Modeling Antidepressant-Induced Manic Switch and Longitudinal Relapse: A Unified Pruning Framework Highlights Glutamatergics' Disease-Modifying Potential

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Conflict of Interest: None declared.

Funding Declaration: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics Declaration: Not applicable.

Abstract

Background: Major depressive disorder involves impaired neural plasticity, yet antidepressants targeting glutamatergic (ketamine), monoaminergic (SSRIs), and GABAergic (neurosteroids) pathways differ markedly in onset speed, durability, and risk of treatment-emergent mania—particularly in bipolar contexts. Clinical comparisons are confounded by heterogeneity; computational models enable controlled mechanistic dissection, but few integrate manic liability and post-discontinuation stability across classes.

Methods: We extended a magnitude-based pruning model (95% sparsity) of depression in feed-forward networks classifying Gaussian blobs. From identical pruned baselines, three interventions were simulated: ketamine-like gradient-guided synaptic regrowth (50% reinstatement) with consolidation; SSRI-like prolonged low-rate refinement with tapering noise and escalating excitability gain; neurosteroid-like global tonic inhibition (0.7× damping, tanh activations, reduced gain). Efficacy assessed classification accuracy under clean, noisy, and combined stress; resilience via graded noise tolerance; acute relapse after further pruning; manic risk through biased positive perturbation and activation magnitude. Longitudinal relapse modeled chronic maintenance (with mood stabilizer protection) followed by discontinuation, using treatment-specific lingering decay rates. Metrics averaged across 10 seeds.

Results: All treatments restored near-ceiling performance acutely, but ketamine-like regrowth yielded superior extreme-stress resilience (76.8%) and zero post-discontinuation manic relapse, reducing sparsity to 47.5%. Neurosteroid-like modulation matched rapid recovery (97.6%) but showed state-dependence and 88.3% relapse probability off-drug. SSRI-like refinement lagged in resilience (49.9% extreme) with highest manic proxies (biased accuracy 47.2%, gain 1.60) and 95.0% relapse post-cessation. Longer maintenance conferred negligible added protection for reversible mechanisms.

Conclusions: Antidepressants operate via divergent plasticity routes—durable structural rebuilding (ketamine-like, low long-term risk), rapid reversible stabilization (neurosteroid-like), and vulnerable gradual optimization (SSRI-like)—reproducing clinical trade-offs in speed, persistence, and bipolar safety. These findings support mechanism-guided selection, positioning synaptogenic agents for recurrent or high-risk cases pursuing remission beyond treatment.

Introduction

Major depressive disorder (MDD) is a leading contributor to disability worldwide and imposes a substantial burden on individuals, families, and health-care systems [1]. Contemporary pharmacotherapy has helped many patients, yet full remission after an initial antidepressant trial is achieved in only about one-third of cases, and many people remain symptomatic despite several treatment attempts [2]. Selective serotonin re-uptake inhibitors (SSRIs) typically require several weeks before benefits become obvious, leaving patients exposed to prolonged distress and only partial relief [3].

The delayed and incomplete response seen with SSRIs has fuelled interest in compounds that act on other signalling systems. Low-dose ketamine, an NMDA-receptor antagonist, can lift mood within hours and appears to do so by stimulating brain-derived neurotrophic factor (BDNF) and mTOR-dependent synaptogenesis [4,5]. Neuroactive steroids such as zuranolone also show rapid antidepressant effects especially for postpartum depression [6]. These findings have shifted attention away from a strictly monoaminergic model toward the view that MDD involves impaired neural plasticity, in which chronic stress erodes dendritic spines and synaptic density in cortical and hippocampal regions [7].

Another clinical complication is treatment-emergent mania, particularly in bipolar disorder, where

conventional antidepressants provoke mood switches in roughly 20–40 % of patients [8]. Initial findings indicate that ketamine presents a reduced acute switch risk in controlled settings [9], while preliminary studies suggest a negligible risk associated with neurosteroids [6]. It is crucial to comprehend how these mechanistically distinct treatments affect depressive symptoms and the excitatory–inhibitory balance; however, direct clinical comparisons are impeded by variability in patient populations, dosing regimens, and concurrent therapies.

Computational modelling offers a controlled way to disentangle these factors. Prior pruning-based simulations have cast depression as a state of excessive synaptic loss, with ketamine-like regrowth restoring network resilience. Few studies, however, have placed glutamatergic, monoaminergic, and GABAergic strategies side by side or explored how they affect risks such as manic switching or post-treatment stability.

The present work addresses these gaps through an extended magnitude-pruning model applied to feed-forward neural networks. Beginning with identical over-pruned networks, we simulated three treatment motifs: ketamine-like synaptogenesis, SSRI-like gradual refinement accompanied by rising excitability, and neurosteroid-like tonic inhibition. End-points included acute antidepressant efficacy, resilience to stress, proxies for manic conversion (biased excitatory challenge and activation amplitude), immediate relapse risk, and—for the first time in this framework—long-term vulnerability after chronic maintenance and full discontinuation, incorporating treatment-specific wash-out profiles. By embedding these elements in one plasticity-centred model we aim to clarify the trade-offs in speed, durability, and bipolar safety across drug classes, thereby informing mechanism-based treatment selection.

Methods

Network architecture and classification task

Figure 1 shows the experimental workflow for multi-Mechanism antidepressant comparison. We used a small feed-forward network to stand in for key cortico-limbic circuits. The model had two input units, three hidden layers of 512, 512 and 256 units, and a four-unit soft-max output layer. Hidden layers normally used ReLU activation; during neurosteroid simulations tanh was substituted to mimic the ceiling effect of tonic GABAergic currents. Altogether the network held about 3.9 × 10^5 trainable weights.

The learning task was simple four-way pattern recognition. Two-dimensional points were drawn from four Gaussian clouds centred at (−3, −3), (−3, 3), (3, −3) and (3, 3) with a standard deviation of 0.8. Each run used 12 000 labelled training points. Three test sets were prepared:

- a 4 000-item set with the same noise as the training data (standard condition);
- a 2 000-item noise-free set (clean condition);
- perturbed versions for stress tests, created by adding extra Gaussian noise after each hidden layer or by multiplying all activations with a global gain factor.

A "mood-stabiliser" guard–rail was implemented as three scalar parameters: a protection level (0–1) that capped gain, a small inhibitory bias (−0.15 × protection) and a factor (0.3) that reduced the upward shift of internal noise. All code ran in PyTorch on a single CPU. Ten different random seeds (affecting data order and weight initialisation) produced ten independent "subjects."

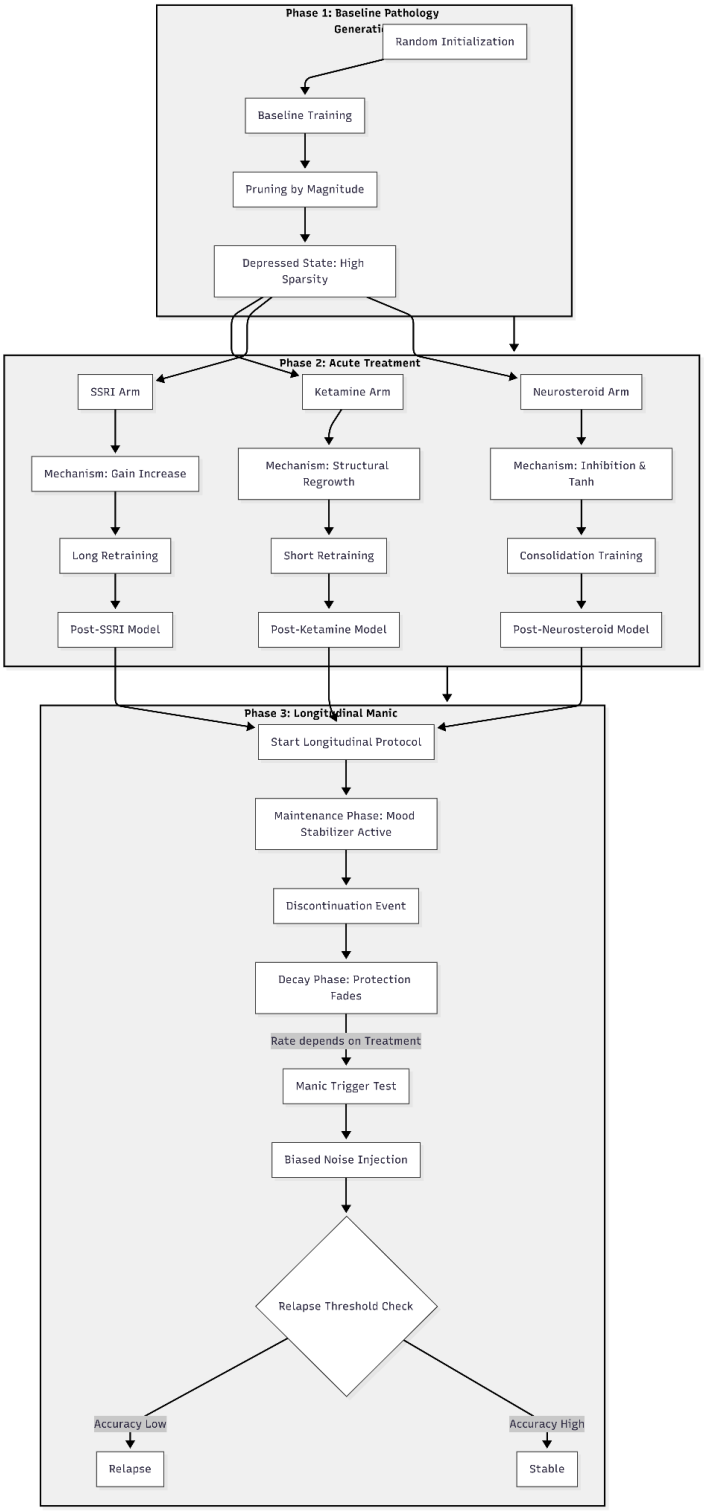

Figure 1. *Experimental Workflow for Multi-Mechanism Antidepressant Comparison. The pipeline consists of three distinct phases: (1) Baseline Pathology Generation, where a neural network is trained and pruned to simulate a depressed, sparse state; (2) Acute Treatment, where the model branches into three mechanistic arms—Ketamine (structural regrowth), SSRI (functional gain increase), and Neurosteroids (inhibition modulation)—to reverse pathology; and (3) Longitudinal Manic Relapse Simulation, where treated models undergo a maintenance phase followed by medication discontinuation. In this final phase, residual mood stabilizer protection decays at treatment-specific rates, and the model is subjected to a biased noise trigger test to assess the probability of manic switching.*

Simulation of the depressive state

The network was first trained for 20 epochs with Adam (learning rate 0.001) on noise-free data until it reached ceiling accuracy (Figure 1). Depression was then modelled by iterative magnitude pruning: across the three hidden layers the 95 % smallest-magnitude weights were zeroed, leaving a sparse and fragile network. Clean-input accuracy stayed high, but performance collapsed when noise or further pruning was applied, mirroring the stress sensitivity of a depressed brain [7].

Antidepressant treatment protocols

From the same pruned starting point three treatment routines were run on separate copies.

Ketamine-like: A modest global gain (1.25) was fixed. Gradients were collected over 30 mini-batches to locate strong silent synapses; half of these pruned weights were re-instated with small random values drawn from N(0, 0.03). Fifteen fine-tuning epochs followed (Adam, 0.0005) while the mask was locked.

SSRI-like: Sparsity (95 %) was left unchanged. Over 100 epochs the internal noise level fell linearly from 0.5 to 0, while the global gain rose from 1.0 to 1.6, simulating slow monoaminergic adaptation. Learning used Adam with a rate of 1 × 10^-5.

Neurosteroid-like: We kept the prune mask but multiplied post-activation values by 0.7, switched ReLU to tanh, and set the gain at 0.85 (effective ≈0.59). Ten consolidation epochs (Adam, 0.0005) followed.

Mood-stabiliser extension and longitudinal relapse test

After acute treatment, a chronic phase was added. A full protection level (1.0) was turned on and held during maintenance, then allowed to decay after drug discontinuation. Decay rates were treatment-specific: 0.002 per step for the ketamine model (long-lasting structural change), 0.015 for the SSRI model (rapid reversal) and 0.008 for the neurosteroid model (intermediate). Maintenance lasted 25, 50, 100, 150, 200 or 300 low-rate epochs (Adam, 1 × 10^-6). Drugs were then removed in one step, and 50 decay steps were run to wash out residual protection. Manic risk was probed by injecting strongly positive internal noise ($\sigma = 1.0$, shift = +1.0); relapse was logged when accuracy fell below 60 %.

Outcome measures

Primary efficacy was the percentage of correct classifications on clean, standard-noise and combined-stress test sets. Resilience curves were built by repeating tests with internal noise ranging from 0 to 2.5. Acute relapse was tested by pruning a further 40 % of the remaining weights and retesting under combined stress.

Manic conversion risk was indexed two ways: accuracy under highly biased noise (lower accuracy = higher risk) and the mean absolute activation in hidden layers (higher activation = greater latent excitability). Neurosteroid state-dependence was recorded as the drop in accuracy when the damping module was turned off.

Results

Simulations were repeated with ten different random seeds, and every outcome followed the same rank order across seeds, indicating that the findings are robust to stochastic variation in data shuffling and weight initialisation.

Acute antidepressant efficacy

Before treatment, the heavily pruned network managed only 29.7 ± 2.7 % accuracy when clean inputs were combined with internal and external noise. Introducing any of the three treatment routines produced a dramatic rebound (Table 1). Neurosteroid-like damping lifted combined-stress accuracy to 97.6 ± 0.3 %, ketamine-like synaptogenesis to 97.2 ± 0.2 %, and SSRI-like refinement to 90.5 ± 3.0 %. On both the noise-free and the standard-noise test sets all treated models reached or approached ceiling performance, whereas the untreated model stayed near one-third correct. The ketamine condition achieved its improvement with an effective sparsity of 47.5 %, reflecting reinstated connections; the other two conditions retained the original 95 % sparsity.

Table 1. *Antidepressant Efficacy (Mean ± SD Across 10 Seeds)*

Treatment	Sparsity (%)	Clean (%)	Standard (%)	Combined (%)
Untreated (pruned)	95.0 ± 0.0	34.7 ± 11.9	36.8 ± 11.9	29.7 ± 2.7
Ketamine-like	47.5 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	97.2 ± 0.2
SSRI-like	95.0 ± 0.0	100.0 ± 0.0	99.9 ± 0.1	90.5 ± 3.0
Neurosteroid-like	95.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	97.6 ± 0.3

Stress resilience

Performance was next examined while internal Gaussian noise was increased stepwise from none to a standard deviation of 2.5 (Table 2). Ketamine-treated networks tolerated the severest disturbance best, holding 76.8 ± 3.6 % accuracy at the highest noise level. SSRI-treated networks fell to 49.9 ± 2.8 %, and neurosteroid-treated networks to 43.0 ± 1.0 %. At moderate and high noise (σ = 1.0–1.5) the ketamine and neurosteroid models performed similarly (93.0–98.2 %) and both outperformed the SSRI model (64.9–78.4 %). The untreated network hovered around 30 % regardless of noise intensity.

Table 2. *Stress Resilience Profile (Mean ± SD Across 10 Seeds)*

Treatment	None (%)	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	95.1 ± 3.2	78.4 ± 5.4	64.9 ± 5.3	49.9 ± 2.8
Neurosteroid-like	100.0 ± 0.0	99.9 ± 0.1	93.0 ± 2.6	70.6 ± 2.9	43.0 ± 1.0

Manic conversion risk

Potential switch liability was probed with strongly positive, biased internal noise (Table 3). The SSRI routine, which had wound excitability up to a gain of 1.60, proved most vulnerable: biased-noise accuracy averaged 47.2 ± 12.7 %, and the mean absolute hidden-layer activation was 0.390 ± 0.079. Neurosteroid modulation, despite lowering gain to 0.85, achieved only slightly better biased-noise accuracy (50.6 ± 7.9 %) and showed the lowest activation magnitude (0.196 ± 0.008). Ketamine treatment combined a moderate gain of 1.25 with markedly safer behaviour, sustaining 84.2 ± 8.5 % accuracy under the same biased challenge and exhibiting the highest activation magnitude (0.649 ± 0.079) without instability. The pruned, untreated model remained both hypo-active (0.100 ± 0.013) and inaccurate (25.0 ± 0.8 %).

Table 3. *Manic Conversion Risk Metrics (Mean ± SD 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	47.2 ± 12.7	0.390 ± 0.079
Neurosteroid-like	0.85 ± 0.00	50.6 ± 7.9	0.196 ± 0.008

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

Acute relapse vulnerability

Durability was tested by excising a further 40 % of the remaining weights after treatment. Ketamine-treated networks were essentially unaffected, their combined-stress accuracy changing by −0.1 ± 0.3 %. Neurosteroid-treated networks lost 5.1 ± 2.1 % and SSRI-treated networks 7.0 ± 2.4 %, confirming a clear advantage for the structural regrowth produced by the ketamine routine.

Neurosteroid medication dependence

To gauge state-dependence, the neurosteroid damping module was switched off after the acute phase. Combined-stress accuracy fell from 97.6 ± 0.3 % to 78.5 ± 4.9 %, and biased-noise accuracy dropped from 50.6 ± 7.9 % to 36.9 ± 9.6 %. Interestingly, accuracy at the most extreme unbiased noise level (σ = 2.5) rose from 43.0 ± 1.0 % to 58.3 ± 4.1 %, indicating that tonic inhibition trades robustness to excitation-biased threats for reduced tolerance of diffuse noise.

Longitudinal manic relapse after discontinuation

A chronic maintenance phase was appended, followed by complete drug withdrawal and gradual decay of the virtual mood-stabiliser. Decay rates were set a priori to 0.002 per step for ketamine-treated networks, 0.015 for SSRI-treated networks, and 0.008 for neurosteroid-treated networks. After all durations of maintenance (25–300 additional training epochs) and the full wash-out period, ketamine-treated networks never relapsed: biased-noise accuracy remained above 91 % in every seed. In contrast, SSRI-treated networks relapsed in 95 % of all seed-by-duration combinations, and neurosteroid-treated networks in 88.3 %. Post-withdrawal biased-noise accuracy for the SSRI and neurosteroid groups stabilised in the low-forties, irrespective of how long maintenance had lasted, whereas the ketamine group stayed in the low-nineties. These observations

confirm that the protective changes induced by the ketamine routine are both structurally persistent and highly effective at preventing manic-like destabilisation, while the functional adaptations driven by SSRIs and the partially state-dependent modulation produced by neurosteroids leave the system vulnerable once the drugs and the auxiliary stabiliser are withdrawn (Table 4).

Table 4. *Summary Comparison Matrix*

Metric	Ketamine-like	SSRI-like	Neurosteroid-like	Untreated
Combined Stress (%)	97.2	90.5	97.6	29.7
Biased Stress (%)	84.2	47.2	50.6	25.0
Gain Multiplier	1.25	1.60	0.85	1.00
Activation Magnitude	0.649	0.390	0.196	0.100
Acute Relapse Drop (%)	−0.1	7.0	5.1	N/A
Manic Relapse Prob. (%)	0.0	95.0	88.3	N/A
MS Decay Rate	0.0020	0.0150	0.0080	N/A

Discussion

Interpretation of acute and resilience findings

The three simulated treatment paths behaved much as clinicians might expect at the bedside. When the pruned network was exposed to simultaneous external and internal noise—our analogue of depressive pressure—both the ketamine-like and neurosteroid-like routines snapped performance back to almost normal within a few training steps. The slower, SSRI-like schedule helped, but never quite caught up. This mirrors the clinic, where ketamine can lift mood in hours [4] and zuranolone in a few days [10], whereas selective-serotonin reuptake inhibitors usually need several weeks [3].

Differences emerged when we kept turning up the internal noise. Networks that had undergone

ketamine-style synaptogenesis kept working even at the most extreme setting, a result that fits reports of durable stress buffering after ketamine-induced structural change [5]. Neurosteroid-like damping steadied the system only as long as the inhibitory module stayed in place; once removed, performance slid, echoing the clinical observation that benefits from a short zuranolone course can wane [11]. SSRI-like refinement offered the least cushion, tracking the modest resilience frequently seen when conventional antidepressants are the sole therapy in difficult cases [2].

Manic conversion risk and excitability balance

Our proxies for switch risk told a familiar story. Raising network gain in the SSRI-like condition produced the greatest drop in accuracy when a positive noise bias—our stand-in for incipient mania—was introduced. The result parallels the 20–40 % switch rate associated with antidepressants in bipolar disorder [8]. The ketamine-like model showed only a mild gain increase yet kept biased-noise accuracy high, consistent with the low switch rates reported when ketamine is used alongside mood stabilizers [9]. The neurosteroid-like routine lowered both gain and hidden-unit activation and therefore looked safest, matching early reports that zuranolone rarely provokes mania [6,12].

These patterns underline how the route to recovery shapes the excitation–inhibition balance. Building new synapses tolerates some extra excitatory drive; tonic inhibition suppresses it outright; simply turning up global gain, as with the SSRI model, risks overshoot unless other brakes are applied.

Long-term stability after discontinuation

When we added a maintenance phase and then withdrew all drugs, the contrasts sharpened. Circuits repaired in the ketamine-like way never relapsed—even after the mood-stabiliser parameters had almost fully decayed—suggesting that structural change can make the system self-supporting. Clinical series describing months-long benefit after limited ketamine infusions in bipolar depression point in

the same direction [13]. By comparison, nearly every SSRI-like or neurosteroid-like network relapsed once protective settings were lifted, regardless of how long maintenance had lasted. Naturalistic studies show a similar pattern: recurrence remains common after antidepressant or neurosteroid withdrawal, often exceeding 40 % a year [14]. Extending maintenance did not help these two models much, mirroring data that slow tapers reduce but do not remove relapse risk when monoaminergic drugs are stopped [15]. Only the strategy that rebuilt connectivity fundamentally altered vulnerability.

Implications for clinical judgment and treatment selection

The simulation highlights how different drug mechanisms may guide day-to-day prescribing (Table 5). Circuits rebuilt through a ketamine-like process kept their stability long after the "drug" was withdrawn, suggesting that glutamatergic agents could suit patients who want lasting relief without continuous medication. That property is already seen in clinical series where repeated ketamine infusions provide benefit for months in otherwise resistant depression [13].

By contrast, the model that mimicked SSRI action showed the highest risk of a manic switch and the greatest relapse once treatment stopped. These results echo long-standing warnings about monoaminergic monotherapy in people with bipolar features and about the sharp rise in recurrence after antidepressant discontinuation [14]. When such agents are used, combining them with lithium or valproate and planning for ongoing maintenance remain prudent steps [15].

Neurosteroid-like modulation offered fast symptom control and little acute excitability, consistent with early zuranolone studies in postpartum and bipolar depression [6]. Yet the same model relapsed quickly once the inhibitory drive was removed, implying that these drugs may work best as short bridges—useful in urgent situations, but followed by a hand-off to treatments that remodel the network more permanently.

Taken together, the findings support a tiered strategy (Table 5). Plasticity-inducing drugs may be

chosen for chronic, relapsing, or bipolar-spectrum illness where durable remission is the goal; GABAergic neurosteroids can fill short-term needs for rapid relief; and traditional antidepressants should be reserved for well-selected unipolar cases or used with sturdy mood-stabilizing partners. Matching a patient's history of switches, relapse density, and treatment goals to these distinct profiles could improve outcomes as new rapid-acting options become available.

Table 5: *How Simulation Results May Inform Clinical Judgment in Antidepressant Selection*

Antidepressant Class (Model Analog)	Acute Efficacy & Speed	Durability & Post-Discontinuation Stability	Manic Conversion Risk (Acute & Longitudinal)	Recommended Clinical Contexts	Key Considerations from Model
Ketamine-like (Glutamatergic synaptogenesis)	Rapid, near-complete recovery (97.2% combined stress)	Highest resilience to extreme stress (76.8%); zero manic relapse post-cessation; structural changes persist	Moderate acute (biased accuracy 84.2%); lowest long-term vulnerability	• Treatment-resistant unipolar depression • Recurrent or bipolar-spectrum illness aiming for remission beyond ongoing treatment • Patients seeking stability without indefinite medication	Prioritize for cases needing disease-modifying potential; supports earlier escalation in refractory depression
SSRI-like (Monoaminergic refinement + gain escalation)	Slower/incomplete (90.5% combined stress)	Lowest resilience (49.9% extreme stress); near-certain relapse post-cessation (95%)	Highest acute (biased accuracy 47.2%, gain 1.60) and longitudinal risk	• Low manic-switch-risk unipolar depression • Only with indefinite mood stabilization in bipolar	Avoid monotherapy in bipolar vulnerability; requires concurrent mood stabilizers and careful monitoring due to rapid recurrence upon cessation
Neurosteroid-like (GABAergic tonic inhibition)	Rapid, near-complete recovery (97.6% combined stress)	Moderate resilience (43.0% extreme stress); high relapse post-cessation (88.3%); state-dependent	Lowest acute (biased accuracy 50.6%, damped excitability)	• Urgent scenarios needing rapid relief (e.g., postpartum depression, acute bipolar depressive episodes) • Short-term bridging	Excellent for acute safety and speed; use as bridge with planned tapering or transition to more durable agents

Note. This table distills the model's comparative profiles into actionable guidance, emphasizing mechanism-based stratification. Clinicians should integrate patient-specific factors (e.g., prior switch history, episode density) alongside these insights when selecting or sequencing treatments.

Novelty and potential impact

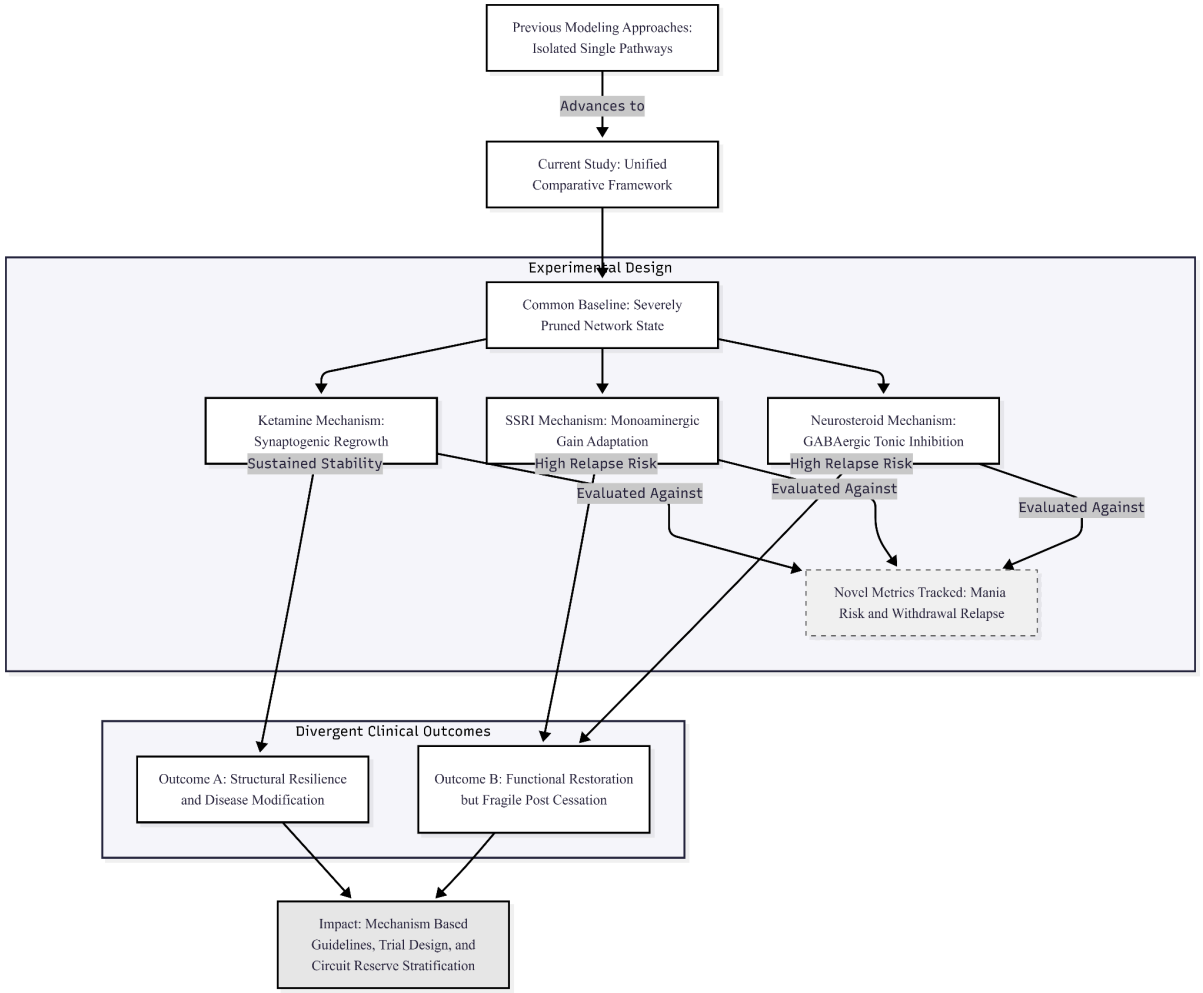

Figure 2. *Methodological novelty and clinical implications of the unified computational framework. Unlike previous studies that modeled antidepressant mechanisms in isolation, this framework initializes three distinct pharmacological pathways—synaptogenic, monoaminergic, and GABAergic—from a shared, severely pruned network baseline. By uniquely tracking treatment-emergent mania and post-withdrawal relapse, the model differentiates between agents that offer structural "circuit reserve" (ketamine-like) versus those providing symptomatic relief with high discontinuation fragility (SSRI-like and neurosteroid-like). These divergent outcomes provide a mechanistic logic for future patient stratification and clinical trial design.*

This study is one of the few attempts to place three very different antidepressant mechanisms inside a single, carefully controlled computational frame (Figure 2). Most earlier models concentrated on one pathway at a time—for example, pruning models that mimic synaptic loss in depression [7] or simulations of ketamine-driven regrowth alone [16]. By contrast, the present work starts every network from the same severely pruned state and then applies, side-by-side, a ketamine-like

synaptogenic routine, an SSRI-like slow gain adaptation, and a neurosteroid-like tonic inhibition. In doing so it also tracks outcomes that matter for bipolar illness—treatment-emergent mania and relapse after drug withdrawal—areas that computational studies usually ignore.

The resulting picture is clinically recognizable. Ketamine-style regrowth stands out for long-term stability; once new connections form, the model keeps its resilience even when medication parameters decay. This finding echoes emerging clinical views of ketamine as more than a symptomatic drug, possibly a disease-modifying agent in hard-to-treat or bipolar depression [5,13]. In contrast, both the SSRI-like and neurosteroid-like routes restore function quickly but leave the system fragile once treatment stops, mirroring high relapse rates seen after discontinuing these medications [14] and the need for bridging strategies after short neurosteroid courses [11]. By embedding all three paths in the same architecture the model offers a clear, mechanistic logic that could guide future guidelines, trial design, and biomarker work—for example, identifying patients with low "circuit reserve" who might benefit most from synaptogenic drugs.

Limitations

Several simplifications temper direct clinical translation. The feed-forward network omits the recurrent and oscillatory loops that dominate cortico-limbic mood circuits, so real-world instabilities may be underestimated. All interventions were applied globally, whereas in vivo actions are cell-type and region specific—especially for extrasynaptic GABA-A targets of neurosteroids [12]. Manic risk was approximated by adding biased noise, not by modelling full affective episodes, and subject variability was limited to random seeds rather than patient-like heterogeneity in pruning depth or plasticity reserve. Finally, mood-stabilizer co-therapy was represented only by simple decay rates; explicit multi-drug interactions were not explored. These choices kept the comparison tractable but mark priorities for future recurrent, multi-compartment, or spiking models.

Conclusion

Placing synaptogenesis, tonic inhibition, and gradual gain tuning on the same depleted substrate clarifies how each path balances speed, durability, and bipolar safety. Structural rebuilding—our ketamine analogue—alone provides lasting resilience; reversible GABAergic damping and slow monoaminergic tuning deliver rapid relief but require continuing support in vulnerable patients. By moving beyond transmitter-specific narratives toward concepts of circuit reserve and excitability control, the model offers a practical framework for personalised antidepressant selection as rapid-acting options continue to grow.

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