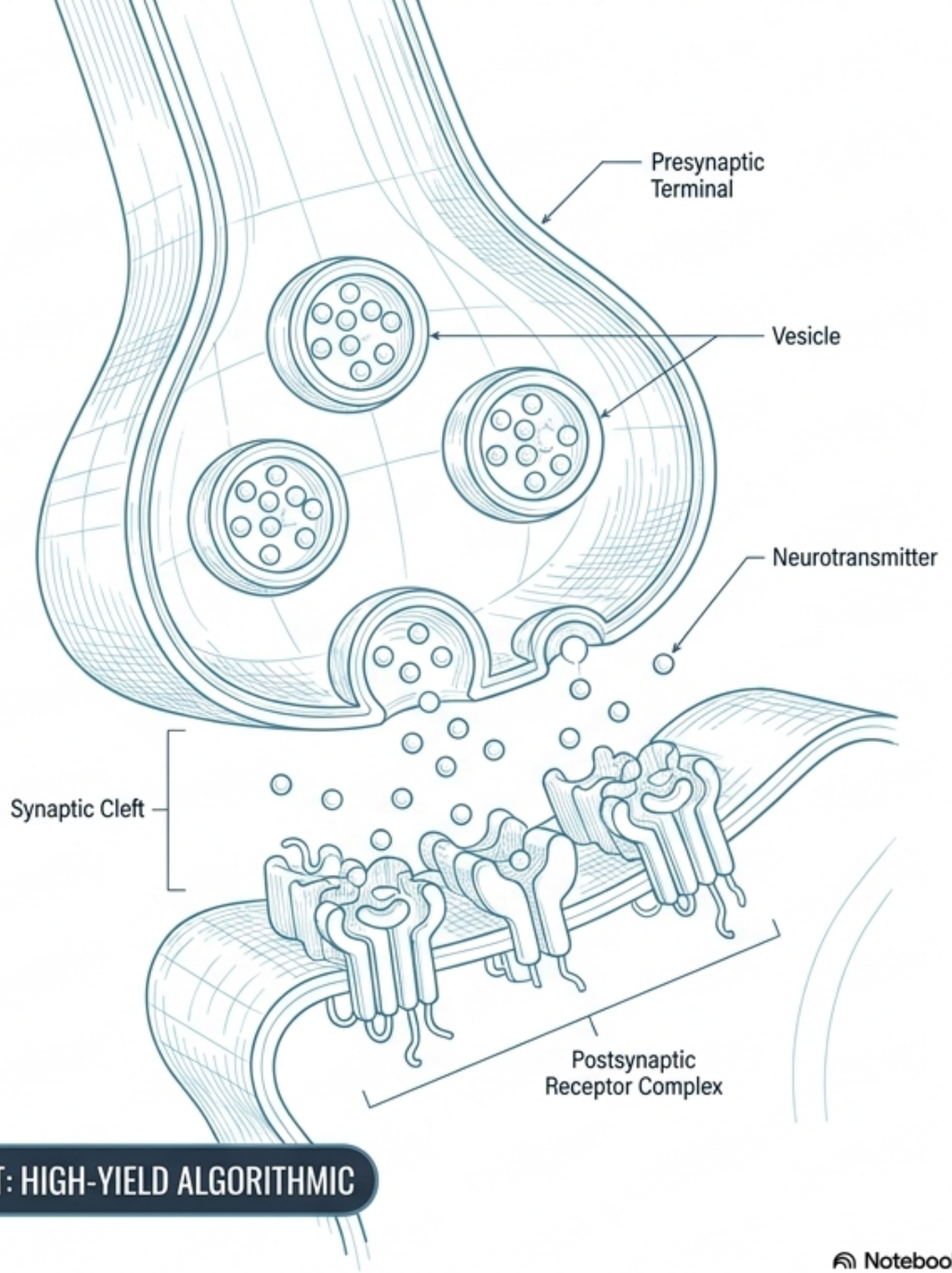
CLINICAL BLUEPRINT: MAJOR DEPRESSIVE DISORDER & DYSTHYMIA

A comprehensive synthesis of pathophysiology, differential diagnosis, and escalating treatment strategies.

TARGET: CLINICIANS

FOCUS: PHARMACOTHERAPY & NEUROMODULATION

FORMAT: HIGH-YIELD ALGORITHMIC



MDD remains the leading cause of disability worldwide

280M

Adults globally affected by depression

GLOBAL PREVALENCE

50%

Estimated treatment gap (individuals who do not receive care)

TREATMENT ACCESS

1M+

Annual suicides worldwide attributed to depression

MORTALITY RISK

The conceptual model has evolved from humors to neuroplasticity

CLASSICAL ERA

"Melancholia" recognized as a humoral imbalance (Hippocrates/Galen).

1950S-80S

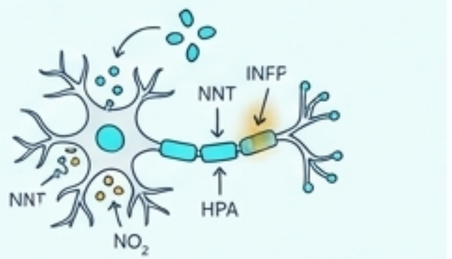
Discovery of TCAs (1957) and standardizing MDD in DSM-III. The Monoamine Hypothesis emerges.

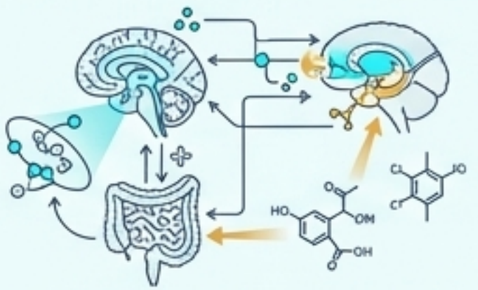
1950S-80S

Discovery of TCAs (1957) and standardizing MDD in DSM-III. The Monoamine Hypothesis emerges.

1990S-2000S

SSRIs dominate. Recognition of neuroinflammation and HPA-axis dysregulation.





2010S-PRESENT

Precision Psychiatry. Focus shifts to neuroplasticity, the gut-brain axis, and rapid-acting glutamatergic agents (ketamine).

CLINICAL PEARL: The Monoamine Hypothesis remains clinically useful for drug targeting, but fails to explain the delayed therapeutic lag or the 30-40% non-responder rate.

Presentation and diagnostic pitfalls vary drastically by age

PEDIATRIC (AGES 6-17)

PRESENTATION

Irritability dominates over sadness; school dysfunction.

TRAPS

Overlap with ADHD. **SSRI FDA black-box warning for suicidality**.

ADULT (AGES 18-64)

PRESENTATION

Work/family dysfunction (presenteeism). Somatic symptoms in specific demographics (e.g., Asian Americans).

DISPARITIES

Black and Latino populations face severe treatment **barriers** and **lower intervention rates**.

GERIATRIC (AGE 65+)

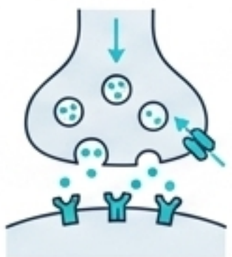
PRESENTATION

“Pseudodementia” (cognitive complaints), vascular depression, anhedonia without sadness.

TRAPS

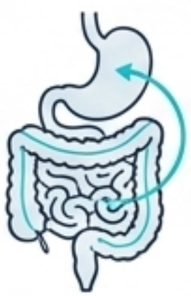
Increased sensitivity to anticholinergics and **hyponatremia** (SIADH).

Depression is a multi-systemic failure, not just a chemical imbalance



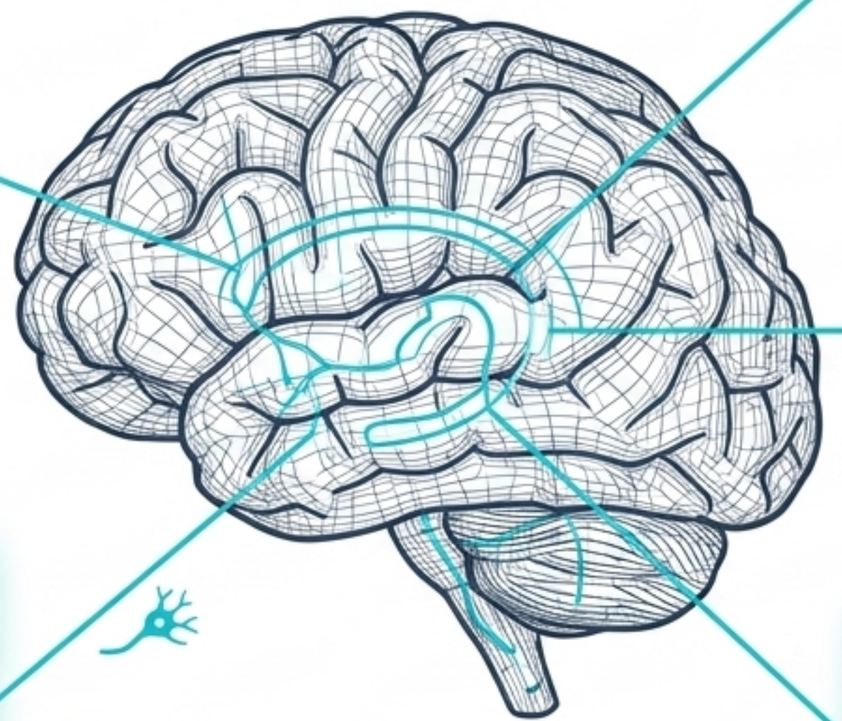
MONOAMINES

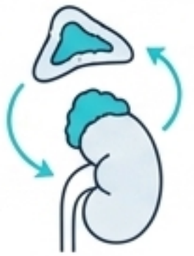
SERT blockade. Downstream neuroplasticity takes weeks.



GUT-BRAIN

Dysbiosis alters SCFA production and tryptophan metabolism via vagal afferents.





HPA-AXIS

CRH hypersecretion -> elevated cortisol -> hippocampal atrophy.

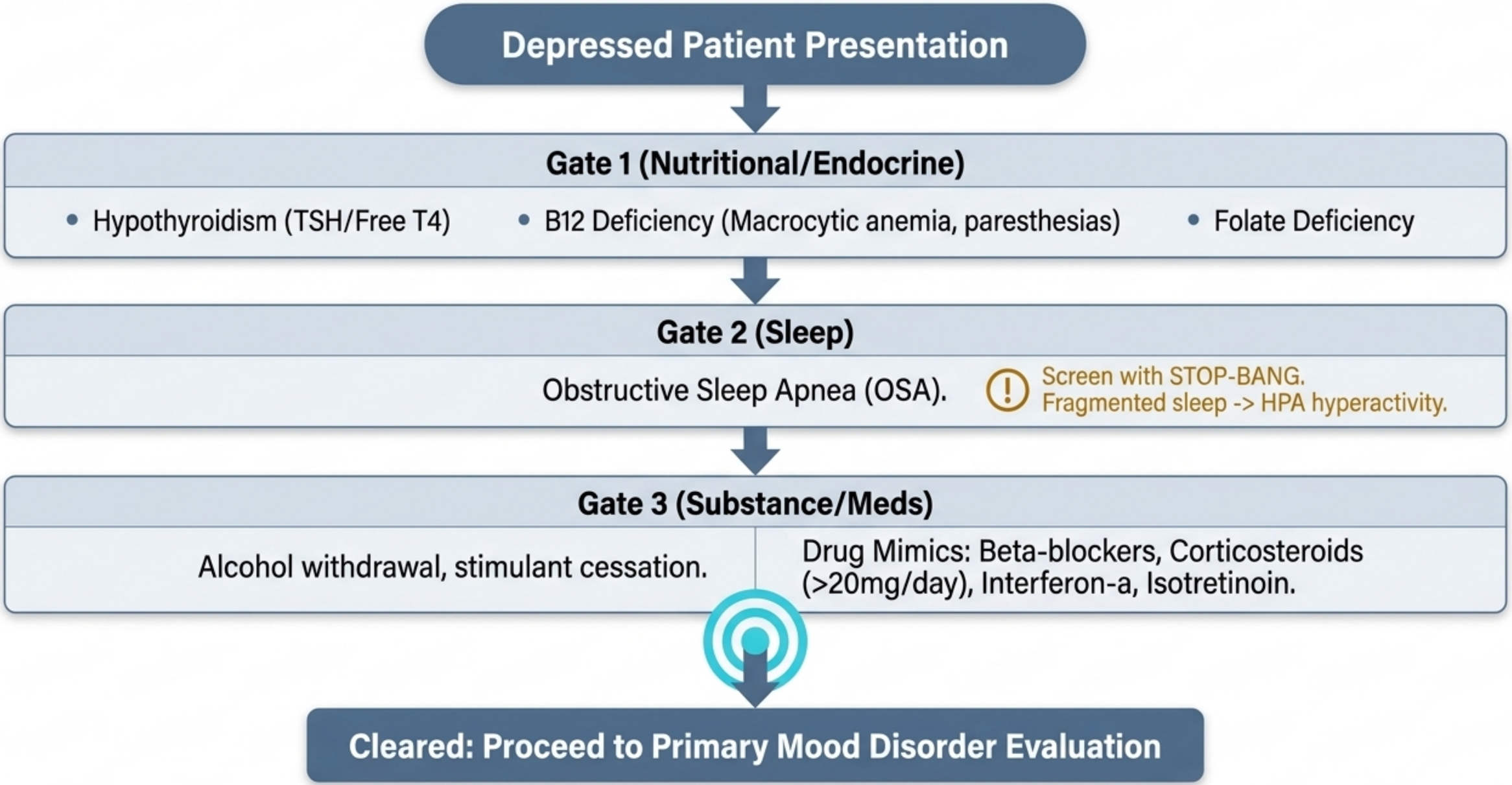
NEUROINFLAMMATION

Elevated IL-6, TNF-α, IL-1B. Microglia activation bypassing the blood-brain barrier.

NEUROPLASTICITY

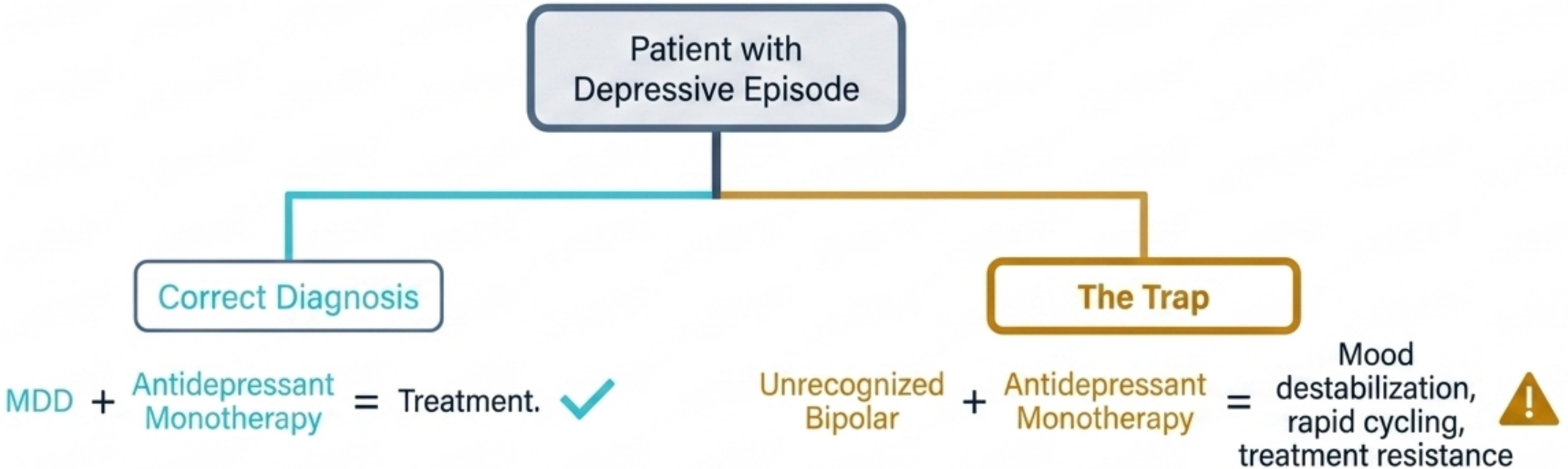
Reduced BDNF, impaired neurogenesis in the dentate gyrus.

Filter out secondary and iatrogenic mimics before treating for MDD



PRECISION PSYCHIATRY BLUEPRINT

The ‘Bipolar Trap’: Monotherapy risk in unrecognized Bipolar Disorder



Screening Checklist

- ☐ Administer Mood Disorder Questionnaire (MDQ).
- ☐ Check family history of mania.
- ☐ Ask about past hypomanic responses to antidepressants.

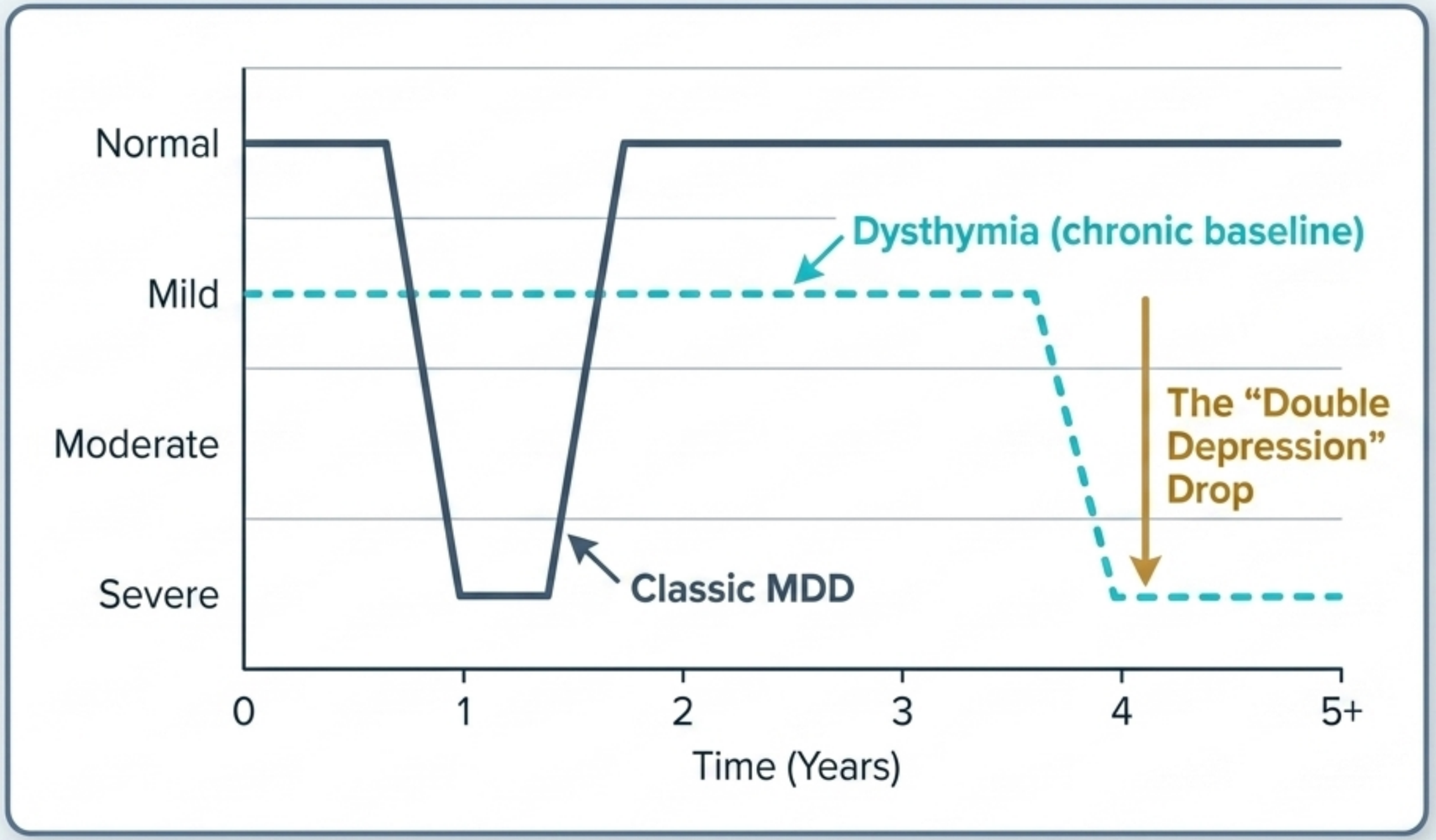
Action: Requires mood stabilizer ± antidepressant.

Clinical subtypes dictate first-line treatment selection

SUBTYPE	CORE FEATURES	TREATMENT PEARLS
MELANCHOLIC	Guilt, morning worsening, early awakening.	💊 More responsive to TCAs/Venlafaxine; ECT highly effective.
ATYPICAL	Mood reactivity, hyperphagia, hypersomnia, leaden paralysis.	💊 SSRIs effective; MAOIs historically superior; avoid TCAs.
PSYCHOTIC	MDD + delusions (guilt, nihility).	💊 Monotherapy fails. Requires Antipsychotic + Antidepressant or ECT.
CATATONIC	Waxy flexibility, mutism.	💊 Lorazepam challenge diagnostic; ECT first-line.
SEASONAL (SAD)	Fall/winter onset.	💊 10,000 lux light therapy x 30 min/day highly effective.

PRECISION PSYCHIATRY BLUEPRINT

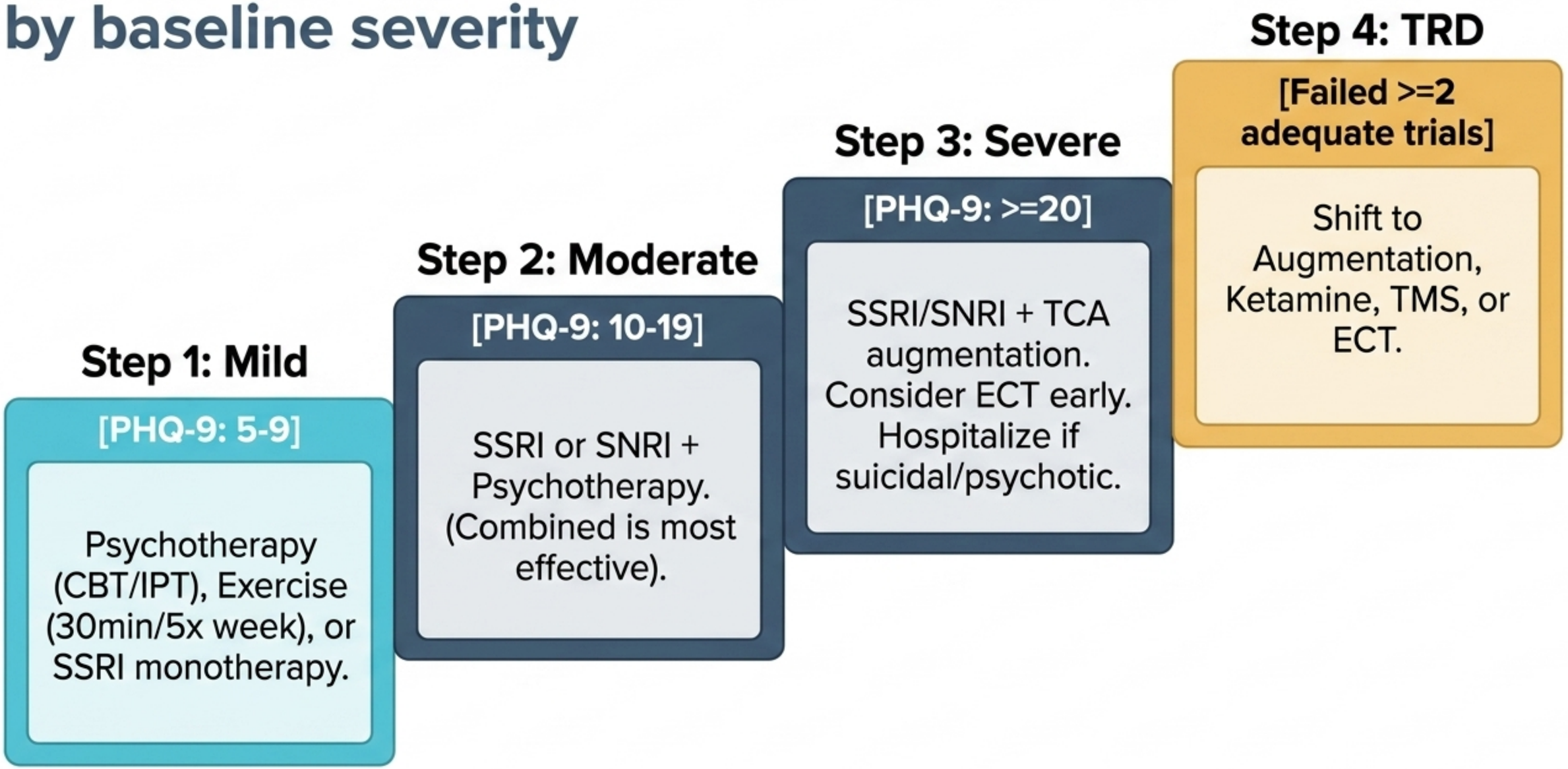
Dysthymia creates a chronic baseline vulnerable to “Double Depression”



Clinical Note

Dysthymia requires longer medication trials; two-thirds of patients experience superimposed MDD episodes.

The stepped escalation algorithm by baseline severity



The Pharmacotherapy Arsenal: Navigating mechanisms and profiles

SSRIs

Sertraline: First-line, safe in hepatic disease.

Escitalopram: Rapid onset. **Warning:** QTc prolongation >20mg.

Atypical/Novel

Bupropion: Activating, no sexual dysfunction, weight loss. **Warning:** Seizure risk.

Mirtazapine: Sedating, increases appetite (give QHS).

SNRIs

Venlafaxine: Dose-dependent (<150mg 5-HT, >=150mg dual). Good for melancholic/TRD.

Duloxetine: Good for comorbid chronic pain.

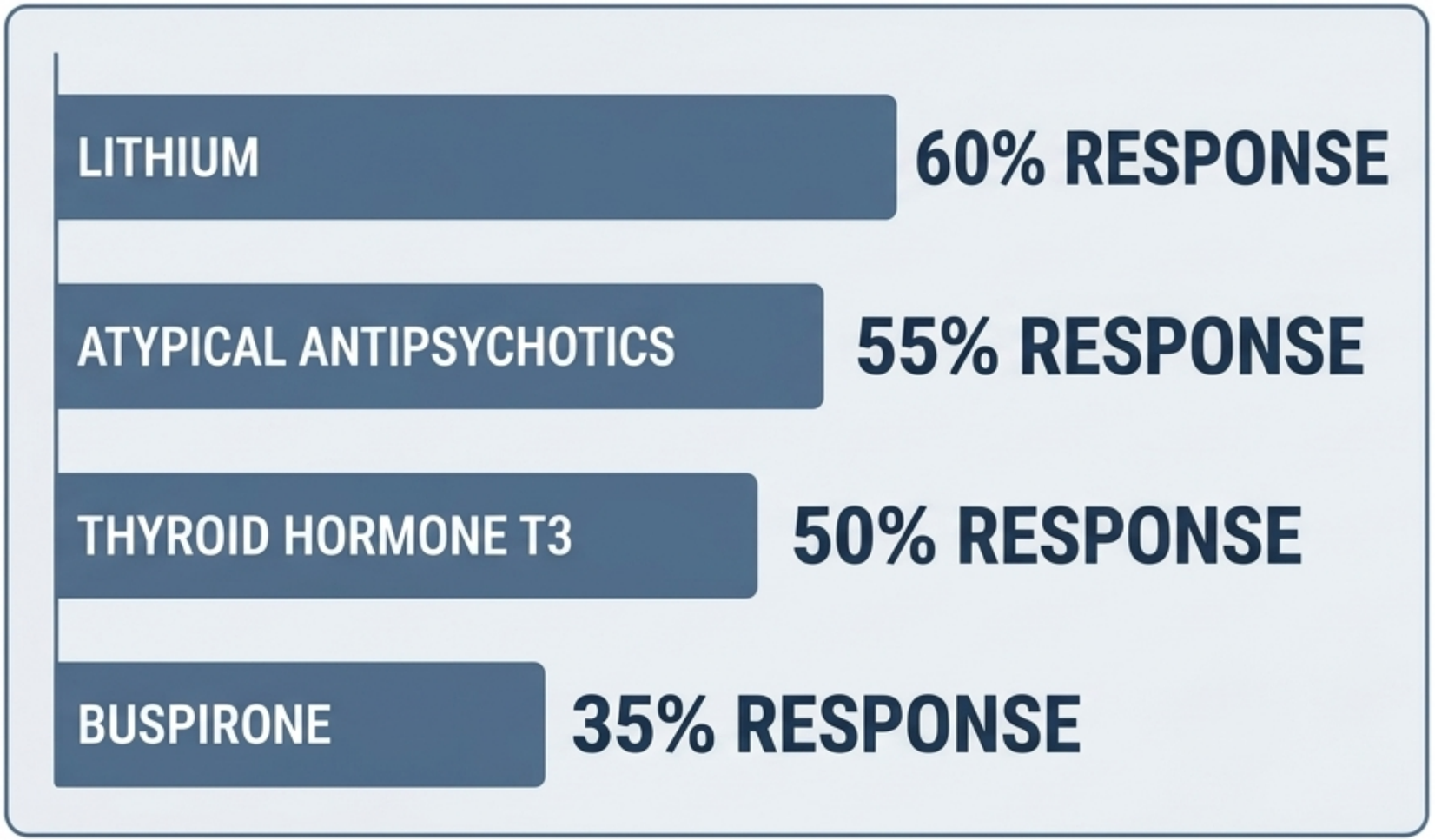
Legacy (TCAs/MAOIs)

Second/third line agents.

Require strict diet (MAOI) or ECG >60yo (TCA).

Lethal in overdose.

CONQUERING TREATMENT-RESISTANT DEPRESSION (TRD)

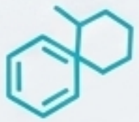


Enhances 5-HT/BDNF
Monitor: TSH, Renal function
Narrow therapeutic index.

Aripiprazole, Quetiapine.
D2 blockade + 5-HT2A antagonism
Drawback: Metabolic risk, weight gain even at low doses.

25-50 mcg/day.
Synergizes with ADs.
Pearl: Works even in euthyroid patients.

Rapid-acting interventions and neuromodulation for severe TRD



KETAMINE/ESKETAMINE

NMDA antagonism. **50-70%** response. Action within hours. **Vital for acute suicidality.**

ECT

Most powerful AD known (**60-80%** response). First-line for catatonia/psychosis. Transient cognitive impairment.

TMS

Non-invasive DLPFC stimulation. **40-50%** response. No systemic side effects.

VNS

Surgical vagus implant. Slow onset (6-12 months), durable efficacy.

PSILOCYBIN (Trial Phase)

5-HT2A agonism. High efficacy in trials; requires paired psychological support (‘set and setting’).

Non-pharmacological foundations rival monotherapy in efficacy

PSYCHOTHERAPY PANEL

CBT: Challenges automatic thoughts (50-60% response).

IPT: Targets role transitions/grief.

MBCT: Best for rumination and relapse prevention.

BEHAVIORAL PANEL

EXERCISE: 30 min aerobic 5x/week shows equivalent efficacy to SSRIs. Increases BDNF.

CHRONOTHERAPY: Sleep deprivation induces paradoxically rapid (but transient) mood improvement. Social rhythm therapy stabilizes circadian function.

The Clinical Management Timeline: Protocol from initiation to taper