Modeling Antidepressant-Induced Manic Switch in a Unified Computational Framework: Insights from Ketamine, SSRIs, and Neurosteroids

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Abstract

Background: Major depressive disorder involves impaired neural plasticity, yet antidepressants spanning glutamatergic (e.g., ketamine), monoaminergic (e.g., SSRIs), and GABAergic (e.g., neurosteroids) classes differ in onset, durability, and risk of treatment-emergent mania, particularly in bipolar disorder. Computational models offer controlled comparison of these pathways, but few integrate manic liability.

Methods: We extended a magnitude-based pruning model (95% sparsity) of depression in feed-forward networks trained on a Gaussian classification task. From identical pruned states, three interventions were simulated: ketamine-like gradient-guided regrowth (50% reinstatement) with consolidation; SSRI-like prolonged low-rate training with tapering noise and escalating excitability gain; neurosteroid-like global tonic inhibition (0.7× damping, tanh activations, reduced gain). Efficacy was assessed via accuracy under clean, noisy, and combined stress conditions; resilience to graded noise and additional pruning; manic risk via biased positive perturbation and activation magnitude. Results were averaged across 10 random seeds.

Results: All treatments restored near-ceiling baseline performance. Ketamine-like regrowth yielded superior extreme-stress resilience (76.8% ± 3.6%) and relapse protection (−0.1% ± 0.2% drop), reducing sparsity to 47.5%. Neurosteroid-like modulation matched acute combined-stress recovery (97.7% ± 0.2%) but showed state-dependence (19% off-modulation loss) and weaker extreme buffering (42.9% ± 1.3%). SSRI-like refinement lagged (90.8% ± 3.1% combined, 50.1% ± 3.7% extreme) with highest relapse vulnerability (8.8% ± 4.3%). Manic proxies ranked SSRI-like highest risk (biased accuracy 47.6% ± 12.8%, gain 1.60), ketamine-like moderate (84.2% ± 8.5%, gain 1.25), neurosteroid-like lowest (50.5% ± 7.4%, effective gain ~0.59).

Conclusions: Antidepressants operate via distinct plasticity routes—structural rebuilding (durable,

moderate risk), reversible stabilization (rapid, low risk), gradual optimization (vulnerable, high risk)—reproducing clinical trade-offs and supporting mechanism-based selection in unipolar and bipolar depression.

Introduction

Major depressive disorder (MDD) is a dominant source of global disability, affecting hundreds of millions of people and exerting heavy personal and economic burdens [1]. Pharmacotherapy has helped many patients, yet outcomes remain modest: only about one-third of individuals remit after a first antidepressant trial, and another third continue to meet criteria for depression even after several treatment steps [2]. Selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed agents but usually take weeks to produce noticeable change, leaving patients exposed to ongoing symptoms and often delivering only partial recovery [3].

The slow and sometimes incomplete benefit of monoaminergic drugs has shifted attention toward interventions that act on glutamatergic and GABA-ergic systems. Low-dose ketamine, an NMDA-receptor antagonist, can relieve depressive symptoms within hours. Pre-clinical and clinical work links this rapid effect to a surge in synaptogenesis mediated by brain-derived neurotrophic factor (BDNF) and mTOR signalling [4,5]. Neuroactive steroids such as brexanolone and zuranolone, which amplify tonic inhibition at extrasynaptic GABA_A receptors, also yield fast improvement and have shown particular promise for postpartum depression [6]. Taken together, these findings call the classic serotonin-deficit narrative into question and support a view of MDD as a disorder of impaired neural plasticity, in which chronic stress trims dendrites and synapses in prefrontal and hippocampal circuits and erodes resilience [7,8].

Treatment-emergent mania (TEM) complicates the picture, especially for people with bipolar disorder.

Traditional antidepressants can provoke mood switches in roughly 20–40 % of bipolar patients, whereas ketamine appears to carry less switch risk in controlled settings, and early reports on neurosteroids suggest minimal liability [9,10,6]. Understanding how different drug classes influence both depressive recovery and excitatory–inhibitory balance therefore remains essential.

Computational models offer a controlled way to dissect these mechanisms. Pruning-based approaches conceptualise depression as excessive synaptic elimination that leaves circuits fragile; ketamine-like regrowth within such models restores performance and resilience [11]. Yet few simulations place glutamatergic, monoaminergic and GABA-ergic strategies side by side or consider the risk of polarity switches.

The present study addresses these gaps. Using a single "depleted" network as a starting point, we compare three antidepressant analogues—ketamine-like synaptogenesis, SSRI-like gradual refinement and neurosteroid-like tonic inhibition. We further incorporate excitability shifts as a proxy for manic risk. By tracking onset speed, durability and switch potential within one coherent framework, we aim to clarify how distinct biological actions translate into clinical strengths and limitations.

Methods

Network architecture and task

The simulations relied on a feed-forward model intended to capture broad properties of cortico-limbic circuits (Figure 1). The network accepted two-dimensional inputs, passed activity through three hidden layers of 512, 512 and 256 units, and produced one of four class probabilities through a soft-max layer. Rectified linear units drove all hidden activations unless stated otherwise. The full configuration contained roughly 397 000 adjustable parameters.

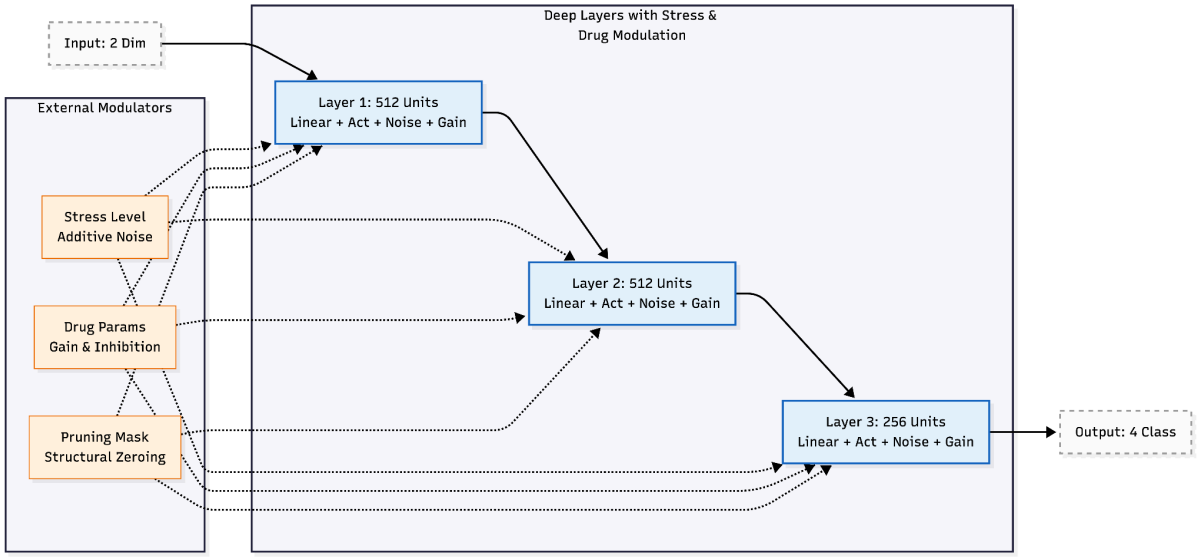

Figure 1: *Condensed Architecture of the Stress-Aware Network. The model processes 2D inputs through three hidden layers (blue) before producing a 4-class output. Each hidden layer block encapsulates four distinct operations in sequence: (1) a fully connected linear transformation subject to structural pruning (orange, Pruning Mask); (2) non-linear activation; (3) stress simulation via additive noise injection (orange, Stress Level); and (4) pharmacological modulation via multiplicative gain and inhibition scaling (orange, Drug Params). This design allows the network to dynamically simulate both structural connectivity changes (synaptogenesis/pruning) and functional state changes (excitability/stress) during the experiment.*

Synaptic stressors could be introduced at two levels. First, additive Gaussian noise was injected after each hidden activation to emulate neuromodulatory disruption. Second, a global multiplicative gain term changed overall excitability and could be combined with an extra damping factor or a switch from ReLU to tanh units when modelling neurosteroid action.

The task itself involved classifying points drawn from four equally sized Gaussian clouds centred on (−3, −3), (−3, 3), (3, −3) and (3, 3) with a shared standard deviation of 0.8. Each training run used 12 000 labelled samples. Performance was monitored on three separate sets: a 4 000-sample "standard noise" set that matched training variance, a 2 000-sample noise-free set, and a "combined-stress" set that added both input and internal perturbations. All code was written in PyTorch and executed on a single CPU core. Ten independent seeds, differing only in data order and weight initialisation, were averaged to obtain each metric.

Simulation of depression

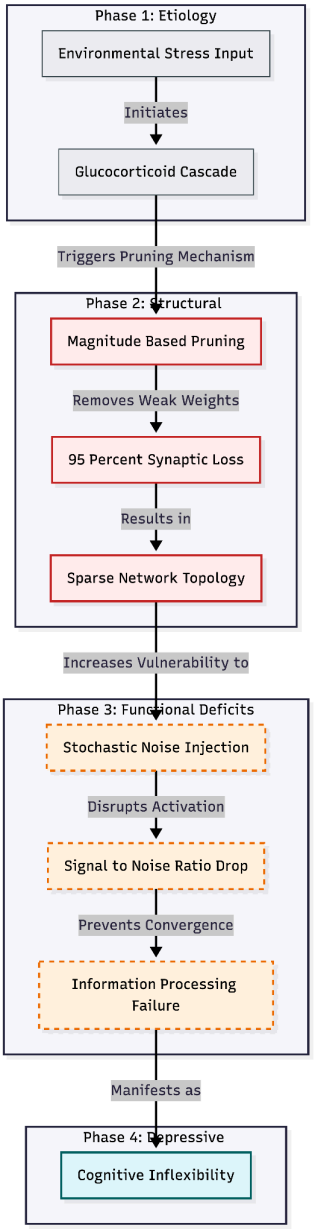

Figure 2: *Computational Modeling of the Depressive State. The diagram outlines the algorithmic simulation of depression implemented in the StressAwareNetwork. Phase 1 represents the environmental triggers. Phase 2 illustrates the structural impact modeled by the PruningManager, where 95% of network weights are removed based on magnitude, simulating dendritic spine loss and cortical atrophy. Phase 3 depicts the functional consequences during the forward pass; the sparse topology makes the network highly susceptible to stress_level noise injection, leading to a collapse in the signal-to-noise ratio. Phase 4 represents the final model output, where the inability to classify inputs correctly serves as a proxy for cognitive inflexibility and anhedonia.*

After 20 epochs of baseline training with Adam (learning rate 0.001) on noise-free data, every model

underwent magnitude-based pruning that removed the smallest 95 % of weights layer by layer. The surviving sparse network maintained reasonable accuracy on clean inputs yet collapsed rapidly when noise or further pruning was applied, mirroring theories that excessive synaptic loss underlies depressive vulnerability [7] (Figure 2).

Antidepressant intervention protocols

Three recovery strategies were examined on separate copies of the pruned network.

Ketamine-like condition: overall gain was fixed at 1.25. Gradients were accumulated over 30 mini-batches, the highest 50 % of previously pruned weights were reinstated with small random values drawn from N(0, 0.03), and parameters were fine-tuned for 15 epochs with Adam (learning rate 0.0005) while preserving sparsity.

SSRI-like condition: sparsity remained at 95 %. Over 100 slow-learning epochs (learning rate 1×10^{-5}) internal noise declined linearly from $\sigma = 0.5$ to 0, while excitability gain rose from 1.0 to 1.6, mimicking gradual monoaminergic adaptation.

Neurosteroid-like condition: sparsity again stayed constant. A post-activation damping factor of 0.7 was applied, ReLU units were replaced by tanh, and global gain was set to 0.85 (effective scaling $\approx$ 0.59). Ten adaptation epochs were run with Adam (learning rate 0.0005).

Outcome measures

Primary efficacy was the classification accuracy on clean, standard-noise and combined-stress test sets. To examine robustness, internal noise was increased stepwise from $\sigma = 0$ to 2.5 while recording accuracy. Relapse risk was evaluated by applying a second magnitude-based pruning that deleted 40 % of the remaining weights and then repeating the combined-stress test.

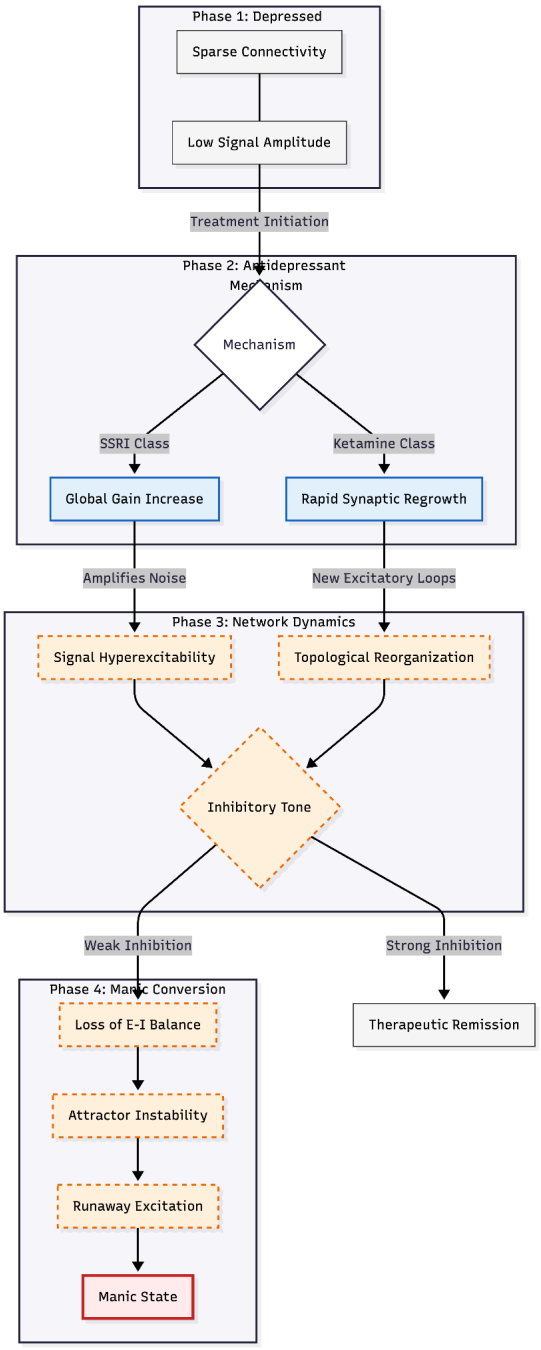

Figure 3: *Computational Model of Pharmacologically Induced Manic Conversion. The diagram illustrates the bifurcation of network dynamics following antidepressant treatment. Phase 1 represents the baseline depressive state characterized by sparse connectivity and low signal amplitude. Phase 2 differentiates the mechanism of action: SSRIs increase the global gain (amplifying existing signals), while Ketamine induces structural plasticity (synaptic regrowth). Phase 3 demonstrates that both mechanisms increase net excitation. The critical checkpoint is the system's "Inhibitory Tone." If inhibition is sufficient, the system stabilizes into remission. However, in the presence of weak inhibition—simulating a deficit in GABAergic control or neurosteroid regulation—the system enters Phase 4, resulting in a loss of Excitation-Inhibition (E-I) balance, attractor instability, and ultimately a transition to a manic state.*

Potential manic conversion was probed in two ways (Figure 3). First, the network was challenged

with biased internal noise ($\sigma = 1.0$, bias = +1.0) and the resulting accuracy recorded; poorer accuracy implied greater vulnerability to hyper-excitability. Second, the mean absolute activation across hidden layers during standard input served as an index of latent excitatory tone. For the neurosteroid analogue, all evaluations were repeated after removing the damping parameters to simulate drug withdrawal.

Data analysis

For every condition, results from the ten seeds were summarised as mean ± standard deviation; pronounced dispersion was also expressed as minimum–maximum ranges. Because the project was exploratory, no formal null-hypothesis tests were undertaken.

Results

Simulations were run under 10 independent random seeds; across seeds we saw the same rank ordering of performance for every outcome that was tracked.

Antidepressant efficacy

Relative to the over-pruned, untreated network (combined-stress accuracy = 29.7 ± 2.7 %), every treatment produced a large gain. Neurosteroid-like modulation finished at 97.7 ± 0.2 % and the ketamine-like synaptogenic routine reached 97.2 ± 0.2 %. The monoaminergic SSRI-like schedule also improved behaviour, but only to 90.8 ± 3.1 %. On clean or standard inputs all treated models scored at (or fractionally below) 100 % accuracy, whereas the untreated baseline remained at 34.7 ± 11.9 % on clean data.

Stress resilience

Noise tolerance diverged sharply as internal noise was increased (Table 1). At the most extreme perturbation (σ = 2.5) the ketamine analogue still classified correctly 76.8 ± 3.6 % of trials. The SSRI-like routine fell to 50.1 ± 3.7 %, and the neurosteroid analogue to 42.9 ± 1.3 %; the untreated control stayed near its baseline (29.6 ± 1.5 %). With moderate noise (σ = 1.0) neurosteroid- and ketamine-like conditions were similar (92.9 ± 2.5 % and 98.2 ± 1.1 %, respectively) and both clearly out-performed the SSRI-like schedule (78.2 ± 5.8 %).

Table 1. *Stress Resilience Profile (Mean ± Standard Deviation Across 10 Seeds)*

Treatment	No Noise (%)	Moderate (σ=0.5) (%)	High (σ=1.0) (%)	Severe (σ=1.5) (%)	Extreme (σ=2.5) (%)
Untreated (pruned)	36.8 ± 11.9	29.9 ± 2.5	29.6 ± 1.8	29.8 ± 1.4	29.6 ± 1.5
Ketamine-like	100.0 ± 0.0	99.9 ± 0.1	98.2 ± 1.1	92.9 ± 2.4	76.8 ± 3.6
SSRI-like	99.9 ± 0.1	95.3 ± 2.8	78.2 ± 5.8	64.5 ± 5.2	50.1 ± 3.7
Neurosteroid-like	100.0 ± 0.0	99.9 ± 0.1	92.9 ± 2.5	70.9 ± 2.5	42.9 ± 1.3

Manic conversion risk

Three risk markers were monitored: gain multiplier, accuracy under positively biased noise, and mean activation magnitude (Table 2). The SSRI-like model showed the largest gain (1.60 ± 0.00) and the poorest accuracy under biased noise (47.6 ± 12.8 %), with a mid-range activation magnitude of 0.390 ± 0.078. The ketamine analogue showed an intermediate gain (1.25 ± 0.00) but maintained high biased-noise accuracy (84.2 ± 8.5 %) even though its activation magnitude was highest (0.649 ± 0.079). Neurosteroid modulation damped excitability (gain = 0.85 ± 0.00; activation magnitude = 0.196 ± 0.008) and achieved a biased-noise accuracy of 50.5 ± 7.4 %. Untreated networks, by comparison, sat at gain = 1.00 ± 0.00, biased-noise accuracy = 25.0 ± 0.8 %, and activation magnitude

= 0.100 ± 0.013.

Table 2. *Manic Conversion Risk Metrics (Mean ± Standard Deviation Across 10 Seeds)*

Treatment	Gain Multiplier	Biased Stress Accuracy (%)	Activation Magnitude
Untreated (pruned)	1.00 ± 0.00	25.0 ± 0.8	0.100 ± 0.013
Ketamine-like	1.25 ± 0.00	84.2 ± 8.5	0.649 ± 0.079
SSRI-like	1.60 ± 0.00	47.6 ± 12.8	0.390 ± 0.078
Neurosteroid-like	0.85 ± 0.00	50.5 ± 7.4	0.196 ± 0.008

Note. Lower biased stress accuracy indicates greater manic conversion vulnerability; higher activation magnitude reflects increased latent hyperexcitability.

Relapse vulnerability and medication dependence

When an additional pruning step was applied to mimic relapse, performance in the ketamine-treated networks was essentially unchanged (-0.1 ± 0.2 %). The SSRI-like condition lost 8.8 ± 4.3 % accuracy and the neurosteroid analogue lost 5.1 ± 2.2 %. Removing the neurosteroid damping altogether revealed strong state-dependence: combined-stress accuracy fell from 97.7 ± 0.2 % on-modulation to 78.5 ± 4.8 % off-modulation.

Seed-to-seed spread was small for most measures, but biased-noise accuracy varied widely with the SSRI (28.2–74.8 %) and ketamine (63.3–96.7 %) analogues, indicating individual-difference sensitivity in those two conditions (Table 3).

Table 3. *Final Comparison Matrix (Means Across 10 Seeds)*

Metric	Ketamine-like	SSRI-like	Neurosteroid-like	Untreated (pruned)
Combined Stress (%)	97.2	90.8	97.7	29.7
Extreme Stress (%)	76.8	50.1	42.9	29.6
Biased Stress (%)	84.2	47.6	50.5	25.0
Gain Multiplier	1.25	1.60	0.85	1.00
Activation Magnitude	0.649	0.390	0.196	0.100
Sparsity (%)	47.5	95.0	95.0	95.0
Relapse Drop (%)	−0.1	8.8	5.1	N/A

Discussion

Interpretation of efficacy and resilience findings

Our simulations reveal three recognisably different therapeutic signatures. Both the ketamine-like synaptogenic programme and the neurosteroid-like GABAergic modulation restored almost full performance when the network was challenged by combined input and internal noise, reaching about 97 % accuracy. The SSRI-style, slow-adaptation schedule also improved accuracy but plateaued roughly six percentage points lower. These results echo clinical impressions: drugs that act through glutamatergic or GABAergic mechanisms often stabilise circuits within days, whereas monoaminergic agents depend on gradual receptor and transcriptional changes that unfold over weeks [7,8].

Durability separated the interventions more clearly. After ketamine-like regrowth, the network continued to perform well under extreme internal noise and was virtually unaffected by an additional round of pruning. This mirrors evidence that a single ketamine infusion can trigger structural plasticity and sustain benefit beyond drug clearance [5]. Neurosteroid modulation, by contrast,

protected the network only while the damping remained active; switching the modulation off produced a 19 % drop in accuracy and a moderate vulnerability to further pruning. Clinical reports of zuranolone show a similar pattern: rapid relief that fades once dosing stops [6]. The SSRI analogue, which merely fine-tuned the sparse remnants, offered the least protection against heavy noise and the greatest loss after re-pruning, a finding that accords with the limited stress resilience seen in many patients who rely on conventional antidepressants alone [4].

Manic conversion risk and clinical parallels

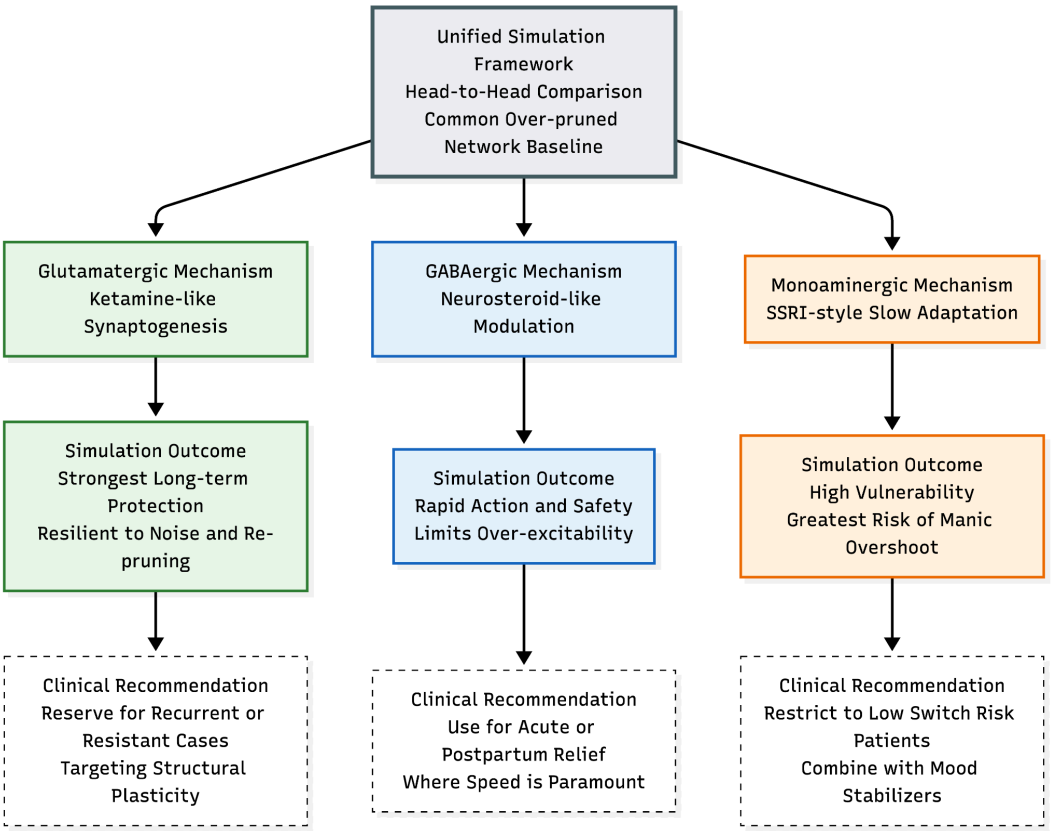

Figure 4: *Translational Framework for Antidepressant Selection. The study leverages a unified simulation architecture to compare three distinct pharmacological mechanisms against a common baseline of network fragility. (Left, Green) The Glutamatergic pathway, modeling ketamine-like synaptogenesis, demonstrates superior durability against stress, supporting its use in treatment-resistant depression. (Center, Blue) The GABAergic pathway, modeling neurosteroid modulation, provides rapid stabilization with minimal excitability risk, aligning with indications for urgent or postpartum care. (Right, Orange) The Monoaminergic pathway, modeling traditional SSRIs, reveals a susceptibility to manic overshoot, reinforcing clinical guidelines that advise caution or concurrent mood stabilizers when treating bipolar depression.*

The simulations demonstrated class-specific variations in mood-switch risk (Figure 4): SSRI-like refinement resulted in the most significant increase in network excitability and the least resistance to positively biased noise, reflecting meta-analytic manic switch rates nearing 40% among bipolar patients on traditional antidepressants [9]; ketamine-like synaptogenesis maintained strong performance even in the presence of biased input, aligning with infrequent reports of mania when ketamine is used with mood stabilizers [10]; and neurosteroid-based tonic inhibition exhibited the highest safety, showing the lowest activation levels and the most effective management of bias-driven errors, corresponding to initial clinical findings of minimal switch liability with zuranolone [12].

Seed-to-seed variability was widest for the SSRI- and ketamine-like conditions, hinting that individual differences in baseline network fragility can influence real-world switch risk, much as prior mood-switch history and family loading predict clinical outcomes [13]. Together, these observations support caution when prescribing monoaminergic monotherapy to patients with bipolar vulnerability and point to plasticity-targeted or GABAergic strategies as potentially safer options.

Novelty and translational impact

This project brings three very different antidepressant mechanisms—glutamatergic, monoaminergic, and GABA-ergic—into one tightly controlled simulation that also tracks the chance of a manic switch. Earlier in-silico work tended to look at one pathway at a time, for example focusing only on ketamine-like synaptogenesis [11]. By beginning with the same over-pruned network in every run and then adding a uniform excitability gain plus skewed noise, we could compare recovery, durability, and opposite-pole risk head-to-head.

Several clinically relevant messages emerge. First, the ketamine analogue delivered the strongest long-term protection: once new synapses were in place, the model withstood heavy noise and an extra pruning step, mirroring reports that ketamine triggers lasting plasticity [5]. Second, the neurosteroid

analogue worked quickly and limited over-excitability, a pattern that fits current interest in zuranolone for urgent or postpartum use where speed and safety are paramount [6]. Third, the monoaminergic schedule, while helpful, left the network most exposed to manic-like overshoot—an echo of long-standing cautions about antidepressant monotherapy in bipolar illness [9,14].

Running all three regimens inside the same architecture therefore offers a mechanistic basis for tailoring treatment: reserve synaptogenic drugs for recurrent or resistant cases, choose fast but state-dependent GABA-modulators for acute relief, and limit classic antidepressants to patients with low switch risk or with added mood stabilisers.

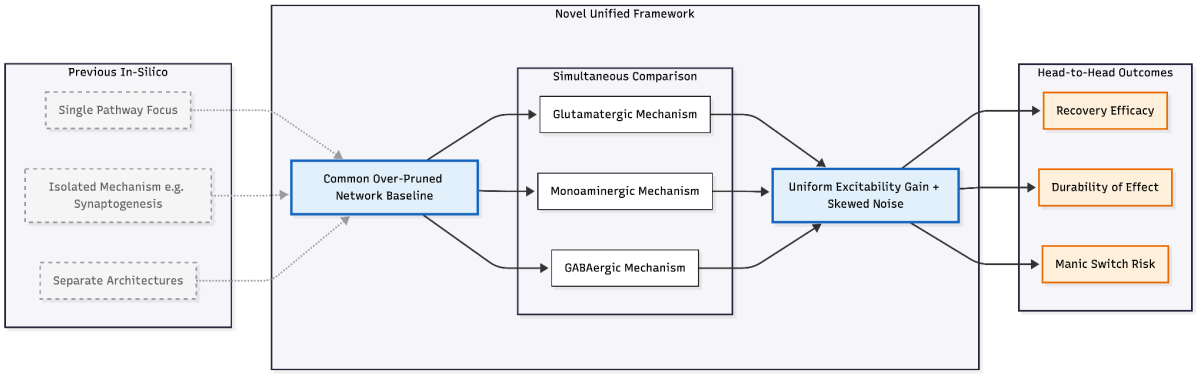

Figure 5: *Conceptual Shift to a Unified Simulation Framework. Unlike previous in-silico studies that typically isolated single pathways (e.g., focusing solely on synaptogenesis), this project introduces a novel unified architecture. By initializing all simulations with an identical over-pruned network baseline and applying standardized excitability gains and skewed noise, the framework allows for a rigorous head-to-head comparison of three distinct pharmacological mechanisms: Glutamatergic, Monoaminergic, and GABAergic. This approach uniquely enables the simultaneous tracking of recovery trajectories, treatment durability, and the risk of manic switching within a single controlled environment.*

Limitations

Important simplifications remain. The feed-forward model omits the feedback loops that shape real cortico-limbic mood circuits; this may downplay potential instabilities. Modulation was applied globally, not by layer or cell class, so subtle pharmacological differences—for example, the varied extrasynaptic actions of neurosteroids noted by [15]—were ignored. Manic liability was estimated

from biased noise and overall activation; these proxies are cruder than clinical ratings taken over time.

Although ten random seeds introduced variability, other "patient" features such as baseline excitation–inhibition balance or depth of synaptic loss were held constant. Mood-stabilising co-therapy, known to reduce switch risk [14], was not simulated. Each of these gaps limits direct clinical translation.

Conclusion

Within these constraints, the study shows that different drug classes restore performance through distinct routes—building new structure, damping excess firing, or slowly tuning weakened links—each with its own balance of speed, staying power, and bipolar safety. Embedding switch risk in the same plasticity frame moves the conversation away from single-transmitter theories toward circuit reserve and excitability control. As rapid-acting treatments gain ground, such models may help clinicians match interventions to individual risk profiles and combine agents more safely.

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