Review

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Synaptic Plasticity—Intrinsic Excitability and Antidepressant Discovery

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Abstract

Major depressive disorder remains a leading cause of disability, and decades of monoamine-centered pharmacology have yielded delayed and often incomplete relief. Rapid-acting antidepressants reshaped the field by linking swift symptom improvement to glutamatergic plasticity, yet durable benefit depends on how newly reconfigured circuits are stabilized and tuned. This review synthesizes evidence that antidepressant efficacy arises from the coordinated engagement of synaptic plasticity, spanning induction and consolidation, and intrinsic excitability, which provides gain control, and proposes an integrated framework to guide future discovery. It first outlines induction through N-methyl-D-aspartate receptors (NMDARs) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), exemplified by ketamine and esketamine, followed by consolidation mediated by tropomyosin receptor kinase B (TrkB) signaling, translational disinhibition via eukaryotic elongation factor 2 kinase (eEF2K), and presynaptic stabilization indexed by synaptic vesicle glycoprotein 2A (SV2A); together, these processes transform transient potentiation into persistent network change. It then highlights intrinsic excitability, emphasizing voltage-gated potassium channel subfamily Q (Kv7), hyperpolarization-activated cyclic nucleotide-gated (HCN), and G protein-gated inwardly rectifying potassium (GIRK) channels as circuit-level governors that normalize firing and limit relapse-prone hyperexcitability. Finally, it presents a phase-aware Induction–Consolidation–Maintenance (ICM) roadmap, supported by SV2A positron emission tomography (PET) and electroencephalography (EEG)/functional magnetic resonance imaging (fMRI) biomarkers, to personalize treatment timing and combinations. This dual-target strategy reframes antidepressants as network reprogrammers and suggests broader relevance for circuit repair across neurology and psychiatry.

Keywords: synaptic plasticity; neuronal excitability; ketamine; esketamine; neurogenesis; signal transduction; excitatory postsynaptic potentials; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors; antidepressive agents; major depressive disorder (MDD)

1. Introduction: Beyond Monoamines to Plasticity and Excitability

Depression remains one of the leading causes of disability worldwide, with prevalence and disability adjusted life years increasing steadily over the past three decades and accelerating after 2019 [1–3]. Nearly one in five individuals experience clinically significant depressive symptoms across the lifespan, with onset often occurring in childhood or adolescence [4–6]. These trends carry profound consequences for education, productivity, physical health, and health care systems, underscoring depression as a sustained and escalating global burden rather than a transient public health challenge [1,6,7] .

For much of the modern era, the monoamine hypothesis has provided a unifying framework for understanding depression and guiding antidepressant discovery [7–10]. By linking symptoms to deficiencies in serotonin, norepinephrine, and dopamine signaling, this model delivered conceptual

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clarity and enabled the development of multiple effective treatments [7–9] However, its clinical limitations have become increasingly apparent [7,8]. Many patients fail to achieve remission, a substantial proportion develop treatment-reistant depression, and relapse rates remain high even after apparent recovery [7,9,11] Therapeutic benefits typically emerge only after weeks of treatment, a delay that complicates acute care and is difficult to reconcile with the rapid pharmacological effects of monoaminergic drugs [7,8,11,12].

Compounding these challenges, depression is highly heterogeneous [7,11,13,14]. Genetic, transcriptomic, and neurobiological studies point to diverse alterations in immune signaling, synaptic plasticity, and network function across patient subgroups, arguing against a single deficit model [7] Together, these observations motivate a mechanistic expansion beyond neurotransmitter availability toward synaptic plasticity, intrinsic excitability, and circuit level regulation as core drivers of antidepressant response and discovery [7,10,11,13,15,16].

The discovery of ketamine marked a conceptual turning point in antidepressant research by demonstrating that depressive symptoms can improve within hours rather than weeks [17–19]. Unlike traditional agents, ketamine exerts its effects through glutamatergic modulation and rapid neuroplastic change, challenging the assumption that therapeutic benefit must arise from slow monoaminergic adaptation [17,20,21] By transiently inhibiting N-methyl-D-aspartate (NMDA) receptors on gamma-aminobutyric acid (GABA)-ergic interneurons, ketamine disinhibits cortical pyramidal neurons, triggers a surge in glutamate release, and enhances α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor throughput [19,20] This cascade rapidly engages brain-derived neurotrophic factor (BDNF) release and mechanistic target of rapamycin (mTOR) signaling, initiating synaptogenesis, dendritic spine formation, and restoration of synaptic strength within prefrontal and limbic circuits [21,22]. These structural and functional changes closely parallel behavioral improvement and can outlast the presence of the drug itself [17,19]

Subsequent work has reinforced this plasticity framework. Ketamine metabolites and enantiomers exhibit synaptogenic properties with distinct side-effect profiles, while downstream signaling pathways such as extracellular signal-regulated kinase (ERK) and metaplasticity mechanisms shape the persistence and scalability of plastic change [22,23]. Importantly, ketamine can restore homeostatic synaptic balance and normalize dopamine-dependent plasticity without disrupting learning-related potentiation, indicating broad circuit-level repair rather than nonspecific excitation [20]. These mechanisms stand in sharp contrast to monoaminergic antidepressants, which rely on chronic receptor engagement and gradual transcriptional remodeling with delayed and variable clinical outcomes [17] As a result, the field has shifted toward synaptic remodeling, intrinsic excitability, and plasticity consolidation as central therapeutic targets, redefining how antidepressant efficacy is conceptualized and pursued [10,17,19].

Intrinsic excitability describes a neuron's inherent tendency to fire action potentials in response to input, determined by its repertoire of voltage and ligand-gated ion channels rather than by changes in synaptic strength [24–26]. Unlike synaptic plasticity, which modifies the efficacy of connections between neurons, intrinsic excitability regulates neuronal gain and input–output transformations at the single cell level [24–26]. In prefrontal and hippocampal circuits, channels such as voltage-gated potassium channel subfamily Q (Kv7), hyperpolarization-activated cyclic nucleotide-gated channel (HCN), and G protein–gated inwardly rectifying potassium gated channel (GIRK; Kir3.x) serve as key determinants of firing probability and network stability [27–29]. Kv7 or M channels act as powerful brakes on depolarization, with their inhibition increasing pyramidal neuron excitability and their activation dampening gain. HCN channels shape resting conductance, resonance, and temporal integration, linking altered channel function to stress sensitivity and anhedonic phenotypes [27,28,30]. GIRK channels further stabilize membrane potential and constrain excitability, contributing to mood regulation and cognitive control [30,31].

Stress robustly engages these mechanisms [27–30] Chronic stress induces cell type specific shifts in intrinsic excitability within medial prefrontal and hippocampal neurons, biasing circuits toward vulnerability or resilience depending on channel composition and neuromodulatory state [25,26].

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These changes can occur independently of synaptic remodeling, yet powerfully influence circuit output and behavioral state [24,26]. Despite their central role in regulating mood relevant networks, intrinsic excitability mechanisms remain underexplored pharmacologically [30,31] With few exceptions, systematic targeting of Kv7, HCN, or GIRK channels in depression has lagged behind synaptic plasticity based approaches, representing a major and underdeveloped opportunity for antidepressant discovery [12,27,30,31].

This review advances a dual framework in which synaptic plasticity and intrinsic excitability jointly govern depressive pathophysiology and antidepressant response. Evidence from rapid-acting interventions demonstrates that restoring synaptic remodeling can rapidly realign network function from molecular signaling to behavior, with strong translational continuity from animal models to human studies [32–34], plasticity of synapses alone is insufficient [35,36]. Dynamic regulation of intrinsic excitability, through ion channel dependent control of neuronal gain and firing probability, acts in parallel to shape circuit output, resilience, and vulnerability [34,35]. Integrating these two dimensions strengthens mechanistic links to clinical phenomena, aligns biomarkers with target engagement, and sharpens translational inference. The purpose of this review is to identify new or underexploited molecular and cellular targets across both domains and to conceptualize antidepressant discovery around coordinated modulation of synaptic remodeling and intrinsic excitability as a unified strategy for faster and more durable therapeutic innovation.

2. Induction and Consolidation of Synaptic Plasticity

Synaptic plasticity comprises two interdependent phases: induction, in which patterns of neuronal activity rapidly alter synaptic efficacy, and consolidation, in which these initially labile changes are stabilized to support persistent circuit reorganization [37,38]. This distinction is particularly relevant to contemporary models of antidepressant action, which increasingly place adaptive plasticity, rather than monoaminergic correction alone, at the center of therapeutic response [39,40]. Within this framework, glutamate serves as the principal excitatory neurotransmitter and the primary molecular interface between acute cellular activation and longer-term synaptic remodeling [41,42]. However, glutamate-dependent induction represents only the opening stage of the process [41,43]. To yield sustained functional benefit, early activity-dependent changes must be captured and reinforced by downstream signaling systems that promote structural stabilization, transcriptional engagement, and de novo protein synthesis [37,44]. These events appear to unfold in a coordinated sequence. Glutamatergic signaling first initiates rapid synaptic potentiation and plasticity-related spine dynamics; tropomyosin receptor kinase B (TrkB) activation then supports the transition from transient potentiation to stabilized synaptic reinforcement; and translational control mechanisms determine whether these newly engaged synapses acquire the molecular substrates required for persistence [39,44]. Together, these interacting cascades provide a mechanistic framework for understanding how brief pharmacological perturbations can drive durable antidepressant effects. The following subsections examine this sequence in turn, focusing on glutamate-mediated plasticity drivers, TrkB-dependent consolidation mechanisms, and translational regulation through eukaryotic elongation factor 2 kinase (eEF2K)-related pathways.

2.1. Glutamate Plasticity Drivers

Ketamine marks a paradigm shift in antidepressant pharmacology by repositioning glutamatergic plasticity as the primary therapeutic mechanism rather than a downstream adaptation [19,45,46]. At subanesthetic doses, ketamine preferentially antagonizes N-methyl-D-aspartate receptors (NMDARs) on fast spiking GABAergic interneurons, releasing pyramidal neurons from inhibitory control [46–50]. The result is a brief but robust glutamate surge that drives enhanced α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) throughput and calcium influx, including through calcium permeable AMPA channels [19,46,51]. This AMPA dominated signaling window is the critical gate for rapid synaptic change [19,45,46]. Elevated postsynaptic activity triggers BDNF release and TrkB receptor activation, which in turn engages mechanistic target

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of rapamycin complex 1 (mTORC1) dependent translational programs supporting dendritic spine growth and synaptic strengthening [19,45,46,52,53]. In parallel, calcium/calmodulin-dependent protein kinase II (CaMKII) acts as a rapid activity sensor, coordinating phosphorylation events and structural stabilization at newly potentiated synapses. These cascades converge to produce long-term potentiation (LTP) like synaptic potentiation across corticolimbic circuits within hours, mirroring the temporal profile of ketamine's antidepressant effects [19,35,45]. Importantly, this mechanism reframes NMDAR antagonism as permissive rather than suppressive, with intact upstream NMDA signaling required to enable AMPA driven plasticity [19,48,49,54]. By inducing rapid, experience independent synaptic remodeling, ketamine redefines both the mechanism and timeline of antidepressant action [19,35,46]. Depression treatment shifts from slow neuromodulatory correction to active circuit reconfiguration, with BDNF, mTORC1, and CaMKII forming the molecular backbone of a plasticity first therapeutic model [19,45,51].

Esketamine and Dextromethorphan (DXM)-bupropion converge on glutamate driven plasticity but diverge in how they bias circuit entry and clinical expression [55–57]. Esketamine displays higher affinity for NMDARs, selectively suppressing NMDA signaling on GABAergic interneurons and triggering a rapid glutamate surge that enhances AMPA throughput and downstream BDNF-mTORC1-dependent synaptic potentiation [49–52,55,58,59]. Its pharmacodynamics are relatively focused, producing robust and fast plasticity at the cost of transient dissociation and sympathomimetic effects [51,58]. By contrast, DXM-bupropion operates through a broader multimodal profile. Weak NMDA antagonism is complemented by sigma 1 receptor activation and dopamine transporter inhibition, shaping excitability, stress resilience, and neurotrophic tone alongside glutamatergic mechanisms [60–62]. Clinically, esketamine nasal spray demonstrates rapid efficacy in treatment-resistant depression (TRD), with improvements emerging within hours to days and sustained by maintenance dosing [56]. Common adverse effects include dissociation, dizziness, and blood pressure (BP) elevation [55,56,58]. DXM-bupropion shows early and durable symptom reduction in phase 3 trials, including GEMINI (Global Evaluation of the Efficacy and Safety of AXS-05 [DXM–bupropion] in Major Depressive Disorder), with significant Montgomery–Åsberg Depression Rating Scale (MADRS) improvements and minimal psychotomimetic liability [58,63,64]. Its oral administration and milder side effect profile improve accessibility [55,65]. Mechanistic overlap lies in rapid plasticity induction, while divergence reflects dopaminergic and sigma mediated modulation in DXM bupropion versus the NMDA centric and dissociative signature of esketamine [55,57,66].

Preclinical studies converge on glutamate-driven plasticity as the immediate engine of rapid antidepressant effects [67–69]. In stressed rodents, ketamine rapidly restores dendritic spine density in the medial prefrontal cortex and hippocampus, reverses stress-induced dendritic atrophy, and normalizes synaptic protein expression [70–72]. Newly formed spines persist alongside sustained behavioral improvement, linking structural remodeling to durable antidepressant-like outcomes [73–75]. Spinogenesis can emerge within minutes, initiated by glutamate-dependent signaling that recruits dopamine D1 receptors in prefrontal pyramidal neurons, coupling early synaptic growth to rapid behavioral rescue [73–75]. A recurring molecular hub is BDNF–mTOR signaling: pharmacological inhibition of mTOR blocks spine formation and abolishes antidepressant-like effects, establishing a causal chain from molecular activation to synaptic morphology to behavior [50,67,70,76,77].

This plasticity program is not ketamine-specific [68,69,78]. Diverse agents that bias glutamatergic throughput, including cannabidiol (CBD), metabotropic glutamate receptor 2 and 3 (mGlu2/3) negative allosteric modulators, psilocybin, and AGN-241751 (4-chlorokynurenine [AV-101]), a positive modulator of the NMDAR glycine site, similarly enhance spine density and synaptic protein expression in prefrontal circuits, accompanied by rapid reductions in despair-like and anhedonic phenotypes [68,75,79]. These structural gains rebalance excitation and inhibition in the medial prefrontal cortex by increasing pyramidal neuron firing while relieving interneuron overactivity, improving network coordination and synchrony during cognitive and affective

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processing [70,79,80]. trophic manipulations further reinforce a shared pathway toward circuit stabilization and behavioral normalization [67,77,81,82].

Rapid glutamate targeting strategies deliver antidepressant effects that are often short lived [21,83,84]. Across clinical trials, ketamine and esketamine reliably produce rapid symptom relief, yet responses frequently decay within days to weeks, with high relapse rates following discontinuation [83–85]. Maintenance regimens extend benefit for some patients but only partially offset this erosion [84–86]. Dissociative and psychotomimetic effects are common, typically transient, and sometimes accompanied by cardiovascular changes [87–89]. The relationship between dissociation and therapeutic efficacy remains unresolved, complicating risk benefit assessments and limiting acceptability for many patients [87,90,91]. Longer term safety signals are still emerging, including concerns related to abuse liability, urinary symptoms, and cumulative neurocognitive effects with repeated exposure [84,88,92]. Mechanistic uncertainty further constrains translation. The relative roles of synaptic versus extrasynaptic NMDARs, interactions with parallel neurotransmitter systems, and optimal dose response relationships remain incompletely defined [19,45,66]. Clinical response is highly heterogeneous, and robust predictors are lacking, underscoring the need for biomarkers and stratified treatment strategies [87,93–95].

Next-generation glutamate therapies aim to preserve rapid antidepressant plasticity while minimizing dissociative and psychotomimetic effects [96,97]. One avenue centers on AMPAR facilitation [97–99]. Classical ampakines and newer agents such as TAK-653 and LT-102 enhance synaptic gain, strengthen BDNF signaling, and engage CaMKII, cyclic adenosine monophosphate (cAMP) response element–binding protein (CREB), protein kinase B (AKT), and mTOR pathways, producing antidepressant-like effects with favorable tolerability [98,100]. Related compounds, including tianeptine and selected iridoids, similarly promote AMPAR trafficking and mTOR-linked plasticity, supporting sustained circuit remodeling [97,99,101]. These approaches position AMPA throughput as a proximal and potentially safer driver of durable synaptic efficacy [98,99]. A complementary strategy involves partial NMDAR modulation [96,97]. Agents such as rapastinel and apimostinel act at the glycine site to facilitate long-term potentiation and restore pyramidal cell excitatory transmission without triggering glutamate surges or dissociation [102–104]. Their pharmacology supports intermittent dosing, improved safety margins, and potential cognitive benefits [102,104]. Combining AMPA facilitation with refined NMDA modulation may consolidate plasticity, extend remission, and improve real-world acceptability [55,96,97].

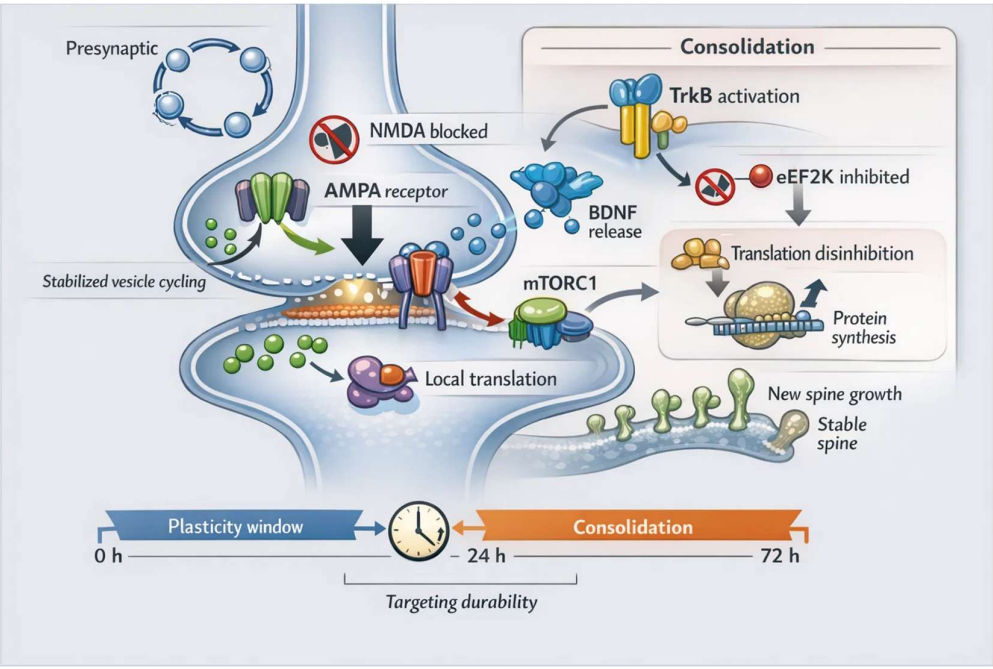

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Figure 1. Plasticity window and consolidation timeline: induction-to-stabilization logic of rapid-acting. This schematic frames rapid-acting antidepressant action as a **two-stage, time-locked process**. **Induction** begins when **NMDAR antagonism** (often via interneuron disinhibition) shifts cortical networks toward a transient glutamate surge and **increases AMPA throughput**, opening a brief **plasticity window** (minutes–hours). Within this window, **BDNF release** and **mTORC1 activation** promote rapid synaptic remodeling, including **new dendritic spine formation** and strengthening of excitatory synapses. Because these early changes are **labile**, durable benefit depends on **consolidation** (hours–days): **TrkB activation** acts as the molecular bridge from transient potentiation to stable circuit reweighting; **eEF2K inhibition** releases translational brakes to sustain local protein synthesis and spine maturation; and **SV2A-mediated stabilization of synaptic vesicle cycling** preserves presynaptic release fidelity. The key message is timing: adjunct interventions are most effective when delivered **within the consolidation phase**, converting fast symptom relief into **durable antidepressant responses**. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; eEF2K, eukaryotic elongation factor 2 kinase; mTORC1, mechanistic target of rapamycin complex 1; NMDA, N-methyl-D-aspartate; SV2A, synaptic vesicle glycoprotein 2A; TrkB, tropomyosin receptor kinase B.

2.2. TrkB PAMs / Direct Agonists

The BDNF–TrkB axis functions as a master regulator that converts transient plasticity into stable synaptic reinforcement [105–107]. At the level of individual spines, activity-dependent BDNF release activates TrkB in an autocrine loop that is essential for both structural and functional long-term potentiation [106,108,109] This signaling captures upstream NMDAR and CaMKII activity and stabilizes it locally, allowing newly formed or enlarged spines to persist beyond the induction phase [108–110]. Within microcircuits, TrkB signaling implements a refinement rule in which mature BDNF strengthens coactive synapses while precursor BDNF (proBDNF) weakens poorly correlated inputs, sharpening ensembles that encode shared activity patterns [106,111,112]. This balance is dynamically regulated by extracellular proteolytic conversion of proBDNF to mature BDNF during coordinated firing [106,111,112].

Local consolidation is coupled to long-range stabilization through TrkB signaling endosomes that traffic to the soma and engage CREB and mTOR-dependent transcription [107,110,113]. These programs align gene expression, dendritic protein synthesis, and cytoskeletal remodeling to support late-phase potentiation and network persistence [105,107,113]. Through coordinated control of spine stability, transcription, and local translation, TrkB provides the molecular bridge that locks labile plasticity into enduring circuit change [105,106,113].

Preclinical studies identify TrkB positive allosteric modulators as key stabilizers of ketamine-induced plasticity, converting a transient signal into a durable synaptic state [35,114,115]. Compounds such as LM22A-4 and 7,8-dihydroxyflavone (7,8-DHF) analogs prolong ketamine's behavioral efficacy by sustaining BDNF-TrkB engagement beyond the initial glutamate driven burst [114,116,117]. At the cellular level, TrkB activation captures early NMDAR-CaMKII dependent potentiation and consolidates it through late LTP programs [35,45,117]. These include local protein synthesis, actin cytoskeleton remodeling, and synaptic tagging processes that preserve elevated expression of activity-regulated cytoskeleton-associated protein (Arc) and other plasticity-related proteins [35,117]. Newly formed spines are not only generated but structurally stabilized, maintaining AMPAR enrichment and functional strength over days [45,78,118].

TrkB signaling further refines network architecture by stabilizing coactive synaptic clusters while pruning asynchronous inputs, sharpening ensembles initially recruited by ketamine [114,115]. Endosomal TrkB signaling propagates to the soma, engaging CREB and mTOR pathways that link dendritic demands to transcriptional output [78,117,119]. Across disease models, TrkB-positive allosteric modulators (PAMs) rescue spine density and preserve mature spine morphology, supporting a model in which TrkB modulation extends antidepressant like plasticity through sustained structural and proteomic reinforcement [35,114,116].

Clinical translation of TrkB targeting strategies aims to harness neurotrophic efficacy while bypassing the limitations of direct BDNF delivery [120–122]. Recombinant BDNF performs poorly in

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humans due to rapid degradation, limited brain penetration, and unstable exposure profiles [120,121,123]. Its inability to efficiently cross the blood-brain barrier (BBB) and the risk of off-target p75 neurotrophin receptor (p75NTR) activation further constrain therapeutic use [120,123,124]. Small molecule TrkB agonists and positive allosteric modulators provide a more tractable route [122,125,126]. Compounds derived from 7,8-DHF show oral bioavailability and central TrkB engagement, with prodrug formulations improving brain exposure and pharmacokinetics [125–127]. Optimized analogs demonstrate sustained signaling with acceptable safety during repeated dosing in preclinical models. Other candidates report high brain to plasma ratios, selective TrkB activation, and low peripheral toxicity, alongside improvements in synaptic structure and cognition [125,127]. Early pharmacokinetic and safety data suggest feasibility, though human data remain sparse [120,125,128]. Biologic approaches such as agonistic antibodies and peptide-based TrkB activators extend half-life and avoid p75NTR engagement but face delivery challenges [121,122,129]. Ongoing debate over target specificity highlights the need for rigorous validation and BBB informed medicinal chemistry [120–122].

Clinical translation of TrkB modulation faces three tightly coupled challenges. Receptor specificity remains the first bottleneck [130–132]. Many proposed small molecules show inconsistent TrkB engagement, partial agonism, or off-target activity across kinome and G protein–coupled receptor (GPCR) panels, with signaling outputs that only partially resemble endogenous BDNF [130–132]. This raises concerns about reproducibility, pathway bias, and unintended network effects [131,132]. A second issue is theoretical oncogenicity. Sustained TrkB activation enhances survival and growth signaling, and Trk family receptors are established oncogenic drivers when aberrantly engaged [133–135]. Chronic exposure could lower apoptotic thresholds or promote maladaptive persistence, arguing for dose ceilings, intermittent schedules, and careful long term surveillance [133–135]. Third, pharmacokinetics remains limiting. Many scaffolds suffer rapid clearance, metabolic instability, and uneven brain exposure [64,131,132]. Prodrug strategies help but durability and regional concentration remain difficult to control [136–138]. Despite these hurdles, prospects are improving [136–138]. Next generation TrkB-PAM scaffolds emphasize biased and bitopic allostery to [138]. Brain selective prodrugs, circuit-targeted delivery, and refined medicinal chemistry offer routes to safer and more precise neurotrophic reinforcement [136–138].

2.3. eEF2K Inhibitors

Translational control is a central driver of rapid synaptic plasticity, with eEF2K acting as a molecular brake on protein synthesis [139–141] Under resting conditions, eEF2K phosphorylates eEF2 and slows ribosomal elongation, constraining dendritic translation [139,140,142]. This restraint is maintained by tonic NMDAR signaling [139,141]. When NMDAR activity is reduced, as with ketamine or (2R,6R)-hydroxynorketamine (2R,6R-HNK), eEF2K activity falls, eEF2 becomes dephosphorylated, and translational inhibition is rapidly lifted [139,141,143]. Protein synthesis accelerates within minutes [140,141,143]. Among the earliest products is BDNF, which activates TrkB, promotes AMPAR recruitment, and strengthens excitatory synapses [139,143]. Experimental inhibition or genetic reduction of eEF2K mimics these effects, increasing synaptic efficacy and facilitating LTP [139,142,143] Electrophysiological signatures include larger miniature excitatory postsynaptic currents (EPSCs) and rapid AMPAR insertion [139,142,143]. Behavioral assays parallel these synaptic changes, showing fast antidepressant like responses across multiple paradigms [141–143]. Together, these findings position eEF2K as a critical link between NMDA antagonism, translational disinhibition, and rapid mood relevant plasticity.

Preclinical studies show that blocking eEF2K reproduces the core synaptic and behavioral effects of ketamine [144–146]. Acute pharmacologic or activity-dependent inhibition of eEF2K rapidly lifts elongation control, triggering a burst of dendritic protein synthesis [144–146]. This response prominently includes BDNF, which is required for downstream synaptic potentiation and antidepressant like behavior [76,144,146] At the synaptic level, eEF2K inhibition increases AMPAR-mediated miniature EPSC amplitudes and induces rapid synaptic scaling, closely matching the

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profile seen after ketamine or 2R,6R-HNK [144,147,148]. Electrophysiological recordings reveal strengthened hippocampal transmission, facilitated long term potentiation, and fast AMPAR insertion, all of which collapse under AMPA blockade [144,145,147]. Behavioral readouts align with these cellular effects [144–146]. Rodents show reduced immobility in forced swim and tail suspension tests, improved novelty suppressed feeding, and reversal of stress-induced anhedonia [144,145,149]. Disruption of BDNF signaling abolishes these gains, while direct eEF2K inhibition is sufficient to restore synaptic efficacy and produce rapid antidepressant-like outcomes [76,146].

eEF2K inhibition offers a distinctive advantage by extending plasticity without driving excitotoxicity [150–152]. Rather than increasing synapse number or global firing, it selectively scales AMPAR mediated currents, producing a controlled gain in synaptic efficacy [145,150,152,153]. This calibrated potentiation supports learning related plasticity while preserving network stability [150–152]. Preclinical models show restoration of LTP, improved memory, and elevated BDNF and synaptic proteins without evidence of neuronal injury or inflammatory activation [145,154]. Strengthening of inhibitory tone and increased seizure resistance further indicate a favorable excitation inhibition balance [151,153]. These properties make eEF2K an attractive adjunct to fast-acting glutamatergic antidepressants [145,152]. NMDA and AMPA modulators initiate rapid relief by triggering glutamate driven plasticity, yet their benefits often fade as translational programs normalize [145,150,155]. By sustaining protein synthesis downstream, eEF2K inhibition could stabilize newly potentiated synapses and extend antidepressant duration [145,154,156]. Combining AMPA centered drive with translational disinhibition offers a rational strategy to deepen and prolong circuit remodeling while limiting overexcitation, particularly in TRD [52,145,150,153].

A major gap remains the lack of clinical grade-eEF2K inhibitors. Despite consistent neuroprotective- and plasticity-enhancing effects across preclinical disease models, all available compounds remain experimental, with unresolved issues in kinase selectivity, brain exposure, and chronic tolerability [157–159]. Advancing the field requires rigorous safety and target engagement strategies, including quantitative phosphorylated eEF2 readouts, pharmacokinetic–pharmacodynamics (PK-PD)-guided dosing, and early toxicity profiling across mitochondrial, cardiac, and genotoxic domains [157,158,160,161]. Equally important is avoiding global disruption of protein synthesis while restoring adaptive translation [159,160]. Beyond chemistry, translational progress will depend on precision deployment [157–159]. eEF2K signaling intersects with excitation inhibition balance and circuit level plasticity, suggesting strong synergy with circuit specific interventions [157,158,162]. Combining eEF2K inhibition with neuromodulation, targeted NMDAR or AMPAR modulation, or timed cognitive training could stabilize translational homeostasis during defined plasticity windows [158,160]. Stratifying patients by circuit dysfunction and aligning drug exposure with network level engagement offers a rational path to clinical relevance and durable benefit [95,157–159].

Table 1. Emerging molecular targets that drive and consolidate synaptic plasticity for durable antidepressant effects. This table summarizes candidate molecular nodes spanning rapid glutamate-driven induction and subsequent consolidation of synaptic change. For each target, mechanisms are paired with representative preclinical support, current clinical translation maturity, tractable biomarkers, and key safety constraints relevant to long-term use. The rightmost column is intentionally left blank to insert study-specific citations during manuscript finalization.

Molecular target / lever	Mechanism in synaptic plasticity	Representative preclinical evidence	Clinical translation status	Associated biomarkers / assays	Major safety considerations	References
glutamate drivers (NMDA	Disinhibition and glutamate	Ketamine-like paradigms	Clinically established for rapid response	MRS Glx/GABA shifts;	Dissociation, BP elevation,	[163–165]

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antagonism, AMPA facilitation, partial NMDA modulation)	surge increase AMPA throughput, triggering rapid potentiation and opening a transient plasticity window that recruits BDNF-mTORC1 programs and structural remodeling.	restore spine density and excitatory/inhibitory balance in stress models, with rapid behavioral effects aligned to synaptic strengthening and network reorganization.	(ketamine/esketamine; DXM-bupropion). Next-generation agents (ampakines; glycine-site NMDA modulators such as rapastinel-class) aim to retain efficacy with improved tolerability.	EEG/MEG spectral markers (e.g., gamma, aperiodic slope); rs-fMRI connectivity changes; peripheral BDNF and downstream phospho-signaling panels.	abuse liability, nausea/sedation; risk of symptom rebound without consolidation support; vigilance for excessive excitation in susceptible circuits.	
TrkB (BDNF-TrkB agonists / positive allosteric modulators)	Acts as a consolidation gate: TrkB activation stabilizes nascent spines, couples local synaptic events to transcriptional programs, and promotes persistence of circuit reweighting after induction.	TrkB PAMs and direct agonist-like compounds (e.g., LM22A-4; 7,8-DHF analogs) prolong ketamine-associated molecular and behavioral signatures and support structural stabilization of new spines.	Primarily preclinical/early translational; limited clinically validated TrkB-targeting drugs in psychiatry. Positioned as an adjunct to extend duration and reduce relapse after induction therapies.	BDNF dynamics; pTrkB and downstream pERK/pAkt readouts in peripheral cells or experimental biopsies; PET/fMRI network integration metrics; task-evoked plasticity readouts (TMS-EEG).	Dose-dependent excitability shifts (seizure threshold concerns), off-target kinase effects, and theoretical proliferative signaling risks; need for selectivity, brain exposure control, and chronic dosing safety.	[166–168]
eEF2K (elongati	Inhibition reduces	Pharmacologic or genetic	Preclinical target with a	p-eEF2 to total eEF2	Potential for	[146,144,151]

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on checkpoint; translational disinhibition)	eEF2 phosphorylation, lifting a local translation brake to enable rapid synthesis of synaptic proteins (including BDNF-linked programs) that mature and consolidate newly potentiated synapses.	reduction of eEF2K increases BDNF translation, enhances AMPAR-mediated transmission, and yields rapid antidepressant-like behavioral effects with electrophysiological correlates.	bottleneck in druggability and selectivity; no widely adopted clinical candidates. Attractive as a timing-specific adjunct to extend plasticity benefits without broad excitotoxic drive.	ratios; proteomic signatures of synaptic translation; immediate early gene induction; electrophysiology (LTP facilitation) and spine maturation indices.	unintended global translation effects, metabolic stress responses, and interactions with seizure/epilepsy biology; careful windowed dosing and off-target profiling required.	
SV2A (vesicle cycling stabilization; synaptic density anchor)	Presynaptic stabilizer linking vesicle priming, calcium-coupled release, and terminal integrity; supports maintenance of neurotransmission fidelity after postsynaptic remodeling and limits relapse-like drift.	SV2A modulation preserves synaptic structure across stress and neurodegeneration-related models; levetiracetam-class engagement supports hippocampal and prefrontal circuit resilience after perturbation.	High clinical readiness via approved SV2A ligands (levetiracetam, brivaracetam) enabling repurposing studies; newer enhancers proposed for maintenance-phase adjunct use following induction therapies.	SV2A PET ligands (e.g., [11C]UCB-J; [18F]SynVesT-1/2) as synaptic density indices; longitudinal PET coupled to symptom trajectories; synaptic protein panels in CSF/extracellular vesicles.	Behavioral adverse effects in some patients (irritability, mood lability), sedation/fatigue; dosing window and long-term tolerability need alignment with plasticity-consolidation schedules.	[169–171]

7,8-DHF, 7,8-dihydroxyflavone; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; DXM, dextromethorphan; EEG,

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electroencephalography; eEF2, eukaryotic elongation factor 2; eEF2K, eukaryotic elongation factor 2 kinase; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; Glx, glutamate+glutamine; LTP, long-term potentiation; MEG, magnetoencephalography; mTORC1, mechanistic target of rapamycin complex 1; MRS, magnetic resonance spectroscopy; NMDA, N-methyl-D-aspartate receptor; pAkt, phosphorylated protein kinase B; pEEG2, phosphorylated eukaryotic elongation factor 2; pERK, phosphorylated extracellular signal-regulated kinase; PET, positron emission tomography; pTrkB, phosphorylated tropomyosin receptor kinase B; SV2A, synaptic vesicle glycoprotein 2A; TMS, transcranial magnetic stimulation.

3. Stabilizing Presynaptic and Network Integrity

Sustained antidepressant benefit hinges on more than exuberant spine growth. Plasticity-inducing agents ignite rapid postsynaptic remodeling in prefrontal and hippocampal circuits, yet long-term remission depends on stabilizing presynaptic release sites, preserving vesicle cycling, and maintaining faithful excitation–secretion coupling within intact networks [172–174]. Presynaptic mechanisms provide that ballast. Fast presynaptic inhibition curbs runaway excitation immediately after Hebbian strengthening, while active zone remodeling and a phospho-signaling hub expand and tune release capacity to consolidate gains over time [19,45,78]. Within this machinery, the vesicle protein SV2A emerges as a molecular anchor that organizes synaptotagmin-1 nanoclusters, supports endocytic retrieval, and enhances fusion efficiency downstream of calcium entry, thereby safeguarding neurotransmission fidelity under repetitive demand [172,173]. Vesicle supply is further sustained by rapid recruitment of releasable pools and by metabolic programs that tether mitochondria to fuel ATP-intensive cycling and calcium clearance during prolonged activity [19,78,161,172,175]. Crucially, SV2A can be visualized in vivo, positioning SV2A positron emission tomography (PET) as a presynaptic integrity biomarker alongside established dopaminergic imaging approaches and network-level readouts that forecast cognitive and clinical trajectories [176–178] The forthcoming sections dissect mechanistic roles of presynaptic stabilizers, synthesize preclinical evidence, appraise imaging biomarkers with clinical potential, and delineate gaps that presently limit translation [19,177,179].

3.1. Synaptic Vesicle Glycoprotein 2A (SV2A) Enhancers

SV2A is a core presynaptic regulator that coordinates vesicle priming, calcium dependent release, and neurotransmitter loading to ensure reliable synaptic transmission [180–182]. Localized to synaptic vesicles, it aligns vesicle readiness with calcium triggered fusion, shaping the efficiency and timing of exocytosis without altering presynaptic calcium entry itself [182–184]. A defining feature of SV2A is its tight coupling to synaptotagmin, the principal calcium sensor for release [185–187]. By binding synaptotagmin and regulating its endocytic retrieval, SV2A ensures accurate recycling and vesicular packaging of this sensor, a requirement for synchronous release and high fidelity signaling [187–189]. SV2A also stabilizes vesicle content and maintains the readily releasable pool, thereby tuning short term plasticity and sustaining output during repeated activity [181,182,190]. Beyond single synapses, SV2A expression scales with synaptic density across cortical and limbic networks and serves as a proxy for presynaptic integrity [169,191,192]. Its influence is particularly pronounced at inhibitory terminals, where it shapes GABA release and constrains network hyperexcitability [169,183,193]. During periods of heightened plasticity, SV2A nanoclusters with synaptotagmin support rapid vesicle recycling and preserve presynaptic identity as demand for precise excitation secretion coupling increases [185,188,189]. Through these convergent actions, SV2A functions as a molecular scaffold that stabilizes presynaptic terminals while postsynaptic strengthening consolidates [171,180,194]. This places SV2A at the center of synaptic resilience, linking vesicle dynamics to durable circuit integrity in health and disease [169,171,191].

Across models of stress, epilepsy, and neurodegeneration, modulation of SV2A preserves synaptic structure and maintains transmission after plasticity induction [169,171,195]. Levetiracetam restores vesicle fusion fidelity, rescues basal transmission, and normalizes synaptic protein composition, effects that depend on direct SV2A engagement and extend to hippocampal volume

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and plasticity recovery [169,171,195]. PET ligands confirm that SV2A density indexes synaptic integrity; ketamine appears to elevate SV2A where baseline is low, aligning structural rescue with symptomatic improvement and suggesting a convergence between plasticity inducers and presynaptic stabilizers [169]. Brivaracetam, with higher affinity and rapid brain entry, similarly occupies SV2A in vivo, supporting a target occupancy to protection relationship that generalizes across compounds and species [196–198]. These actions are not purely neuronal [199,200]. Both agents reduce pathologic astroglial glutamate release, supporting glutamatergic homeostasis during periods of heightened network demand [199,200].

Functionally, SV2A modulation limits the slide from induced plasticity to maladaptive remodeling and relapse-like behavior [171,195,201]. In stress-sensitized and developmental perturbation paradigms, levetiracetam reverses anxiety-like, cognitive, and social deficits while rebalancing hippocampal and mesolimbic activity, consistent with network-level stabilization of prefrontal–hippocampal circuits [171,195]. After ketamine or other plasticity-promoting interventions, preserving vesicle cycling and maintaining a competent readily releasable pool appear crucial for sustaining gains; animal studies link antidepressant durability to synaptic integrity supported by SV2A pathways and complementary signaling through ERK and calcium channels [195,197,201]. Together, these data position SV2A as a presynaptic gatekeeper that consolidates structural and functional benefits after plasticity induction, mitigating synaptic loss and reducing behavioral recurrence across disease-relevant contexts [171,195,197].

PET targeting SV2A has matured into a practical readout of synaptic density in vivo, with carbon-11 (^{11}C) and fluorine-18 (^{18}F) ligands enabling cross-species translation [202–204]. [^{11}C]UCB-J established high brain uptake and specificity, creating the benchmark for human and preclinical studies, while [^{18}F]SynVesT-1 and [^{18}F]SynVesT-2 extend accessibility through longer half-life, favorable kinetics, and validated simplified quantification protocols suited to clinical workflows [170,204,205]. In rodents and nonhuman primates, these tracers map regional SV2A with reliability and support longitudinal designs, including occupancy and therapeutic challenge paradigms [205,206].

Across disorders, SV2A PET consistently reveals synaptic loss [206–208]. Depression cohorts show lower binding with evidence that pharmacologic challenges can probe synaptogenesis in vivo [208,209]. In Alzheimer's disease, widespread reductions, particularly in hippocampus and association cortex, correlate with cognitive impairment and track amyloid/tau/neurodegeneration (A/T/N) pathology; similar decreases emerge in Parkinsonian and other neurodegenerative conditions, underscoring presynaptic vulnerability across networks [202,207,210–212]. As a translational biomarker, SV2A PET is well-positioned to monitor antidepressant-induced synaptic restoration [209,212–214]. Proof-of-concept data demonstrate partial recovery after fluoxetine in a depression model, and early work suggests ketamine may normalize low-baseline SV2A signal, linking circuit plasticity to presynaptic stabilization [163,213,214]. Together, these advances support SV2A PET as an integrative tool for diagnosis, progression tracking, and therapeutic monitoring across neuropsychiatric disease [14,202,203,207].

Levetiracetam analogs and newer SV2A enhancers are attractive maintenance-phase adjuncts because they directly stabilize presynaptic function after induction therapies [171,195,201]. Brivaracetam provides higher SV2A affinity, faster brain entry, and robust target occupancy, attributes that may consolidate network gains established by agents such as ketamine and reduce relapse risk through sustained vesicle cycling competence and dampening of pathological glutamate release [171,196,197,215]. Padsevonil and related ligands extend this pharmacology with optimized SV2A engagement and limited drug interaction profiles, positioning the class for chronic adjunctive use where synaptic resilience and clean tolerability are essential [171,215,216]. Preclinical and translational data also indicate that levetiracetam normalizes vesicle fusion and curbs amyloidogenic stress, with mitochondrial SV2A contributions to cognitive preservation, suggesting presynaptic and metabolic protection during maintenance [161,175,217–219].

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Clinically, both levetiracetam and brivaracetam have favorable safety, simple kinetics, and flexible dosing that support long-term administration [220,221]. Brivaracetam may show improved behavioral tolerability in some patients, and switching within the class is feasible when adverse effects emerge, enabling continuity of presynaptic stabilization [215,221]. PET studies verify dose-dependent SV2A occupancy at therapeutic levels, offering a pharmacodynamic bridge to personalized maintenance strategies and trial designs that couple synaptic target engagement with network connectivity metrics [196]. Conceptually, SV2A enhancers complement plasticity modulators by securing the presynaptic substrate needed to translate spine growth into durable circuit performance, a metaplasticity framework that aims to extend remission and minimize recurrence across neuropsychiatric disorders [201,222,223].

Progress will hinge on next-generation SV2A modulators that potentiate presynaptic function without distorting vesicle recruitment, priming, or endocytic sorting [185,188,224]. Current ligands confirm druggability, yet specificity remains blunt at the level of vesicle dynamics, raising concerns about activity-dependent depression, altered release probability, and unintended network dampening during chronic use [185,188,224]. Medicinal chemistry should prioritize bias for physiological coupling with synaptotagmin pathways, sparing mechanisms that constrain the readily releasable pool [188,225,226]. Parallel pharmacology needs rigorous off-target screens and in vivo assays that capture high-frequency transmission and metabolic resilience across cortical and limbic circuits [188,227,228].

Key design questions are unresolved. What dosing windows best stabilize presynaptic fidelity after induction therapies, and do these windows shift with age, hormonal state, or comorbidity? [229–231]. Sex differences in pharmacokinetics and plasticity trajectories remain largely unmapped, despite evidence that network biomarkers and treatment prediction are sensitive to demographic and biological heterogeneity [95,229–231]. Longitudinal SV2A PET is poised to answer these gaps, but validation demands harmonized kinetic modeling, test–retest data across centers, and standardized reference strategies from mouse to human cohorts [202,211,232,233]. The field should converge on multimodal trials that combine SV2A-targeted maintenance with plasticity inducers, while tracking synaptic density, dynamic connectivity, and behavioral endpoints to build durable, relapse-resistant network resilience [202,228].

4. Intrinsic Excitability Tuning (Gain Control)

Intrinsic excitability refers to the non-synaptic control of how neurons translate inputs into spikes, operating alongside synaptic plasticity to set firing probability, temporal precision, and network gain [234–236]. By tuning voltage- and ligand-gated conductances, excitability plasticity can recruit or exclude cells from active ensembles, stabilize population activity after learning, and shape the robustness of mood-relevant circuits in prefrontal, hippocampal, and mesolimbic networks [234,235,237]. In this context, three modulatory systems emerge as central governors of neuronal tone and promising antidepressant targets. Kv7 channels provide a non-inactivating outward current that restrains repetitive firing and supports gamma-rhythmic coordination; pharmacological inhibition or enhancement shifts excitability and cognitive performance with clear translational leverage [235,238,239]. HCN channels, through hyperpolarization-activated current (Ih), set resting membrane potential and dendritic integration; their trafficking and microdomain targeting regulate affective behavior, with selective modulation yielding antidepressant-like effects while sparing cardiac liabilities [234,236,239]. GIRK channels dampen excitability downstream of G protein signaling (RGS); their partial inhibition elevates firing and produces antidepressant-like actions, highlighting a therapeutically tractable brake on network activity [36,240,241]. The section proceeds from mechanistic principles to translation. I first outline how Kv7, HCN, and GIRK currents gate excitability and co-regulate with synaptic scaling. This section then synthesizes preclinical evidence across stress and antidepressant models, before surveying emerging clinical probes and candidate modulators. Finally, dosing and safety considerations are mapped to inform integrative strategies for durable circuit resilience.

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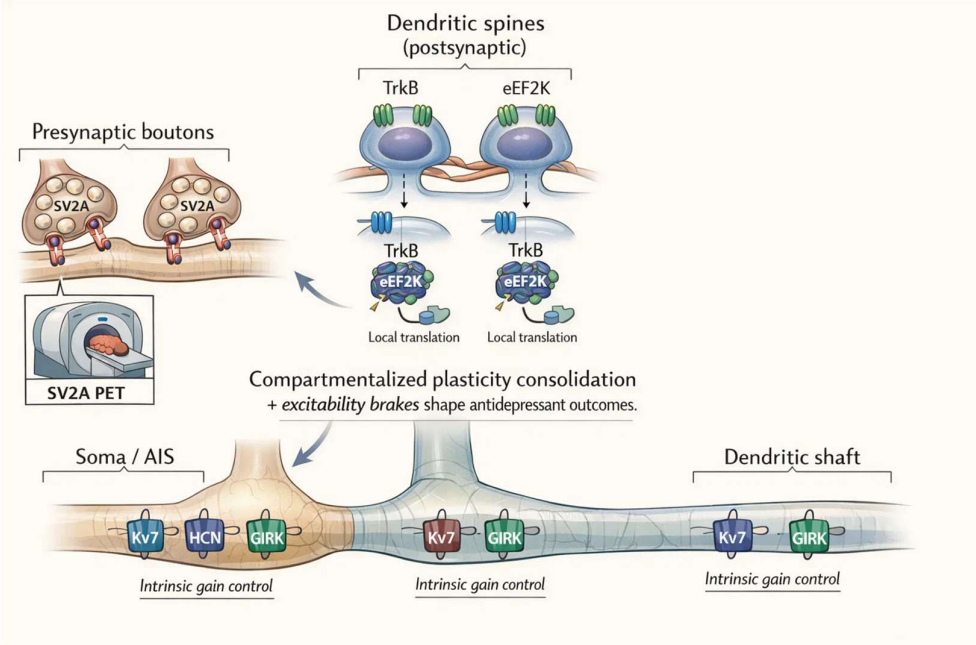

Figure 2. Target map on a cortical pyramidal neuron: compartmentalized plasticity consolidation and intrinsic gain control. Cartoon schematic of a cortical pyramidal neuron highlighting **where** key antidepressant-relevant targets act along the synapse-to-spike axis. **Postsynaptically**, **TrkB** is positioned at dendritic spines as a consolidation "gate" linking transient potentiation to stable spine maturation, while **eEF2K** is shown within the spine cytosol as a local **translation checkpoint** whose inhibition releases a brake on protein synthesis that supports strengthening and persistence of remodeled synapses. **Presynaptically**, **SV2A** is mapped to vesicle-rich boutons as a stabilizer of vesicle cycling and release fidelity, conceptually anchoring maintenance of neurotransmission after synaptogenic induction and aligning with SV2A PET as a translational readout of synaptic density. **Intrinsic excitability modulators** (**Kv7, HCN, GIRK**) are distributed over soma and dendrites to emphasize gain control—ion-channel "brakes" that restrain bursting, tune dendritic integration/resonance, and prevent relapse-prone hyperexcitability during and after plasticity engagement. eEF2K, eukaryotic elongation factor 2 kinase; GIRK, G protein-gated inwardly rectifying potassium channel; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; Kv7, voltage-gated potassium channel subfamily Q; PET, positron emission tomography; SV2A, synaptic vesicle glycoprotein 2A; TrkB, tropomyosin receptor kinase B.

4.1. Voltage-Gated Potassium Channel Subfamily Q (Kv7) Openers

Kv7 channels formed by potassium voltage-gated channel subfamily Q member 2–5 (KCNQ2–5) subunits generate the M-current (muscarinic-sensitive potassium current), a non-inactivating conductance that opens near resting membrane potential, stabilizes membrane potential, and raises the threshold for spike initiation [242–244]. By providing a steady outward conductance at the axon initial segment, these channels curb afterdepolarizations and limit high-frequency firing; loss of function or reduced membrane targeting disrupts this brake and promotes pathological bursting with cognitive and seizure phenotypes [239,244,245]. Molecular studies show that phosphatidylinositol-4,5-bisphosphate and small-molecule openers such as retigabine bias the pore toward the open state, offering a structural rationale for pharmacologic control of excitability [242]. Conversely, closure via Gq-coupled receptor pathways or direct blockers like paroxetine and linopirdine depolarizes neurons and increases release probability, a double-edged mechanism that can enhance cognition yet risk hyperexcitability when unchecked [241–243].

Within prefrontal and limbic circuits, Kv7 activity normalizes neuronal gain and suppresses stress-evoked firing escalation that impairs working memory and mood regulation [238,246,247]. In rodent cortex and hippocampus, openers reduce burst propensity, rescue hyperexcitability and

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seizure-related mortality, and limit excitotoxic injury after traumatic brain insult, underscoring disease-modifying potential [239]. Together, these data position Kv7 channels as nodal determinants of intrinsic excitability whose activation stabilizes network dynamics and protects mood-relevant circuits from maladaptive bursting [244,245,247].

Kv7 openers consistently dampen hyperexcitability, promote stress resilience, and stabilize affective behavior across rodent paradigms. Retigabine and related ligands shift channel activation toward more negative potentials, increase resting conductance, and suppress burst firing, which translates into robust antidepressant-like and mood-stabilizing effects after chronic social defeat and other stressors [241,248,249]. In the ventral hippocampus and ventral tegmental area (VTA), pharmacologic activation or genetic upregulation of potassium voltage-gated channel subfamily Q member 2 (Kcnq2) normalizes pathological firing and restores social interaction and anhedonia metrics; adjunct retigabine amplifies ketamine's sustained benefits, linking intrinsic excitability control to durable antidepressant action [241,249,250]. Pan-selective Kv7 openers such as Lu AA41178, a brain-penetrant Kv7.2–Kv7.5 potassium channel activator, extend these findings, reducing depressive-like behavior while elevating seizure thresholds without major off-target liabilities, suggesting a favorable translatability profile for network stabilization [251,252].

Prevention of relapse aligns with neuroprotection. The Kv7 potassium channel enhancer QO-83, a small-molecule KCNQ/Kv7 channel opener, limits infarct volume, edema, and cognitive decline after ischemic injury while curbing microglial activation, pointing to attenuation of excitotoxic cascades that often follow stress or drug withdrawal [248,251–253]. Notably, agents that inhibit Kv7, including paroxetine at relevant concentrations, increase excitability and could heighten vulnerability to rebound hyperexcitability when plasticity inducers are tapered, underscoring the mechanistic rationale for Kv7-guided maintenance strategies [243,244,254]. Converging data across serotonergic, hippocampal, and mesolimbic nodes further indicate anxiolytic actions of Kv7 activation, consolidating a preclinical case for mood stabilization and relapse prevention through targeted M-current augmentation [241,243,249].

Human data with Kv7 openers such as retigabine and ezogabine provide an early clinical window into intrinsic excitability modulation as a mood-stabilizing strategy. In major depressive disorder with prominent anhedonia, ezogabine produced meaningful reductions in depressive symptoms and improved reward sensitivity in randomized and open-label studies, with parallel changes in ventral striatal connectivity and reward learning [255–257]. These observations align with preclinical evidence that Kv7 activation restores resilience in stress-sensitized networks and dampens pathological hyperexcitability, suggesting particular relevance for patients with affective lability, dysphoric agitation, or anxiety-driven reward blunting [249,257,258]. Beyond mood, ezogabine reduces cortical and spinal motor neuron excitability in amyotrophic lateral sclerosis and decreases seizure frequency in refractory epilepsy, demonstrating target engagement in human hyperexcitable states and supporting its transdiagnostic potential to quiet unstable circuits [252,258,259].

Clinical translation is not without friction. Chronic ezogabine is associated with dose dependent dizziness, somnolence, confusion, urinary retention, and, most notably, blue or purple pigmentation of retina, nails, and skin due to drug and metabolite accumulation in melanin rich tissues [249,254,258]. These liabilities, along with the need for urologic and ophthalmologic monitoring, ultimately limited widespread use. Still, the pharmacology remains compelling. Retigabine and newer derivatives can attenuate negative affect, reduce anxiety like states, and suppress maladaptive reward seeking, including cocaine self-administration, while supporting longer term stabilization of excitability [250,257,260]. This positions Kv7 openers, or next generation photostable, better tolerated analogs, as rational adjuncts for relapse prone, labile mood subtypes rather than broad first line antidepressants [250,255,257].

Next-generation Kv7 modulators are converging on greater selectivity, cleaner safety, and circuit-aware deployment. Structure-guided chemistry and in silico design have produced Kv7.2/7.3-biased agonists with order-of-magnitude potency gains over retigabine, improved pharmacokinetics, and reduced liabilities linked to earlier chemotypes [261–263]. Brain-penetrant exemplars such as Lu

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AA41178 and SCR2682, pan-Kv7 (KCNQ2–5) potassium-channel activators, demonstrate broad antiexcitability efficacy without major off-target activity, while clinical candidates including azetukalner and BHV-7000, Kv7.2/7.3-selective channel activators, aim to retain efficacy while avoiding pigmentation and urinary liabilities associated with earlier chemotypes [239,258,263]. Subtype control is now tractable: minimal substitutions can invert activity across isoforms, enabling selective activation of Kv7.2/7.3 over Kv7.4/7.5 and allowing circuit-tailored effects [239,262,264]. Natural-product leads like echinocystic acid and endogenous modulators such as dehydroepiandrosterone sulfate (DHEAS) expand chemotype space and suggest allosteric stabilization strategies that preserve physiological gating [263,265].

Therapeutically, combinatorial approaches should pair Kv7 openers with plasticity inducers to convert rapid symptom relief into durable remission. Targeted Kv7 activation can stabilize VTA–nucleus accumbens (NAc) and prefrontal ensembles after induction, limit rebound hyperexcitability, and extend benefit windows; dual-target constructs that couple Kv7.2/7.3 agonism with transient receptor potential vanilloid 1 (TRPV1) inhibition offer further resilience without added side effects [239,250,266]. Rational sequencing with synaptogenic agents and circuit-specific delivery will be central to translation [258,261,263].

4.2. Hyperpolarization-Activated Cyclic Nucleotide-Gated (HCN) Channel Modulators

HCN channels open with membrane hyperpolarization to conduct the mixed cation current Ih, a slowly activating inward flux that depolarizes dendrites, lowers input resistance, and tightens the temporal window for integration [267,268]. Enrichment of HCN channels in distal apical tufts equips pyramidal neurons with band-pass properties, so inputs near theta and low beta frequencies are preferentially transmitted while slower components are shunted [269–271]. This resonance is not hard-wired [267,268,272]. Ih is tuned by cAMP and the auxiliary subunit tetratricopeptide repeat–containing Rab8b-interacting protein (TRIP8b), and it cooperates with inwardly rectifying potassium channel subfamily 2 (Kir2) and M-type K^+ conductances to set effective gain [272–274]. At the network level, hyperpolarization-activated cyclic nucleotide–gated channel 4 (HCN4) sustains thalamocortical rhythms that scaffold cortical timing, linking molecular gating to mesoscale oscillations [268,273,275]. Depending on dendritic location and partner channels, Ih can either dampen or sharpen excitatory postsynaptic potentials (EPSPs), yielding a context-dependent balance of excitatory and inhibitory effects that stabilizes activity yet preserves rapid responsiveness [269,270,276]. Together, these mechanisms establish oscillatory gain control from single dendrites to distributed circuits [267,268].

In prefrontal cortex, hyperpolarization-activated cyclic nucleotide–gated channel 1 (HCN1)-driven Ih stabilizes intrinsic persistent firing and supports working memory by maintaining depolarized up-states and filtering distractors within resonant frequency bands [271,273,277]. Developmental increases of Ih in pyramidal neurons, along with cell-type specific regulation by synaptic plasticity and fragile X mental retardation protein (FMRP), refine this gain control and may delineate windows of vulnerability to cognitive dysfunction [273,274,277]. Computational and experimental studies in layer V show that Ih facilitates proximal inputs while constraining distal summation, thereby shaping how rhythmic afferents from limbic and thalamic sources influence cortical excitability [269,270,276]. Through this bidirectional, location-sensitive control, Ih tunes the impact of oscillatory drive on mnemonic maintenance and modulates emotional tone by gating limbic–prefrontal coupling [271,277]. Dysregulated HCN signaling alters resonance and timing, contributing to network states linked to mood and executive symptoms, whereas targeted modulation promises restoration of frequency-specific gain without sacrificing the dynamical flexibility essential for adaptive cognition [268,273].

Across preclinical systems, convergent evidence indicates that tempering Ih via partial HCN downregulation can normalize large-scale dynamics associated with perseverative self-focus [278–280]. Causal manipulations that attenuate default-mode drive reduce its pathological coupling: optogenetic silencing of the lateral habenula diminishes default mode network (DMN)

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hyperconnectivity in a depression model, while chemogenetic suppression of anterior cingulate cortex reconfigures DMN edges and improves behavior aligned with reduced rumination liability [280–282]. Molecular levers point the same way [163,279,283]. In post-stroke mice, hippocampal HCN1 inhibition lowers Ih, suppresses NOD-, LRR-, and pyrin domain–containing protein 3 (NLRP3) signaling, and ameliorates depression- and anxiety-like phenotypes; chronic hippocampal cAMP elevation similarly reduces HCN surface expression and rescues stress-induced cognitive deficits, consistent with a network shift away from internally oriented attractor states [278,279,283]. A brain-penetrant HCN blocker produces antidepressant-like effects, supporting target validity while underscoring the need for dose-limited, partial modulation [279,284].

Region and circuit specificity remain pivotal [279,284,285]. HCN1 upregulation in lateral habenula drives anxiety during morphine withdrawal, and its inhibition or knockdown reduces this burden [285]. By contrast, antagonizing HCN channels in ventral tegmental dopamine neurons or blocking HCN in basolateral amygdala prolongs inhibition and heightens anxiety, cautioning against indiscriminate blockade [279,284]. Network-level corroboration comes from white-matter disruption of forceps minor that perturbs DMN connectivity, increases anxiety, and normalizes with recovery, linking DMN integrity to affective behavior and strengthening the translational rationale for calibrated HCN modulation to curb rumination-like and anxiety-related outcomes [280,281].

Translational signals point to a tractable phenotype defined by cognitive inertia and slowed affective transitions, in which HCN-driven gain is a modifiable bottleneck [286,287]. Clinically, dorsolateral prefrontal transcranial direct current stimulation (tDCS) yields the largest benefits in patients with psychomotor retardation and executive disturbance, and meta-analytic datasets suggest comparable efficacy to several standard treatments when dose and resistance are considered, with emerging hints of cognitive improvement alongside mood change [286]. These responders likely benefit from rebalancing large-scale networks in which Ih tunes prefrontal resonance and thalamo-hippocampal drive [287,288]. Converging preclinical work strengthens the mechanistic bridge: chronic stress elevates HCN1 and Ih in dorsal Cornu Ammonis area 1 (CA1), reducing excitability and producing depressive behaviors, while lowering HCN surface expression via cAMP signaling or direct HCN1 inhibition rescues stress-related cognitive deficits and post-stroke affective slowing [285,288,289]. Medicinal chemistry efforts now pursue brain-biased ligands and TRIP8b-guided strategies to avoid cardiac liabilities, and first-generation brain-penetrant HCN inhibitors reverse social and cognitive susceptibility in mice [279,290,291]. In parallel, circuit-level interventions such as tDCS, and potentially deep brain stimulation (DBS) targeting medial prefrontal–subgenual loops, offer complementary leverage over HCN-sensitive pathways [286,287].

Current pharmacology still lacks truly isoform-selective HCN modulators, which constrains both inference and dosing [292,293]. Canonical blockers such as ivabradine, a clinically approved HCN channel inhibitor, and ZD7288, a widely used experimental HCN channel blocker, bind within the HCN1 pore with modest affinity and broad cross-reactivity, while many “isoform-preferring” tools have incomplete pharmacokinetic and off-target profiling, resulting in narrow therapeutic windows and variable central effects [273,294]. Structural and biophysical advances point to a path forward. High-resolution conductance measurements across homomeric and heteromeric channels, coupled with emerging cyclic nucleotide–binding domain (CNBD)-focused screening platforms and auxiliary-subunit aware design, provide blueprints for subtype and state selectivity that remain to be realized in vivo [295,296]. Until such agents mature, trials need mechanistic readouts that scale from rodents to humans [287]. Electroencephalography (EEG) offers direct indices of Ih-linked resonance, including theta coherence, right frontal theta during control, and slow-wave power during sleep; seizure-model signatures and threshold-tracking paradigms add sensitivity to network instability [287]. Complementary functional magnetic resonance imaging (fMRI) metrics, particularly resting-state DMN coupling and task-evoked deactivation, can register circuit-level normalization. Integrating these EEG–fMRI biomarkers into early-phase studies will de-risk development and anchor dose selection to HCN biology [287].

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4.3. G protein–Gated Inwardly Rectifying Potassium Gated Channel (GIRK) Openers

GIRK channels are G protein–gated inwardly rectifying potassium conductances that convert inhibitory GPCR signaling into membrane hyperpolarization and reduced input resistance [297–299]. At pyramidal cell dendrites and somata, activation by gamma-aminobutyric acid type B (GABA_B) and 5-hydroxytryptamine receptor 1A (5-HT$_1$A) receptors releases G protein βγ (Gβγ) to open inwardly rectifying potassium channel subfamily 3 (Kir3.x) pores, lowering excitability and truncating EPSP duration, while preserving temporal precision of synaptic drive [297–299]. The resulting outward K^+ flux restores baseline tone during sustained neuromodulatory input and prevents runaway firing during high synaptic load [298,300,301]. Mechanistically, signaling gain and kinetics are sculpted by regulator of RGS proteins of the R7 family, which accelerate guanosine triphosphatase (GTPase) activity and impose receptor selectivity, by co-activation of convergent inhibitory GPCRs that sum on GIRK, and by intracellular Na^+ that boosts GIRK2 gating during bursts [297,302,303]. Channel activity is further tuned by redox state and direct lipid or small molecule interactions [298,302] Pharmacology underscores tractability: a GIRK1-selective opener and other direct activators hyperpolarize hippocampal pyramidal neurons and reduce seizure susceptibility, and photoswitchable openers provide millisecond control of inhibitory tone for circuit dissection and therapeutic prototyping [297,301,304].

By reinstating a K^+-dependent safety brake, GIRK channels rebalance hyperactive pyramidal ensembles and dampen circuit noise that degrades computation [300,301]. Increasing GIRK conductance lowers variance of subthreshold fluctuations, suppresses spontaneous bursting, and raises the signal-to-noise ratio for behaviorally relevant inputs. In hippocampal and cortical circuits, GIRK-dependent inhibition supports forms of plasticity that require stable excitability set points, and selective perturbation of GIRK activity in CA1 pyramidal neurons disrupts learning, highlighting its role in cognitive control [300,301,305]. When inhibitory reserve is compromised, as in early amyloid-β pathology or disease states with GIRK2 mislocalization, pyramidal hyperexcitability and oscillatory instability emerge; restoring GIRK function counters these phenotypes and normalizes inhibitory long-term plasticity [306–308]. Emerging therapeutics that enhance GIRK opening therefore offer a principled route to quiet pathological activity without silencing computation [297,301,309]. In concert with endogenous GABA_B and 5-HT$_1$A signaling, and aided by domain-targeted modulators, GIRK channels provide a tunable lever for homeostatic gain control across limbic and associative networks [298,300].

Pharmacological activation of GIRK channels delivers a coherent anti-agitation profile by lowering pyramidal cell gain and stabilizing limbic rhythms [301,310]. Selective GIRK1/2 channel openers, including ML297, a prototype small-molecule GIRK1/2 activator, and GAT1508, a next-generation brain-penetrant GIRK1/2 modulator, hyperpolarize principal neurons, reduce avoidance and anxiety-like behaviors, and facilitate extinction of conditioned fear without motor or cardiac liabilities, consistent with strengthened stress resilience and cleaner signal transmission through amygdalo-hippocampal pathways [310,311]. Direct GIRK agonists that bypass receptors, including GIRK agonist 1 (GiGA1), a direct GIRK channel activator, suppress seizure severity and agitation by curbing network hyperexcitability, while chemogenetic evidence confirms that GIRK conductances mediate GPCR-driven reductions in excitability in striatal circuits [312,313]. In prefrontal cortex, stress weakens GIRK1 signaling and impairs cognitive flexibility; restoring GIRK tone with ML297 rescues performance, positioning GIRK activation as a mechanistic counterweight to stress-sensitized noise in associative networks [314,315].

Sleep stabilization emerges as a complementary benefit. ML297 increases non–rapid eye movement (NREM) time, reduces wakefulness, and mimics GABA_B-linked sleep regulation, while brain-biased GIRK modulators similarly promote NREM in rodent models [301,316]. At the pacemaker level, GIRK2 is required for melatonin's suppression of suprachiasmatic activity and for circadian phase shifts, anchoring a causal link between GIRK opening, decreased arousal, and normalized sleep–wake architecture [317]. Balanced activation remains essential, as excessive GIRK

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drive can perturb plasticity; nevertheless, calibrated GIRK enhancement reliably dampens limbic excitability and supports restorative sleep states in preclinical systems [300,318].

Converging clinical and translational evidence positions GIRK channel facilitation as a rational strategy for depressive phenotypes marked by agitation, suicidality risk, and insomnia [301,319]. By converting inhibitory GPCR signals into stabilizing potassium currents, GIRK modulators can quiet hyperactive cortical–limbic ensembles while preserving information throughput, an effect profile that differs from global central nervous system (CNS) suppressants [301,319]. Early small-molecule openers illustrate this promise in preclinical anxiety and seizure models, suggesting that region- and subunit-selective targeting could attenuate arousal and irritability without cognitive blunting or abuse liability, a key consideration for agitated depression and mixed presentations [311,319]. In parallel, clinical trials link sleep restoration to reductions in suicidal ideation, indicating that normalizing nocturnal physiology is not merely symptomatic relief but a pathway to risk mitigation [320–322]. Pharmacologic hypnotics can reduce ideation in severe insomnia when carefully deployed, yet their complex risk profile argues for circuit-tuned alternatives [320,321]. Brief behavioral insomnia therapies likewise improve sleep and mood in suicidal patients, supporting a stepped approach in which GIRK-guided, sedative-yet-non-suppressive modulation complements sleep-focused interventions to stabilize affect and lower acute risk [320,322,323].

Progress is constrained by a thin toolbox. Most GIRK activators show modest subtype resolution, incomplete coverage of heterotetramers, and uneven brain exposure, which complicates dose selection and inflates off-target risk [297] Even exemplars illustrate the gap: ML297 favors GIRK1-containing channels but only partially discriminates subunit context and exhibits suboptimal CNS penetration; newer scaffolds such as GAT1508, VU0810464, a neuronal-biased GIRK channel opener, and VU0529331, a next-generation GIRK activator, improve neuronal bias yet still face selectivity and pharmacokinetic liabilities [297]. Structure-guided discovery is beginning to change the landscape. Cryo-EM views of PIP_2 regulation, G protein family interfaces, and femtomolar-scale conductance features now inform SAR and virtual screening, enabling identification of GIRK1-preferring activators like GiGA1 and rare isoform-specific tools such as. Nevertheless, BBB constraints remain a central translational hurdle [124]

A practical pipeline should braid high-resolution modeling with medicinal chemistry for allosteric pockets that encode state and subunit selectivity, then validate across heteromeric compositions and red-flag panels [312]. Parallel work must incorporate brain-relevant permeability screens and predictive BBB models early, rather than late rescue. Circuit precision will also matter: chemogenetic or ligand-directed delivery can focus GIRK enhancement to limbic and prefrontal ensembles that drive agitation and sleep disruption while sparing brainstem and cardiac populations [297] Finally, assay batteries should pair ion-channel pharmacology with translational readouts, including EEG markers of network stability and fMRI connectivity metrics, to anchor mechanistic engagement before large trials [297].

Table 2. Excitability modulators and their translational potential: phenotype-linked gain-control targets (Kv7, HCN, GIRK) with biomarker-guided paths to clinic. Comparative overview of intrinsic excitability targets positioned along the synapse-to-spike axis. Kv7 openers lower firing gain and suppress stress-linked bursting, aligning with anxiety/affective-lability phenotypes. HCN modulation tunes Ih-dependent dendritic resonance and default-mode engagement, linking to rumination and cognitive inertia. GIRK activation reinstates GPCR-coupled inhibitory tone to reduce agitation, sleep disruption, and circuit noise. Across channels, translational readiness is strengthened by stratification using EEG spectral slope (E/I balance), rACC theta, and rs-fMRI connectivity (PFC–limbic/DMN coupling), enabling adaptive dosing and sequencing.

Channel target /	Representative modulators	Mechanistic lever (intrinsic	Phenotype-linked profile	Preclinical highlights	Emerging clinical / translational evidence	Biomarker strategy (examples)	References

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compartment	(examples)	gain control)	(clinical signal)				
Kv7 (KCNQ2–5) Soma, AIS, proximal dendrite	retigabine / ezogabine; next-gen Kv7.2/7.3-biased agonists (preclinical)	M-current enhancement → higher spike threshold, reduced burst propensity, stabilization after induction	Anxiety / affective lability; agitation with hyperarousal; relapse-prone hyperexcitability	Openers dampen cortical/limbic hyperexcitability, normalize ensemble stability, reduce anxiety-like behavior; neuroprotection signals consistent with relapse prevention	Human experience with retigabine/ezogabine supports mood/anxiety modulation; translation limited by tolerability but informs subtype-targeted adjunct use	EEG spectral slope flattening as E/I index; rs-fMRI PFC–limbic coupling; symptom-linked arousal metrics (sleep/actigraphy) as supportive readouts	[241,324,325]
HCN (Ih; HCN1-enriched) Dendritic shaft (often distal)	tool blockers (e.g., ZD7288); ivabradine (non-selective, limited CNS utility); circuit neuromodulation affecting Ih (tDCS/DBS)	Ih tuning → altered dendritic resonance/ temporal integration, reduced default-mode drive, improved oscillatory coherence	Rumination; cognitive inertia / slowed affective processing; maladaptive DMN engagement	Partial inhibition or circuit-level Ih reduction normalizes DMN-like hyperconnectivity and reduces rumination-/anxiety-like behaviors in models; strong region specificity expected	Selective agents remain scarce; emerging translational angle is phenotype-defined deployment with imaging/EEG guidance and neuromodulation co-design	rs-fMRI DMN and PFC network connectivity; EEG theta coherence and slow-wave power; EEG slope as complementary E/I proxy	[267,326,327]

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GIRK (Kir3.x) Soma and dendrites (GPCR-coupled)	GIRK activators/ openers (e.g., ML297, ML29; preclinical exemplars); GPCR pathways engaging GIRK (GABA_B, 5-HT1A)	Increased K+ conductance via Gβγ → restored inhibitory tone, lower input resistance, reduced subthreshold variance and spontaneous bursting	Agitation; irritability; sleep instability; stress-evoked limbic overdrive	Activation reduces circuit noise and avoidance/ anxiety-like behaviors; sleep stabilization reported in stress paradigms; supports "safety-brake" concept for hyperactive networks	Toolbox and selectivity constrain human translation; progress points to allosteric, subtype-biased modulators plus brain-penetrant optimization	EEG slope and arousal state metrics; rs-fMRI limbic–prefrontal coupling; behavioral agitation/ sleep endpoints as proximal translational anchors	[298,300,310]

AIS, axon initial segment; CNS, central nervous system; DBS, deep brain stimulation; DMN, default mode network; EEG, electroencephalography; E/I, excitation/inhibition; fMRI, functional magnetic resonance imaging; GABA_B, gamma-aminobutyric acid type B receptor; GIRK, G protein-gated inwardly rectifying potassium channel; GPCR, G protein-coupled receptor; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; Ih, hyperpolarization-activated current; KCNQ2–5, potassium voltage-gated channel subfamily Q member 2–5; K+, potassium ion; Kir3.x, inwardly rectifying potassium channel family Kir3 (GIRK) subunits; Kv7, voltage-gated potassium channel subfamily Q; PFC, prefrontal cortex; rACC, rostral anterior cingulate cortex; rs-fMRI, resting-state functional magnetic resonance imaging; tDCS, transcranial direct current stimulation; ZD7288, HCN channel blocker compound ZD7288; 5-HT_{1A}, 5-hydroxytryptamine (serotonin) receptor 1A.

5. Multi-Point Strategies and Combinatorial Approaches

Enduring antidepressant effects rarely arise from a single molecular nudge; they emerge when plasticity is first opened, then consolidated, and finally stabilized across interconnected networks. Depression reflects distributed circuit dysfunction that spans hippocampus, prefrontal cortex, and thalamocortical loops, so a credible pipeline must act at multiple nodes rather than chase a lone receptor. Rapid-acting agents and neuromodulation converge on metaplasticity, the regulation of how readily plasticity can later be induced, and BDNF–TrkB signaling, creating a time window of enhanced rewiring capacity that behavioral inputs can shape toward healthier attractor states [328,329]. Within this framework, three tiers organize translation. First, plasticity plus stabilizers: pair inducers of iPlasticity, a juvenile-like reopening of experience-dependent plasticity, or TrkB activation with homeostatic mechanisms that prevent rebound noise and consolidate new connectivity, for example lithium, activity-dependent routines, or interneuron-targeted TrkB engagement [330]. Second, Plasticity plus excitability control: combine agents that restore synaptic strength with conductance-level brakes that normalize gain during reconnection, such as selective channel modulators to temper hyperexcitability while plasticity unfolds [32,329]. Third, AMPA-facilitating add-ons: bolster glutamatergic throughput and synapse stabilization by enhancing AMPAR trafficking or receptor drive, as illustrated by tianeptine, which promotes AMPAR

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trafficking and mTOR-linked synaptic plasticity, and by mGlu5-to-AMPAR coupling mechanisms that amplify downstream plasticity signaling [33,331]. The rationale is integrative. Pharmacology sets the stage, targeted neuromodulation aligns oscillatory gateways, and structured behavioral experiences write the final pattern, turning short-lived plasticity into durable network recovery [32,328].

5.1. Plasticity Core + Stabilizers

Rapid antidepressant action begins with an induction phase driven by balanced NMDA antagonism and AMPA facilitation, as seen with ketamine and esketamine. Transient NMDAR blockade suppresses eEF2K and disinhibits local BDNF translation, while a shift toward Ca^{2+}-permeable AMPAR signaling amplifies postsynaptic gain and initiates synaptogenesis [57,332]. This early potentiation sets a metaplastic state in which subsequent activity patterns can reorganize fronto-limbic connectivity. Durable benefit, however, requires a consolidation phase that secures these nascent changes. TrkB activation triggers ERK and mTORC1 cascades, extends protein synthesis windows, and supports dendritic spine maturation; methyl-CpG-binding protein 2 (MeCP2)-linked transcriptional programs lock in circuit reconfiguration over days [59,333]. In parallel, stabilization of presynaptic architecture indexed by SV2A helps restore synaptic density in patients with low baseline SV2A, aligning molecular repair with symptom relief [51,334]. Reinforcing these early gains prevents networks from sliding back into high-inertia, internally focused attractor states characteristic of depression. Practical implementations layer induction with targeted consolidation: ketamine or esketamine to open plasticity, followed by strategies that maintain TrkB signaling, sustain eEF2K inhibition within physiological bounds, and preserve synaptic vesicle competence via SV2A. Such sequencing links rapid glutamatergic rebalancing to structural and transcriptional maintenance, converting short-lived potentiation into persistent normalization of connectivity and affective dynamics [54,97].

Across animal models, pairing a fast plasticity inducer with a consolidation enhancer consistently converts transient synaptic gains into durable remission. Induction can be achieved with ketamine or AMPA-potentiating ampakines of the CX series, which rapidly boost Ca^{2+}-permeable AMPAR drive, elevate BDNF, and engage mTOR-ERK pathways while sparing Hebbian learning capacity [335,336]. Consolidation then extends and stabilizes these changes: TrkB agonism or positive modulation with 7,8-DHF restores thin spine maturity, prevents stress- or age-related synaptic erosion, and sustains cognitive recovery across hippocampal, amygdalar, and cortical circuits [337,338]. Direct combinations are especially informative. In chronic stress paradigms, (R)-ketamine co-administered with LY341495, a selective group II mGlu2/3 antagonist, yields rapid and long-lasting behavioral improvement through BDNF-TrkB and AMPAR mechanisms, with synaptogenesis that outlasts single-agent effects [336,339]. Ketamine or its metabolite 2R,6R-HNK induces enduring AMPAR remodeling in mesolimbic pathways, while boosting ERK activity further prolongs antidepressant responses for weeks to months, indicating that downstream reinforcement is both necessary and sufficient for durability [335,340]. Postoperative and anesthesia-related depression models show similar synergy, where ketamine plus TrkB-dependent signaling reverses synaptic loss and maintains affective recovery [338,341].

Head-to-head work underscores the principle: agents that combine robust induction with TrkB-linked consolidation produce larger, longer-lived gains in spine density, fewer relapses after stress re-exposure, and superior functional rescue compared with either strategy alone [337,341].

Clinical translation benefits when pharmacological induction of plasticity is precisely coupled to consolidation via sleep, circadian alignment, psychotherapy, and neuromodulation. Rapid antidepressant responses need an induction phase followed by sleep-driven stabilization, orchestrated by slow oscillations, spindles, and ripples that support replay and synaptic renormalization [36,328]. Multi-component sleep and circadian programs improve psychiatric outcomes when practiced at biologically suitable times, with phase-sleep coupling mediating symptom change and durability from youth cohorts to depressive disorders [36,342]. Targeting

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circadian timing with light, activity schedules, melatonin, and dose timing can open or extend windows of plasticity; digital phenotyping personalizes scheduling, while mixed results from intensive care unit (ICU) circadian-intervention studies emphasize the importance of protocol fidelity to circadian biology [343,344]. Psychotherapy should be layered onto these windows. Cognitive enhancers and memory modulators administered just before or shortly after exposure-based work can gate encoding and reconsolidation, though agent choice and minute-scale timing remain decisive, particularly in trauma-focused care with mixed efficacy [345,346]. Sequential integration of pharmacotherapy followed by structured cognitive behavioral therapy (CBT) reduces relapse, likely converting state-dependent gains into enduring skills [346]. Repetitive transcranial magnetic stimulation (rTMS) or intermittent theta-burst stimulation (iTBS), delivered alone or in combination with medications, increases cortical plasticity and strengthens therapeutic effects when paired with task engagement, especially in individuals with higher baseline plasticity [346,347].

Translational pairings can extend rapid symptom gains into durable remission. Ketamine produces swift mood elevation, while iTBS supplies a modifiable scaffold whose effects often persist longer than infusion benefits, inviting sequencing to prolong response and minimize relapse [348,349]. Accelerated iTBS, delivered in clustered daily sessions, is safe, fast acting, and well suited to the first days after ketamine when metaplastic windows are most permissive [348,350]. Real-world multisite data confirm effectiveness and safety of left prefrontal iTBS, supporting routine integration into combinatorial care [348,349]. A practical map would initiate ketamine to unlock synaptic potentiation, then deliver targeted iTBS with symptom-contingent tapering and session timing aligned to circadian stability, aiming to convert state change into trait resilience [348,350].

Pharmacologic pairing follows the same logic. DXM with bupropion brings NMDA modulation, sigma-1 signaling, and monoaminergic support, offering a versatile backbone for augmentation [351,352]. Combination therapy outperforms monotherapy in many contexts, yet bupropion pairings show heterogeneous effects, which argues for precision add-ons and patient stratification [352]. Inhibiting eEF2K could amplify translation and synaptic strengthening downstream of glutamatergic modulation, creating a plausible synergy with DXM-bupropion that merits phase Ib signal-seeking trials [351,352]. Multimodal designs should incorporate pharmacokinetics, target engagement biomarkers, adaptive randomization, and personalized scheduling of behavioral activation and sleep regularization around predicted peaks of plasticity for each participant.

5.2. Plasticity + Excitability Control

Plasticity induction is not purely beneficial; without constraint it can push networks toward hypersynchrony, unstable bursting, and loss of information fidelity. Homeostatic mechanisms counter this drift by sensing activity history and restoring gain around an operating point through synaptic scaling and intrinsic adjustments [353,354]. After deprivation or strong potentiation, neurons upregulate hyperpolarization-activated currents and reshape burst dynamics, a response that curbs run-away excitation and normalizes firing statistics [353,355]. Excess extracellular glutamate, shifts in inhibition, or impaired chloride handling can otherwise widen excitability, erode signal-to-noise, and degrade learning rules [356,357]. At the network level, connectivity is rebalanced to preserve stable population activity, yet this compensation is slow and incomplete without intrinsic brakes [354].

Ion channel tuning provides that brake and preserves gain precision. Kv7 channels furnish a non-inactivating M-current that stabilizes the axon initial segment; redistribution or pharmacologic enhancement reduces spurious spiking and limits burst afterdepolarizations [356,358]. Conversely, agents that inhibit Kv7 can transiently widen plasticity but risk hyperexcitability unless paired with compensatory controls [356,359]. HCN channels add negative feedback through Ih, accelerating membrane recovery and dampening resonance that seeds pathological bursting [353,355]. GIRK channels hyperpolarize the membrane and raise rheobase, offering a tractable target for post-induction stabilization [357] . Additional levers refine this clamp: GABAergic axo-axonic input tunes initial segment structure and thresholds, SK2 gating sculpts spike clusters, endocannabinoid-driven

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Kv7 augmentation quiets circuits after LTD, and ERK-linked control of Kv7.3 aligns molecular state with excitability demands [354,358].

Combinatorial pharmacology can turn rapid state shifts into stable trait change by pairing induction of neuroplasticity with precise excitability control. Ketamine arrests pathologic bursting in the lateral habenula and rebalances prefrontal microcircuits, producing fast antidepressant effects that nevertheless require stabilization to curb relapse [78,360]. Kv7 openers supply a tonic brake on pyramidal neurons via the M-current, lowering burst propensity at the axon initial segment and sharpening gain; diverse chemotypes with translational promise, including QO-83, reduce hyperexcitability and improve cognition in preclinical systems [361,362]. This pharmacodynamic logic supports a sequence in which ketamine initiates synaptogenesis and rebalancing of excitatory/inhibitory (E/I) activity, followed by timed Kv7 augmentation that suppresses rebound bursting and preserves signal fidelity during consolidation [360,363]. Calibration matters, since nonselective Kv7 inhibition by agents like paroxetine can widen excitability and potentially erode benefits if left unchecked [364]. HCN channels offer a complementary lever. Ketamine alters gamma rhythms and inhibits HCN1, while direct HCN modulation produces ketamine-like, sustained antidepressant effects and normalizes midbrain hyperactivity; carefully titrated HCN agents may therefore enhance oscillatory coherence, reduce dysrhythmia, and improve cognitive emotional balance when layered onto ketamine's plasticity window [78].

A second pairing focuses on limbic damping with DXM-bupropion combined with a GIRK opener. DXM modulates NMDARs and sigma-1 sites, while bupropion supports catecholaminergic tone; together they deliver rapid symptom relief with good tolerability in early clinical work [346,363]. GIRK channels hyperpolarize neurons and raise rheobase, the minimum current required to evoke an action potential, providing a direct counterweight against network hyperactivity implicated across mood and psychosis spectra; potassium channel portfolios already highlight GIRK as a tractable target with cross-diagnostic potential [15,346,361]. Adding a GIRK opener to DXM-bupropion could therefore damp limbic overdrive during plasticity induction, reduce stress reactivity, and steady fronto-limbic coupling, which may translate to fewer lapses and smoother affective control [346,363]. Multimodal trials should test these pairings with target engagement biomarkers, oscillatory readouts, and relapse endpoints, integrating individualized timing maps that align drugs to the patient's peak plasticity and network state [346,360].

Biomarkers can steer both timing and dose in combination strategies by indexing plasticity readiness and network stability. Three readouts are particularly actionable. First, the EEG spectral slope, a proxy for excitation to inhibition balance, flattens with cortical disinhibition and steepens as inhibition strengthens; tracking slope before and after induction can gate consolidation inputs and prevent overshoot during vulnerable windows [365,366]. Second, rostral anterior cingulate cortex (rACC) theta power is a robust prognostic marker. Higher baseline rACC theta predicts greater symptom improvement across modalities and differentiates responders, enabling dose titration and early switching when trajectories look suboptimal [337,366]. Third, fMRI connectivity within prefrontal limbic circuits forecasts treatment response. Dorsolateral prefrontal cortex (DLPFC)-to-subgenual anterior cingulate cortex (sgACC) and broader salience network coupling stratify rTMS outcomes, while default mode and cingulo frontal patterns predict remission to medication and can guide selection between CBT and pharmacotherapy [366,367]. Multimodal frameworks that combine EEG and fMRI outperform clinical features alone and support precision sequencing in prospective designs [211,368,369].

An adaptive workflow follows a sense decide act loop. Establish a biomarker baseline. Induce plasticity. Recheck EEG slope and rACC theta within hours to map consolidation timing. Adjust neuromodulation targets from fMRI connectivity and iterate dosing or modality accordingly. Closed loop principles, validated in other disorders using electrophysiological control signals, can be translated to psychiatry to deliver responsive, biomarker driven care that prioritizes durability and cognitive emotional balance [337,365].

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Table 3. Combination strategies for durable antidepressant efficacy: induction–consolidation–maintenance (ICM) pairings that lock rapid symptom relief into stable circuit change. Matrix of ICM strategies that sequence a rapid inducer with a consolidation driver and a maintenance stabilizer. Rows illustrate mechanistically rational pairings (e.g., ketamine + TrkB potentiation + iTBS; DXM–bupropion + eEF2K inhibition; esketamine + Kv7 opening) aligned to expected benefits, biomarker readouts (EEG spectral slope/rACC theta, rs-fMRI network coupling, SV2A PET where relevant), and relapse-prevention logic. The goal is phenotype-informed dosing and timing that promotes synaptic consolidation while preventing rebound hyperexcitability.

ICM strategy (example)	Induction (I) rapid plasticity engagement	Consolidation (C) stabilize synaptic change	Maintenance (M) relapse prevention	Expected clinical benefits (phenotype fit)	Biomarkers / monitoring (examples)	Relapse-prevention potential (rationale)	Implementation notes (timing / safety)	References
Ketamine + TrkB PAM + iTBS	Ketamine (or esketamine) to open a brief plasticity window and reduce depressive burden quickly	TrkB positive allosteric modulation to bias BDNF signaling toward spine stabilization and persistence	Intermittent theta-burst stimulation (iTBS) to reinforce adaptive network reweighting during the consolidation window	Rapid relief + improved anhedonia and cognitive flexibility; suited to stress-reactive depression with network rigidity	EEG spectral slope (E/I balance) and rACC theta; rs-fMRI PFC–limbic/DMN coupling; symptom dynamics across sessions	Pairs molecular consolidation with circuit-level training to reduce rebound and extend remission	Time iTBS within hours–days after infusion; monitor dissociation/BP with ketamine; avoid excessive stimulation load in high anxiety	[370–372]
DXM–bupropion + eEF2K inhibitor	DXM–bupropion (multimodal: NMDA/	eEF2K inhibition to release translational brake and support	Behavioral activation / structured engagement during consolidati	Broader symptom coverage (mood + motivation);	EEG slope; task-evoked EEG/E	Translation-centric conso	Drug–drug interaction vigilance	[64,154,373]

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	sigma-1 plus catecholaminergic support) for sustained induction signal	protein synthesis–dependent stabilization	on (task-coupled learning)	potentially beneficial for rumination + low drive phenotypes	RP indices; rs-fMRI connectivity changes in cognitive control networks	lidation may improve durability beyond symptomatic induction	(bupropion); seizure-risk screening; prioritize daytime dosing if activating	
Esketamine + Kv7 opener	Intranasal esketamine to trigger rapid symptom reduction and synaptogenic signaling	Consolidation through targeted gain stabilization (reduce post-induction hyperexcitability that destabilizes remodeling)	Kv7 (KCNQ) channel opener to lower firing gain and suppress relapse-prone bursting	Best fit for agitation/hyperarousal, affective lability, and stress-evoked reactivity	EEG slope flattening as E/I index; sleep/actigraphy; rs-fMRI PFC–limbic coupling; arousal metrics	Directly counters rebound excitation and supports network stability after rapid induction	Tolerability can be limiting (sedation, dizziness; agent-specific AEs); consider low-dose, nighttime maintenance	[258, 374,375]
Ketamine + rapamycin (timed consolidation adjunct)	Ketamine to initiate rapid plasticity and symptom relief	Rapamycin timed to influence consolidation biology (immune/metabolic gating; candidate durability	Standard antidepressant backbone + psychotherapy for maintenance	Potential durability extension in selected patients; may suit inflammatory	Peripheral inflammatory markers; EEG slope; clinica	Targets consolidation “environment” to prote	Immunosuppression risk; infection screening; strict timing relative	[36,45,376]

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		enhancer in reports)		signatures or relapse-prone courses	l trajectory of relapse timing	ct newly remodeled synapses and networks	to ketamine; specialist oversight	
Ketamine/esketamine + lithium maintenance	Rapid inducer (ketamine or esketamine) for acute symptom drop	Consolidation supported by structured sleep/circadian alignment and learning-based interventions	Lithium as maintenance stabilizer to reduce recurrence risk and support homeostatic set-points	Relapse prevention in recurrent, high-risk depression; potential benefit for mood instability	Clinical staging + relapse history; sleep regularity metrics; EEG slope as supportive physiology	Maintenance stabilizer reduces drift back to maladaptive attractor states after induction	Renal/thyroid monitoring; drug interaction review; avoid dehydration; patient education on toxicity signals	[36,377,378]
Rapid inducer + SV2A ligand stabilization (exploratory)	Ketamine/esketamine or DXM–bupropion to initiate plasticity	Activity-dependent consolidation supported by rehabilitation/psychotherapy	SV2A ligand (e.g., levetiracetam/brivaracetam class; exploratory) to stabilize vesicle cycling/release fidelity	May fit agitation/irritability with circuit noise; conceptual bridge to synaptic density monitoring	SV2A PET (where available); EEG slope; rs-fMRI network stability measures	Presynaptic stabilization may support maintenance of strengthened synapses	Evidence base is emerging; monitor mood/irritability AEs; consider only in research/precision frameworks	[171,216,379]

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and reduce destabilizing release variability

AEs, adverse events; AIS, axon initial segment; BDNF, brain-derived neurotrophic factor; BP, blood pressure; DMN, default mode network; DXM, dextromethorphan; EEG, electroencephalography; eEF2K, eukaryotic elongation factor 2 kinase; E/I, excitation/inhibition; ERP, event-related potential; fMRI, functional magnetic resonance imaging; ICM, induction–consolidation–maintenance; iTBS, intermittent theta-burst stimulation; KCNQ, potassium voltage-gated channel subfamily Q; Kv7, voltage-gated potassium channel subfamily Q; NMDA, N-methyl-D-aspartate; PFC, prefrontal cortex; PET, positron emission tomography; rACC, rostral anterior cingulate cortex; rs-fMRI, resting-state functional magnetic resonance imaging; SV2A, synaptic vesicle glycoprotein 2A; TrkB, tropomyosin receptor kinase B.

5.3. AMPA-Facilitating Add-Ons

Across pharmacologic and device-based interventions, a common denominator emerges: durable improvement tracks with enhanced AMPAR throughput that re-establishes prefrontal drive and plasticity while avoiding runaway excitation. Rapid-acting agents increase synaptic AMPA expression or function, often engaging calcium-permeable AMPA receptors (CP-AMPARs) to initiate BDNF and mTOR signaling that supports spine formation and circuit reweighting; blocking AMPA receptor-mediated transmission abolishes these benefits in preclinical models [380,381]. Convergence extends beyond ketamine: mGlu-dependent accelerators, monoaminergic agents, natural compounds, and even deep brain or cortical stimulation all funnel efficacy through AMPA-mediated gain, consistent with the observation that raising the AMPA to NMDA ratio predicts speed and durability of response [380,382]. Crucially, AMPAR-centric strategies can sustain network performance without excitotoxicity when the qualitative features of throughput are tuned. Positive allosteric modulators with minimal intrinsic agonism, transporter-supported glutamate clearance, and a bias toward glutamate ionotropic receptor AMPA type subunit 2 (GluA2)-containing receptors collectively preserve calcium homeostasis and signal-to-noise, yielding antidepressant and pro-cognitive effects with favorable safety profiles [381,382]. In this framework, AMPA drive is not a hazard but a calibrated engine for restoring adaptive gain.

Adjuncts that subtly raise AMPA throughput while engaging monoaminergic tone are gaining clinical traction. Brexpiprazole, a partial dopamine D_2 and 5-hydroxytryptamine 1A (5-HT_{1A}) agonist with 5-hydroxytryptamine 2A (5-HT_{2A}) antagonism, facilitates AMPAR-mediated transmission in medial prefrontal cortex through a dopamine D_1-dependent cascade, particularly when combined with selective serotonin reuptake inhibitors (SSRIs) such as escitalopram [383]. This profile echoes ketamine's reliance on CP-AMPARs upregulation to drive rapid synaptic strengthening, suggesting a shared downstream gateway that converts transient state change into more durable network reweighting [384]. Because AMPA activation in prefrontal circuits can secondarily recruit dorsal raphe serotonergic output, brexpiprazole may amplify this cortico-monoaminergic loop and improve mood and cognition without excessive excitatory load [383].

Vortioxetine offers a complementary route. Its multimodal serotonergic actions reshape cortical information flow and acutely boost expression of plasticity related genes tied to glutamatergic signaling in frontal cortex, consistent with an AMPA enhancing mechanism distinct from classic

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SSRIs and temporally separable from ketamine [384] Convergent frameworks of rapid acting antidepressants place both ketamine and serotonergic agents on a common pathway that culminates in AMPA mediated plasticity and synaptic gain, albeit through different entry points [384]. These overlaps argue for rational pairing or sequencing with AMPA facilitating agents to stabilize prefrontal output, enhance cognitive control, and extend remission while maintaining excitatory safety through targeted dosing and biomarker guided timing [383,384].

Augmentation studies increasingly show that coupling adjuncts to rapid-acting antidepressants improves remission and functional recovery. Network meta-analyses in TRD report higher response and remission with atypical antipsychotic augmentation, with brexpiprazole among the most consistent options [385]. Phase 2 and 3 trials, including Brexpiprazole Efficacy and Safety in Major Depressive Disorder (BLESS) and larger randomized studies at 2 to 3 mg, demonstrate significant symptom and functioning gains with acceptable tolerability, and effects that emerge early and persist across symptom clusters [386]. Real-world switching data echo these benefits, with improvements in depressive symptoms, cognition, and overall functioning after moving to adjunctive brexpiprazole [386]. Mechanistic and preclinical work supports synergy with antidepressants and restoration of plasticity markers, while case series combining brexpiprazole with ketamine or esketamine suggest rapid clinical recovery in complex presentations and motivate controlled multimodal trials [387]. The field now needs longitudinal, biomarker-anchored designs. Stratification by inflammatory load, as in the C-reactive protein (CRP)-guided vortioxetine plus celecoxib protocol, and null findings without stratification underscore the value of precision enrollment and timing analytics for durable remission and cognitive outcomes [52,388].

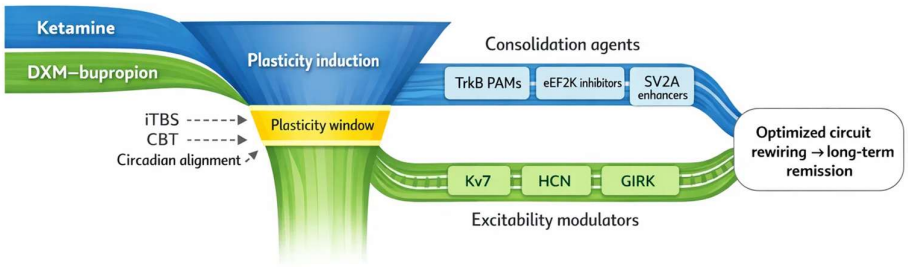

Figure 3. Combination strategies schematic. The schematic illustrates a staged, time-sensitive approach to enhance durable symptom remission by coupling rapid plasticity induction with targeted stabilization and excitability tuning. Plasticity inducers (ketamine or DXM–bupropion) open a transient **"plasticity window"** during which maladaptive circuit weights are most amenable to change. Within and immediately following this window, consolidation agents—**TrkB positive allosteric modulators**, **eEF2K inhibitors**, and **SV2A enhancers**—are positioned to amplify BDNF/translation-dependent synaptic strengthening and support presynaptic release reliability, thereby "locking in" newly encoded network states. In parallel, intrinsic excitability modulators (**Kv7**, **HCN**, and **GIRK** targets) provide gain control to prevent hyperexcitability, shape oscillatory dynamics, and improve signal-to-noise during relearning. Neuromodulatory and behavioral timing interventions (**iTBS**, **CBT**, and **circadian alignment**) are depicted as most effective when delivered inside the plasticity window,

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maximizing circuit rewiring and promoting long-term remission. BDNF, brain-derived neurotrophic factor; CBT, cognitive behavioral therapy; DXM, dextromethorphan; eEF2K, eukaryotic elongation factor 2 kinase; GIRK, G protein-coupled inwardly rectifying potassium channel; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; iTBS, intermittent theta-burst stimulation; Kv7, voltage-gated potassium channel Kv7 family; PAM, positive allosteric modulator; SV2A, synaptic vesicle glycoprotein 2A; TrkB, tropomyosin receptor kinase B.

6. Closing Synthesis and Future Directions

Depression recovery is best understood as a dynamic, multi-phase biological process in which acute relief is encoded, consolidated, and subsequently renormalized across time, with sleep and experience shaping each transition [36]. At its core lie two interacting themes: synaptic plasticity that rewires connectivity, and intrinsic excitability that sets the gain of neuronal ensembles [329]. Stress skews both, degrading cortical and reward circuit function, while rapid-acting and conventional antidepressants restore synaptic strength, spine architecture, and network communication through metaplastic and homeostatic programs that prime future adaptation rather than a single static endpoint [35,389]. Convergent molecular hubs link these levels, notably BDNF– TrkB signaling and PI3K–Akt–mTOR pathways, as well as synaptic organizers such as neurexins that stabilize sustained benefit after agents like ketamine or psilocybin [390]. Bioenergetic resilience and mitochondria further tune plasticity capacity, connecting cellular metabolism to circuit repair and behavior [175]. Translational work shows that macro- and microstructural brain changes track with synaptic remodeling, and that intrinsic network connectivity can forecast remission, underscoring the need for integrated biomarkers that bridge molecules, circuits, and symptoms [175,391]. This section proceeds as follows: a unified model of recovery that couples plasticity with excitability, candidate biomarkers across scales, principles for trial design that assay plasticity readiness, key research gaps, and a future outlook that prioritizes durable, mechanism-anchored interventions [33]

Recovery from depression can be framed as an integrated control problem in which synaptic plasticity writes the map and intrinsic excitability sets the compass. Plasticity induction allocates change to specific synapses through activity-dependent mechanisms, while consolidation stabilizes these changes via molecular programs such as synaptic tagging and capture, coordinated receptor trafficking, and mTOR or CREB signaling that secure long-term efficacy at the appropriate connections [392,393]. In parallel, intrinsic excitability retunes the gain of neuronal ensembles through ion channel modulation, neuromodulatory tone, and inhibitory plasticity, keeping network dynamics within a regime that is both responsive and robust. This pairing allows plasticity to sculpt adaptive connectivity and excitability to ensure stability and precision during information flow and decision making [78,394].

Circuit-level observations make the logic concrete. Coupling between hippocampus and prefrontal cortex depends on long-term potentiation and long-term depression working in concert with oscillatory synchrony under the influence of serotonin, dopamine, and other neuromodulators, and this coupling falters in depression with measurable consequences for cognition and affect [392,395]. In the amygdala, neuroinflammatory states raise glutamatergic drive and intrinsic excitability, biasing engram formation toward threat; targeted disinhibition or serotonergic regulation can rebalance excitation and inhibition and restore controlled retrieval of emotional memories [253,396]. Amygdala activity can also reset the dynamic range of hippocampal plasticity, exemplifying bidirectional regulation across nodes that jointly tune connectivity and gain [397]. At the systems scale, deficits in hippocampal and prefrontal plasticity seen in susceptible strains are reversible when interventions reset both synaptic strength and excitability, whether via pharmacology, experience-dependent enrichment, electroconvulsive therapy, or molecular levers such as SIRT1 that couple intrinsic firing properties to synaptic throughput [12,344,398].

Taken together, therapeutic recovery emerges when connection strength and control are restored simultaneously. Plasticity sets where the network can go; excitability decides how confidently and safely it gets there. Durable remission therefore requires coordinated strategies that

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induce and consolidate the right synapses while tuning gain to preserve accuracy and resilience across circuits [399].

A multimodal biomarker strategy should connect molecular events at synapses to mesoscopic network dynamics and daily behavior, enabling phase-specific tracking of recovery. SV2A PET anchors the synaptic tier by indexing presynaptic terminal density, which is reduced in depression and partially restored with treatment, thereby providing a direct readout of structural plasticity and its therapeutic modulation. Yet synaptic density alone does not fully predict functional organization. Combined SV2A PET and resting-state fMRI demonstrate regional network changes that are only partly explained by density, arguing for integrated models rather than single-modality thresholds. Magnetic resonance spectroscopy then quantifies excitatory and inhibitory tone. Glx and GABA levels, particularly in anterior cingulate and prefrontal cortex, correlate with resting connectivity and default-mode interactions, while trimodal PET–MR–EEG indicates that inhibitory processes strongly constrain canonical networks, refining interpretation of E to I balance in vivo. Importantly, unimodal MRS shows inconsistent prognostic utility, reinforcing the need for multimodal designs and larger samples [400,401].

At the network scale, resting-state fMRI yields robust predictors of treatment outcome, including strengthened frontoparietal integration and reliable default-mode suppression; time-resolved metrics such as dwell time in coactivation states forecast early response and capture consolidation dynamics. Electrophysiology closes the temporal gap. Resting EEG topology differentiates responders, while spectral slope and rostral anterior cingulate theta index cortical excitability and plasticity readiness, offering rapid, repeatable assays that complement imaging-derived connectivity maps. Actigraphy supplies the behavioral layer, quantifying circadian alignment and sleep regularity that gate synaptic renormalization and stabilize network states across days [402,403].

Together, these measures form a layered pipeline. SV2A PET and MRS report synaptic resources and E to I balance during induction. rs-fMRI and EEG resolve evolving connectivity and excitability through consolidation. Actigraphy verifies maintenance by demonstrating entrained rhythms and stable behavior. Multimodal fusion, including graph learning across EEG–fMRI with structural priors, yields individualized signatures that guide phase-specific interventions and real-time course corrections [404,405].

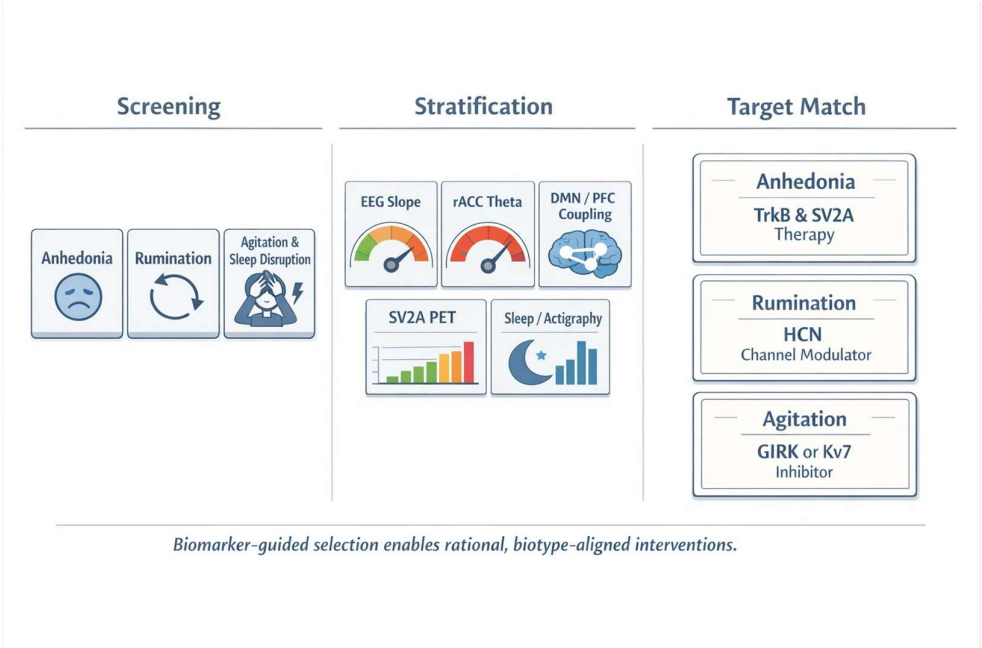

Figure 4. Biotype-specific treatment roadmap. Flowchart linking clinically salient depression phenotypes to mechanistically matched target strategies, supported by a pragmatic biomarker scaffold. **Anhedonia** is routed

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toward interventions that strengthen synaptic resources and reward-circuit plasticity via **TrkB** potentiation and **SV2A**-linked presynaptic stabilization. **Rumination and cognitive inertia** are mapped to **HCN (Ih) modulation**, reflecting the role of dendritic resonance and default-mode network (DMN) dominance in perseverative self-focus and slowed affective updating. **Agitation and sleep disruption** are directed to **GIRK** and/or **Kv7** targets to restore inhibitory tone and anti-burst "gain control," aiming to damp limbic overdrive while stabilizing arousal and sleep. Biomarker-guided selection is illustrated as the bridge to precision psychiatry, using multimodal readouts such as **EEG spectral slope** and **rACC theta** (excitability/plasticity readiness), **rs-fMRI DMN and PFC–limbic coupling** (network state), **SV2A PET** (synaptic tier), and **sleep/actigraphy** (circadian alignment) to stratify patients and personalize intervention choice. DMN, default-mode network; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; GIRK, G protein-coupled inwardly rectifying potassium channel; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; Ih, hyperpolarization-activated current; PFC, prefrontal cortex; PET, positron emission tomography; rACC, rostral anterior cingulate cortex; rs-fMRI, resting-state functional magnetic resonance imaging; SV2A, synaptic vesicle glycoprotein 2A; TrkB, tropomyosin receptor kinase B.

Clinical trials should capitalize on transient plasticity windows by synchronizing pharmacological induction with behavioral or neuromodulatory consolidation. Evidence that recovery speed reflects a plasticity by context interplay suggests timing is not a luxury but a mechanism, with interventions succeeding when behavioral input arrives during peak metaplastic readiness rather than after it has waned [397]. Protocols can prespecify window-locked pairings: an inducer to open the gate, followed within hours to days by consolidation tactics such as structured psychotherapy modules, targeted neuromodulation, or sleep and circadian alignment to stabilize network reconfiguration [397]. Multimodal biomarkers embedded at repeated intervals, including circuit scores, EEG indices, and molecular panels, can verify that the window was captured rather than merely assumed [406,407]

Stratification should move beyond coarse symptom subtypes that underperform in moderating treatment effects and toward biologically anchored phenotypes that guide drug–device pairings. High-excitability profiles, indexed by frontolimbic hyperconnectivity or rACC theta, may benefit from consolidation with inhibitory-biased neuromodulation and sleep regularization after a pharmacological primer. Low-plasticity profiles, identified by network inefficiency or proteomic signatures of impaired neurotrophic signaling, may require stronger inducers and cognitive scaffolding to capture newly available synapses. Pharmacogenomic tools add a complementary layer for medication selection, with multiple blinded trials and meta-analyses showing modest yet reliable gains in response and remission, particularly when switching to genetically congruent agents, thereby enriching strata and reducing futile exposure [408,409].

Designs should be adaptive and explicitly longitudinal. SMART frameworks enable data-driven sequencing and timing choices using repeated outcomes and biomarkers to adjust dose, interval, and consolidation intensity in real time [410]. Extensions of 2-in-1 designs allow early selection of responsive biomarker subpopulations while preserving confirmatory power, improving efficiency without sacrificing rigor. Deep learning models that fuse clinical, genetic, neuroimaging, and EEG features can drive interim decision rules, while smartphone-based digital phenotypes provide high-frequency behavioral readouts to refine window placement between visits. Together, these elements convert trials into responsive systems that test not only what to deliver, but precisely when and to whom [36,411].

Table 4. Research gaps and experimental approaches: from target-level uncertainties to biomarker-anchored, biotype-guided translation for durable antidepressant plasticity.Forward-looking inventory of unanswered questions spanning postsynaptic consolidation (TrkB, eEF2K), presynaptic stabilization (SV2A), and intrinsic gain control (Kv7, HCN, GIRK). For each domain, the table links key gaps in mechanism, safety, and patient selection to practical experiments—from short proof-of-concept drug–device timing studies to longer biotype-guided trials. Candidate readouts include EEG spectral slope/rACC theta, rs-fMRI network coupling, SV2A PET,

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and digital relapse metrics, aiming to accelerate translational readiness while de-risking adverse excitability and tolerance liabilities.

Target/ domain	Key unanswered question / gap	Why it matters (clinical/biological)	Proposed experimental approach	Biomarkers / readouts (examples)	Translational readiness milestone	Safety / tolerability focus	References
TrkB (postsynaptic consolidation)	When is TrkB potentiation beneficial vs maladaptive (state-, region-, or dose-dependent effects)?	Determines durability vs instability of newly formed spines; informs timing with rapid inducers	Window-mapping studies: inducer (ketamine/esketamine) ± TrkB PAM delivered at staggered delays; add iTBS/learning tasks during consolidation	EEG slope; rACC theta; rs-fMRI PFC–limbic/DMN coupling; behavioral flexibility tasks	Define optimal timing/dose rules + responder phenotype; establish mechanistic target engagement	Mania/hypomania risk in vulnerable patients; sleep disruption; overstimulation when combined with neuromodulation	[343,371,412]
eEF2K (translation checkpoint)	Which neuronal compartments/cell types mediate benefit, and what is the minimum translation release needed for persistence?	Avoids overbroad protein synthesis effects; supports precision consolidation without toxicity	Spine-resolved assays (ribopuromycylation, proteomics) with selective eEF2K tools; combine with DXM–bupropion-like induction signals	EEG/ERP plasticity indices; synaptic protein signatures; rs-fMRI control-network changes	Demonstrate dose–response + CNS penetration + on-target biomarkers; establish pairing logic with	Off-target kinase liabilities; seizure-threshold effects if excitation rises; drug–drug interactions	[151,154,413]

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					induction		
SV2A (presynaptic stabilization)	Does SV2A modulation improve durable remission by stabilizing vesicle cycling, and in which symptom phenotypes (agitation vs anhedonia)?	Clarifies whether presynaptic "maintenance" can extend rapid-response durability; links to imaging	Short POC trials adding an SV2A ligand after induction; longitudinal SV2A PET + relapse tracking; parallel rodent synapse imaging	SV2A PET; EEG slope variability; rs-fMRI network stability; digital relapse markers (sleep/actigraphy)	Show concordance between SV2A PET change and symptom durability; specify best-fit biotype	Irritability/mood AEs with some SV2A ligands; cognitive side effects; dosing for tolerability	[209,214,414]
Kv7 (gain control / anti-burst)	Can Kv7 opening prevent post-induction rebound hyperexcitability without blunting antidepressant plasticity?	Balances stability vs plasticity—too much brake could block consolidation; too little permits relapse	Sequence studies: inducer first, Kv7 opener delayed (hours–days) vs concurrent; include physiological stratification	EEG slope flattening; sleep stability; arousal metrics; rs-fMRI PFC–limbic coupling	Identify timing that preserves acute response and improves time-to-relapse; tolerable dose range	Sedation/dizziness; urinary/visual AEs depending on agent; cognitive slowing at high dose	[258,266,415]
HCN (dendritic resonan	Which direction of HCN modulatio	HCN effects are highly circuit-	Circuit-guided approach: combine	rs-fMRI DMN connectivity; EEG	Develop selective,	Bradycardia risk with peripheral HCN	[286,416,417]

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ce / DMN coupling)	n is therapeutic in rumination-dominant biotypes, and what regions should be targeted?	specific; wrong direction risks cognitive dulling or mood worsening	neuromodulation (iTBS/tDCS) with pharmacologic Ih tuning in models; human imaging-guided N-of-1 crossover	theta coherence /slow-wave power; cognitive rumination tasks	brain-penetrant modulators or validated device proxies; define target circuits	blockade; attention/processing-speed effects; sleep architecture shifts	
GIRK (GPCR-coupled inhibitory tone)	Can GIRK activation reduce agitation/irritability and stabilize sleep without tolerance or affective blunting?	Addresses high-arousal relapse pathways; may serve as safety-brake adjunct after induction	Develop subtype-biased allosteric GIRK modulators; test in stress/agitation models; early-phase trials with sleep-first endpoints	EEG slope + arousal markers; polysomnography; rs-fMRI limbic–prefrontal coupling	Demonstrate brain penetration + on-target physiology + symptom-specific benefit	Sedation, dizziness; interaction with other sedatives; depressive blunting if over-inhibited	[316,319,418]
Drug–device combinations (timing rules)	What is the optimal device timing (iTBS/ECT/tDCS) relative to pharmacologic induction for maximal consolidation?	Defines scalable protocols that convert short-lived plasticity into durable network change	Adaptive timing trials: vary stimulation onset post-dose; closed-loop stimulation triggered by EEG signatures of plasticity window	EEG state markers (slope, theta); symptom time-series; rs-fMRI coupling pre/post stimulation blocks	Consensus timing algorithms; practical clinical workflow; reproducible responder enrichment	Seizure risk with overstimulation; autonomic effects; interaction with dissociation/anxiety states	[419–421]
Biomarker	Which biomarker	Enables precision	Prospective biotype-	EEG spectral	Validated	False stratificatio	[422–424]

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strategy & biotypes	panel best stratifies patients to consolidation vs gain-control adjuncts?	prescribing and reduces failed trials from heterogeneity	guided trials: pre-register EEG+fMRI strata; assign adjuncts (TrkB/eEF2K vs Kv7/HCN/GIRK) by physiology and phenotype	slope, rACC theta; rs-fMRI DMN/PFC–limbic coupling; SV2A PET (subset); digital relapse metrics	stratification algorithm + clinically meaningful effect sizes within strata	n risk; site variability; burden/cost of imaging—need minimal viable panel	
Long-term durability & relapse biology	What maintains remission months later—synapse number, release fidelity, homeostatic set-points, or behaviorally reinforced networks?	Guides maintenance selection and duration (how long to treat after response?)	Longitudinal cohort studies post-induction with repeated biomarkers and relapse modeling; incorporate psychotherapy/learning exposure as consolidation probe	SV2A PET trajectories; EEG slope drift; rs-fMRI stability; relapse hazard models from symptom + digital data	Mechanistic predictors of time-to-relapse; stopping rules for maintenance therapy	Tolerance, dependence-like patterns, cognitive side effects; long-term safety monitoring frameworks	[425–427]

AEs, adverse events; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; DMN, default mode network; DXM, dextromethorphan; ECT, electroconvulsive therapy; EEG, electroencephalography; eEF2K, eukaryotic elongation factor 2 kinase; E/I, excitation/inhibition; ERP, event-related potential; fMRI, functional magnetic resonance imaging; GIRK, G protein-gated inwardly rectifying potassium channel; GPCR, G protein-coupled receptor; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; iTBS, intermittent theta-burst stimulation; Ih, hyperpolarization-activated current; Kv7, voltage-gated potassium channel subfamily Q; N-of-1, single-patient crossover design; PFC, prefrontal cortex; PET, positron emission tomography; POC, proof of concept; rACC, rostral anterior cingulate cortex; rs-fMRI, resting-state functional magnetic resonance imaging; SV2A, synaptic vesicle glycoprotein 2A; tDCS, transcranial direct current stimulation; TrkB, tropomyosin receptor kinase B.

Immediate priorities should test tightly coupled drug + device + therapy combinations that target induction and consolidation within defined windows. Ketamine paired with intermittent theta burst stimulation is a strong candidate: intravenous dosing opens a brief plasticity gate, while iTBS can steer circuit-specific consolidation to prolong benefit. Signals from rTMS combined with pharmacotherapy on depressive symptoms and sleep quality, along with dose and timing sensitivity of ketamine, motivate prospective evaluation of order, spacing, and intensity. Retrospective and case-based reports of combined TMS and ketamine in resistant depression suggest feasibility, durability,

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and tolerability at higher stimulation intensities, warranting controlled protocols with standardized parameters. Parallel proofs of concept should examine DXM or related NMDAR modulators coupled to sleep and circadian realignment, using structured schedules or orexin receptor antagonists to stabilize overnight synaptic renormalization and translate acute gains into durable change [428,429].

Trials must be small, fast, and mechanistically anchored. Biomarker batteries should verify the hypothesized interaction: frontolimbic connectivity on functional neuroimaging to index guided consolidation, midline theta or spectral slope to quantify excitability set points, and magnetoencephalography or EEG signatures sensitive to drug and stimulation synergies. Designs should predefine response patterns that trigger within-subject adjustments of dose and intersession interval, converting feasibility pilots into learning engines that refine protocols in real time [430,431].

Translation barriers require explicit mitigation. Preclinical rTMS often uses antidepressant-sensitive strains and stimulation geometries that do not mirror human focality. Species differences in oscillatory markers complicate selection of target frequencies and endpoints. Drug kinetics in animals rarely match human infusion profiles, shifting the induction window relative to stimulation. Mechanistic pilots should harmonize dosing, oscillatory targets, and timing across species, and replicate in treatment-resistant models to better reflect clinical heterogeneity [430,432].

Long-term progress depends on modulators that are both selective and safe, with effects that translate from receptor to circuit. Kv7 openers illustrate the promise and the pitfalls: medicinal chemistry has improved potency and subtype focus, yet clinical use still faces off-target actions, tissue specificity, and tolerability ceilings that constrain dose and duration. TrkB remains a central plasticity hub, but ligand bias, regional heterogeneity, and complex transmembrane signaling demand structure-guided design and context-sensitive deployment, particularly in inflammation-linked depression. Parallel glutamatergic strategies, including positive AMPA modulators and rapid-acting agents, must solve subunit selectivity and pharmacokinetic control while delivering reliable in vivo engagement markers. Additional targets such as eEF2K, SV2A, and GIRK require the same precision, along with plans for chronic safety monitoring and brain region specificity [52,433,434].

Equally important is a longitudinal biomarker scaffold that ties molecular engagement to network repair and daily function. Neuroimaging predictors show potential but vary across sites; durable utility will require harmonized protocols, repeated measures, and fusion with electrophysiology that reads cortical gain in real time. Digital phenotyping can supply high-frequency measures of sleep, mobility, and social rhythm, closing the loop between laboratory signals and lived behavior. A practical stack would pair PET or MRS for target engagement, fMRI for evolving connectivity, EEG for excitability dynamics, and smartphones for circadian alignment on a shared temporal axis [435,436].

Computational advances can integrate these layers. Deep graph learning across EEG and fMRI already forecasts treatment response and reveals network signatures, yet needs larger prospective datasets and strict controls to prevent data leakage and inflated accuracy (1,15). Next-generation models should simulate circuit-level drug effects, link pharmacokinetics to network dynamics, and output dose–timing schedules that can be pre-registered and tested in confirmatory trials [437,438].

Future antidepressants should be conceived within an ICM framework in which induction, consolidation, and maintenance form a continuous arc of network reprogramming. Induction opens a time-limited window of heightened plasticity and excitability through mechanisms such as metaplastic priming, increased GluA1 trafficking, and TrkB engagement, enabling rapid reversal of stress-related synaptic deficits. Consolidation secures these changes by stabilizing new spines, strengthening ensembles, and leveraging homeostatic plasticity during sleep and circadian alignment so that rewired circuits persist beyond the pharmacological pulse. Maintenance then preserves adaptive connectivity with periodic, lower-intensity inputs calibrated to sustain gain control and resilience rather than chase symptoms [35,36].

Within this model, next-generation agents are network reprogrammers, not mere neurotransmitter correctors. They will target plasticity hubs and adhesion systems that determine where connections form, while tuning intrinsic excitability to decide how precisely they operate in

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context. Personalization follows naturally. Multi-point interventions can pair a plasticity inducer with circuit-specific neuromodulation and structured behavioral entrainment during the open window, measured with imaging and electrophysiology to verify engagement and timing. Computational tools that integrate fMRI and EEG already recover predictive signatures of response and can propose dose and timing schedules aligned to individual network states [14,40,177].

In sum, the ICM paradigm synthesizes molecular, circuit, and behavioral science into a practical roadmap: open the window, secure the rewrite, and keep the network steady. As plasticity and excitability research converges, antidepressant discovery in the coming decade will be redefined by phase-aware, circuit-informed, and personalized strategies that aim for durable remission rather than transient relief [36]

7. Conclusion

Effective antidepressant discovery increasingly depends on recognizing that lasting recovery arises from the integration of synaptic plasticity and intrinsic excitability rather than from monoaminergic modulation alone. Across this review, a continuous mechanistic arc has emerged: glutamatergic induction rapidly initiates receptor trafficking, dendritic spine remodeling, and synaptic potentiation; consolidation then stabilizes these early changes through BDNF–TrkB signaling, activity-dependent translation, and cytoskeletal reinforcement; finally, presynaptic integrity and excitability tuning preserve the functional consequences of remodeling at the circuit level. In this framework, monoamines may contribute to symptomatic improvement, but durable remission requires reorganization of the neural networks that encode mood, cognition, and stress responsiveness. Antidepressant action is therefore best understood not as simple neurotransmitter replacement, but as coordinated circuit repair.

This perspective carries an important translational message. Future therapeutics must engage multiple levels of plasticity at once, spanning molecular signaling, structural remodeling, and electrophysiological stabilization. Agents that trigger rapid synaptic change may open a therapeutic window, but sustained benefit will depend on interventions that consolidate and maintain those gains across vulnerable networks. Biomarkers such as SV2A PET, magnetic resonance spectroscopy, and EEG provide a practical bridge between mechanism and clinic, helping define when treatment should be delivered, which patients are most likely to benefit, and how interventions might be personalized. Within this context, the Induction–Consolidation–Maintenance model offers a clinically useful framework: induction to trigger adaptive plasticity, consolidation to encode and stabilize change, and maintenance to preserve network integrity while reducing relapse risk.

Looking ahead, the next generation of antidepressants will likely function as neuroadaptive therapies that are precisely timed, circuit-specific, and biomarker-informed. Progress in neuroimaging, computational modeling, and neurotechnology is steadily improving the capacity to identify dysfunctional circuits, monitor target engagement, and refine treatment according to individual neurobiological profiles. This shift opens the possibility of interventions that do more than suppress symptoms temporarily. By coupling plasticity induction with sustained modulation of intrinsic excitability, future therapies may reinforce adaptive firing patterns, prevent relapse-prone instability, and promote resilient remission. The most effective treatments will therefore be those that coordinate rapid rewiring with mechanisms that preserve and refine network stability over time.

Ultimately, mood recovery should be understood as circuit recalibration rather than chemical correction alone. Resilience emerges when plasticity is balanced by stability, when new synaptic configurations are supported by appropriate control of neuronal gain, and when adaptive change becomes durable enough to resist pathological drift. This unifying view moves the field beyond older transmitter-centered models toward a framework grounded in dynamic network homeostasis. The next generation of antidepressants will not simply elevate mood; they will rewire its biology.

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Abbreviations

The following abbreviations are used in this manuscript:

2R,6R-HNK	(2R,6R)-hydroxynorketamine
5-HT_{1A}	5-hydroxytryptamine receptor 1A
5-HT_{2A}	5-hydroxytryptamine 2A
7,8-DHF	7,8-dihydroxyflavone
^{11}C	carbon-11
^{18}F	fluorine-18
AGN-241751	4-chlorokynurenine [AV-101]
AIS	axon initial segment
AKT	protein kinase B
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
Arc	activity-regulated cytoskeleton-associated protein
A/T/N	amyloid/tau/neurodegeneration
BBB	blood-brain barrier
BDNF	brain-derived neurotrophic factor
BLESS	Brexpiprazole Efficacy and Safety in Major Depressive Disorder
BP	blood pressure
CA1	Cornu Ammonis area 1
CaMKII	calcium/calmodulin-dependent protein kinase II
cAMP	cyclic adenosine monophosphate
CBD	cannabidiol
CBT	cognitive behavioral therapy
CNBD	cyclic nucleotide–binding domain
CNS	central nervous system
CP-AMPAR	calcium-permeable AMPA receptor

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CREB	cyclic adenosine monophosphate response element–binding protein
CRP	C-reactive protein
CSF	cerebrospinal fluid
DBS	deep brain stimulation
DHEAS	dehydroepiandrosterone sulfate
DLPFC	Dorsolateral prefrontal cortex
DMN	default mode network
DXM	Dextromethorphan
ECT	electroconvulsive therapy
eEF2	eukaryotic elongation factor 2
eEF2K	eukaryotic elongation factor 2 kinase
E/I	excitation/inhibition
EPSC	excitatory postsynaptic current
EPSP	excitatory postsynaptic potential
ERK	extracellular signal-regulated kinase
ERP	event-related potential
FMRP	fragile X mental retardation protein
GABA	gamma-aminobutyric acid
GABA_B	gamma-aminobutyric acid type B receptor
Gβγ	G protein βγ
GEMINI	Global Evaluation of the Efficacy and Safety of AXS-05 [dextromethorphan–bupropion] in Major Depressive Disorder
GIRK	G protein-gated inwardly rectifying potassium channel
GIRK1	G protein–gated inwardly rectifying potassium channel 1 (Kir3.1)
GIRK2	G protein–gated inwardly rectifying potassium channel 2 (Kir3.2)
GluA2	glutamate ionotropic receptor AMPA type subunit 2
GPCR	G protein-coupled receptor
GTPase	guanosine triphosphatase
HCN	hyperpolarization-activated cyclic nucleotide-gated channel
HCN1	hyperpolarization-activated cyclic nucleotide–gated channel 1
HCN4	hyperpolarization-activated cyclic nucleotide–gated channel 4
ICM	Induction → Consolidation → Maintenance
ICU	intensive care unit
Ih	hyperpolarization-activated current
iTBS	intermittent theta-burst stimulation
Kcnq2	potassium voltage-gated channel subfamily Q member 2
KCNQ2–5	potassium voltage-gated channel subfamily Q member 2–5
Kir2	inwardly rectifying potassium channel subfamily 2
Kir3.x	inwardly rectifying potassium channel subfamily 3
Kv7	voltage-gated potassium channel subfamily Q
Kv7.3	voltage-gated potassium channel subfamily Q member 3
LTP	long-term potentiation

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MADRS	Montgomery–Åsberg Depression Rating Scale
MeCP2	methyl-CpG-binding protein 2
mGlu2/3	metabotropic glutamate receptor 2 and 3
MRS	magnetic resonance spectroscopy
mTOR	mechanistic target of rapamycin
mTORC1	mechanistic Target Of Rapamycin Complex 1
NAc	nucleus accumbens
NLRP3	NOD-, LRR-, and pyrin domain–containing protein 3
NMDA	N-methyl-D-aspartate
NMDAR	N-methyl-D-aspartate receptors
NREM	non–rapid eye movement
p75NTR	p75 neurotrophin receptor
PAM	positive allosteric modulator
PET	positron emission tomography
PFC	prefrontal cortex
PK-PD	pharmacokinetic–pharmacodynamics
POC	proof of concept
proBDNF	precursor brain-derived neurotrophic factor
rACC	rostral anterior cingulate cortex
RGS	G protein signaling
rTMS	Repetitive transcranial magnetic stimulation
sgACC	subgenual anterior cingulate cortex
SSRI	selective serotonin reuptake inhibitor
SV2A	synaptic vesicle glycoprotein 2A
TBS	enhanced remission durability
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation.
TRD	treatment-resistant depression
TRIP8b	tetratricopeptide repeat–containing Rab8b-interacting protein
TrkB	tropomyosin receptor kinase B
TRPV1	transient receptor potential vanilloid 1
VTA	ventral tegmental area
ZD7288	HCN channel blocker compound ZD7288

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