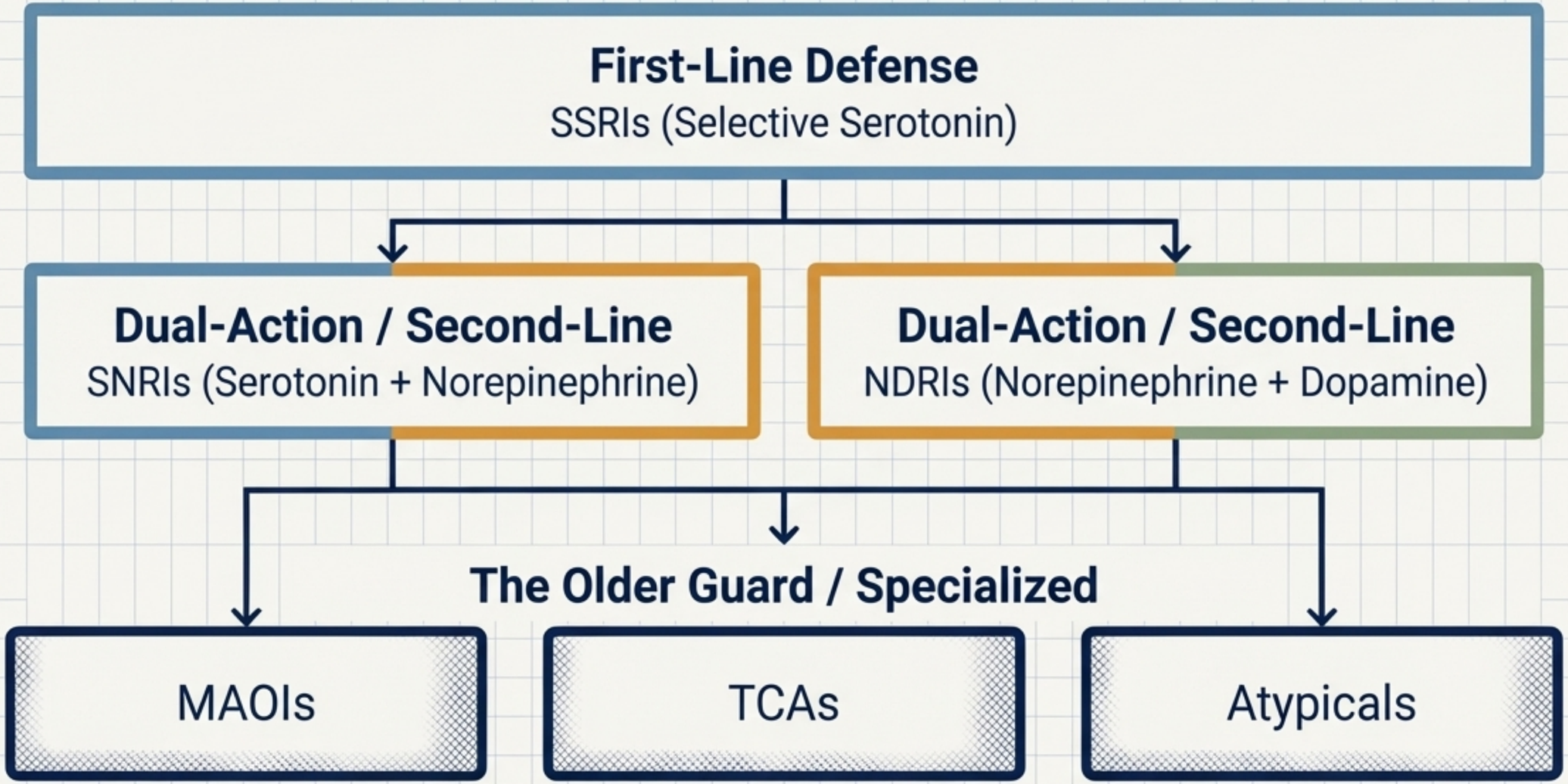
- **Premise:** Stress causes a loss of neurotrophic support (low BDNF, low tyrosine kinase receptor activity, low apoptosis protection), leading to atrophic structural changes in the hippocampus and frontal cortex.
- **Action:** Antidepressants slowly restore **Brain Plasticity**.

Therapeutic efficacy relies on slow brain plasticity, not immediate synaptic flooding

High-Yield Rule: Do not judge treatment efficacy before an 8-week trial.



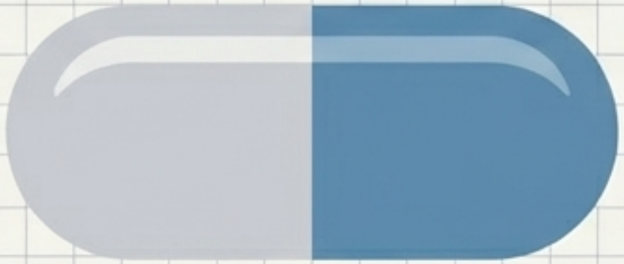
The pharmacological arsenal targets specific combinations of monoamine reuptake



SSRIs are the first-line standard but carry distinct side effect profiles and warnings

Key Drugs

- **Fluoxetine:** Long half-life, less discontinuation syndrome, significant P450 interactions.
- **Paroxetine:** Sedating properties, CYP2D6 inhibition.
- **Sertraline:** Higher GI adverse reactions.



Side Effects (Hours/Days)

GI upset, insomnia/sedation, anxiety/restlessness, and a 30%+ incidence of sexual dysfunction. Long-term use may cause personality blunting.

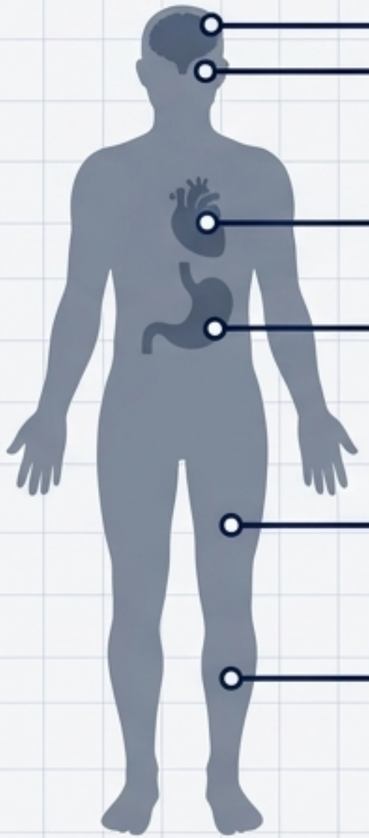
⚠ Black Box Warning

High inherent serotonin in young adults (18-24) combined with SSRIs increases thinking motivation before mood improves, temporarily elevating suicidal thoughts.

Abrupt discontinuation and overlapping interactions present distinct clinical emergencies

Discontinuation Syndrome

Caused by physical dependence (not addiction) after 6+ weeks of use. Arises in 24-72 hours if stopped abruptly.



F - Flu-like symptoms (fatigue, muscle aches)

I - Insomnia (vivid dreams)

N - Nausea

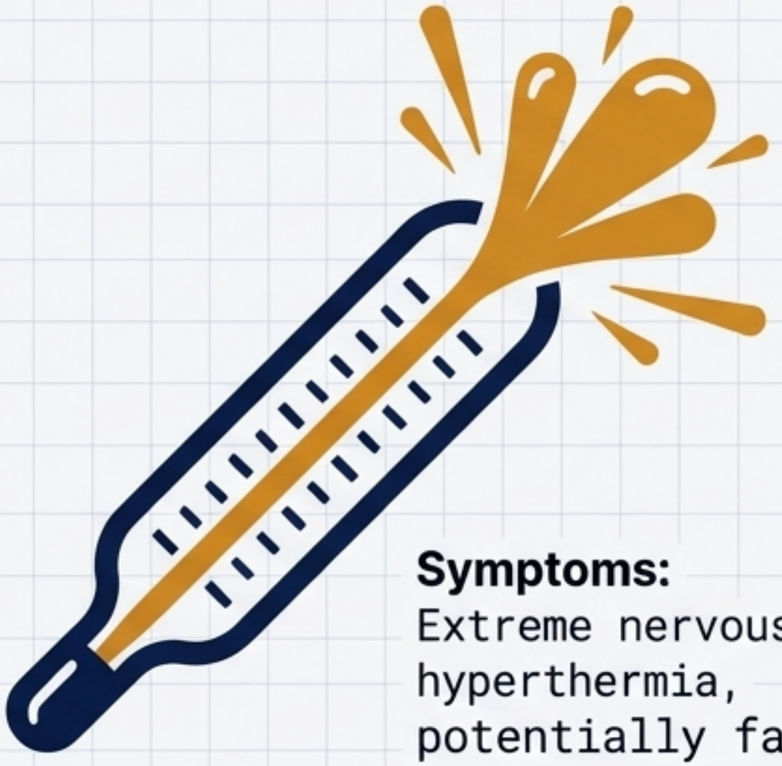
I - Imbalance (vertigo, dizziness)

S - Sensory (electric shock/brain zaps)

H - Hyperarousal (anxiety)

Serotonin Syndrome

Caused by overdose or combining multiple serotonin-enhancing drugs (e.g., SSRI + SNRI/TCA/MAOI).



Symptoms:
Extreme nervousness, hyperthermia, potentially fatal.

Dual-action agents recruit norepinephrine and dopamine to optimize patient-specific therapy

SNRIs (Venlafaxine, Duloxetine)

Serotonin Norepinephrine

Pros: Slightly greater efficacy and fewer adverse effects than SSRIs.

Cons: Can cause a 10-15 mmHg dose-dependent increase in diastolic blood pressure in ~10% of patients due to sympathetic activation (NE).

NDRIs (Bupropion)

Norepinephrine Dopamine

Mechanism: Inhibits reuptake of Dopamine and NE. Zero serotonin effect.

Pros: Excellent augmenting agent. No weight gain, no sexual side effects, no sedation.

Cons: Does not treat anxiety (can cause agitation/insomnia). Avoid in bipolar mania.

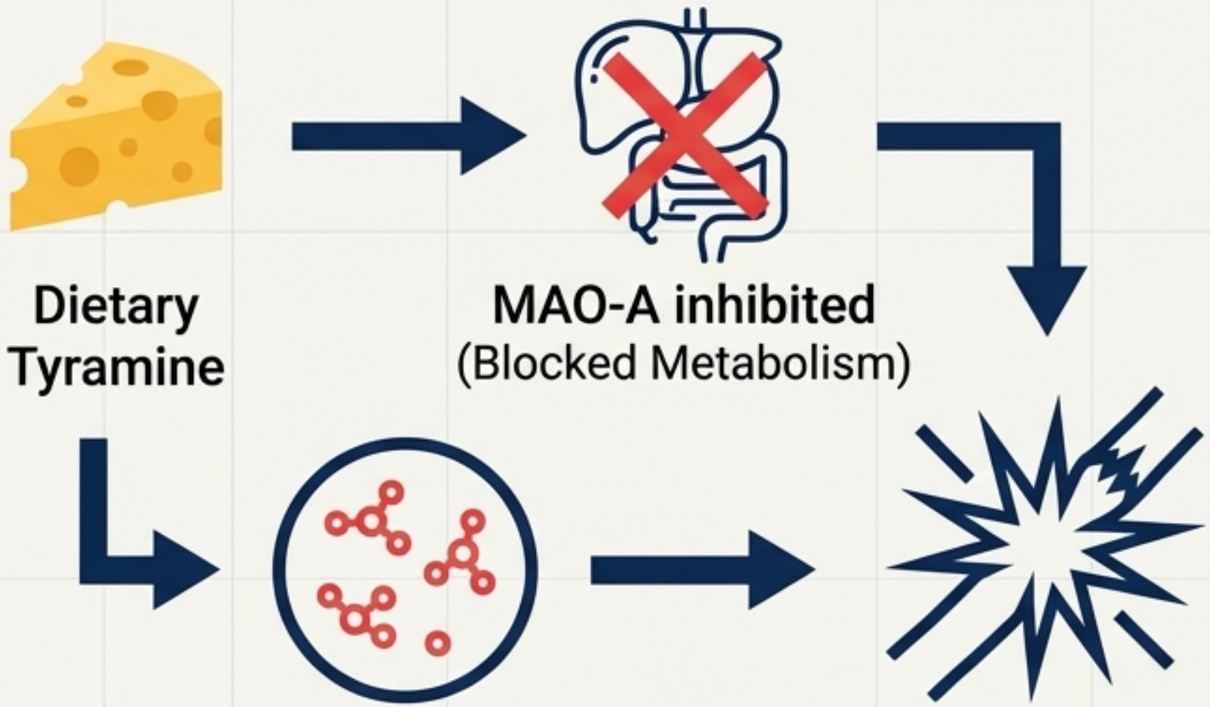
MAOIs require strict dietary management to prevent hypertensive emergencies

The Enzymes

- **MAO-A** oxidizes **Epinephrine**, NE , and Serotonin (target for depression).
- **MAO-B** oxidizes phenylethylamine (target for Parkinson's).
- Both oxidize Dopamine.

Clinical Use: Reserved for atypical depression when other treatments fail. Never combine with SSRIs.

The Tyramine Trap



TCAs and Atypicals serve specialized roles outside primary depression management

Tricyclic Antidepressants (TCAs - Amitriptyline)

Use: Often used for pain management (e.g., fibromyalgia) as pain is linked to depression.

Risk: Highly toxic in overdose (arrhythmias).

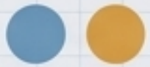
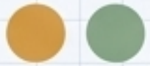
Rule: Strictly avoid combining with other serotonin-enhancing drugs to prevent Serotonin Syndrome.

Atypicals (Trazodone & Mirtazapine)

Mechanism: Less impactful on serotonin; mechanisms not fully understood.

Use: Often prescribed off-label for their highly sedating properties.

The Pharmacological Arsenal: Comparative Clinical Matrix

Drug Class	Targets	Key Drugs	Major Clinical Pros	Major Cons & Risks
SSRI		Fluoxetine, Paroxetine, Sertraline	First-line efficacy	Sexual dysfunction (30%), Discontinuation Syndrome, BBW for young adults. Clinical annotations: Roboto Mono
SNRI		Venlafaxine, Duloxetine	Greater efficacy	Dose-dependent diastolic BP increase.
NDRI		Bupropion	No weight/sexual SEs, great augment	Can cause anxiety; avoid in bipolar mania.
MAOI		N/A	Treats atypical depression	Tyramine diet restriction, Hypertensive crisis risk.
TCA		Amitriptyline	Treats fibromyalgia/pain	Highly toxic in overdose.

Successful management requires an 8-week trial followed by long-term maintenance