

Review

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Review

# Targeting the NMDA–AMPA Axis to Restore Synaptic Plasticity in Trauma-Related Disorders: Mechanistic Principles and Clinical Observations

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## Abstract

Chronic exposure to severe stress is known to erode synapses in prefrontal-limbic circuits, a biological change that can be reversed by treatments that push glutamatergic signalling away from NMDA receptors and toward AMPA receptors. Ketamine infusions confirm the value of that mechanism, yet cost, monitoring demands, and dissociative side-effects make the intravenous route hard to scale. This review looks at a fully oral, four-drug strategy intended to mimic ketamine's neuroplastic effects with inexpensive, widely available medicines. The proposed stack pairs dextromethorphan for NMDA blockade with a strong CYP2D6 inhibitor (fluoxetine, paroxetine, or bupropion) to keep dextromethorphan active longer; adds piracetam to enhance AMPA throughput; and supplements l-glutamine to replenish presynaptic stores of glutamate. Retrospective reports covering complex PTSD, dissociative fugue, and trauma-linked depression suggest that the combination can ease flashbacks, nightmares, somatic over-arousal, and even suicidality within days to a few weeks. Importantly, these benefits have been observed without the dissociation or blood-pressure spikes that often accompany ketamine infusions. Although the evidence is still limited to small case series, the early signal supports formal trials to test efficacy, safety, and the specific contribution of each component.

**Keywords:** trauma; PTSD; glutamatergic; neuroplasticity; depression; NMDA; AMPA

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## Introduction

Chronic stress and traumatic experiences are now recognized to obliterate synaptic connections in the medial prefrontal cortex, hippocampus, and amygdala—areas that affect fear learning and mood regulation [1,2]. Intravenous ketamine can repair those connections in a matter of hours, but widespread use is restricted by infusion logistics, dissociative side-effects, and cost. An oral formulation, dextromethorphan combined with bupropion (Auvelity®), represents a partial advancement towards a practical solution, delivering sustained NMDA-receptor antagonism. Nonetheless, it exerts a limited influence on the downstream AMPA component of the plasticity cascade, resulting in a delayed clinical onset and less pronounced clinical effects [3].

To imitate ketamine's full mechanistic profile using low-cost, pharmacy-shelf drugs, Cheung [4] presented a four-drug strategy: (a) dextromethorphan (DXM) for NMDA blockade; (b) a robust CYP2D6 inhibitor—typically fluoxetine, paroxetine, or bupropion—to extend DXM exposure; (c) piracetam to improve AMPA throughput; and (d) oral l-glutamine to replace presynaptic glutamate and decrease excitotoxic risk. Initial case series suggest that this combination may be particularly advantageous for trauma-spectrum presentations—such as intrusive memories, hypervigilance, somatic amplification, and dissociation—when conventional monoaminergic therapies have proven ineffective [5].

## Mechanistic Foundation

### *NMDA Blockade and Disinhibition*

Dextromethorphan (DXM) has the same main effect as ketamine: at low doses, it blocks NMDA receptors on  $\gamma$ -aminobutyric acid interneurons that inhibit other neurons. When these "brakes" are removed, cortical pyramidal neurons fire more freely, and a temporary surge of extracellular glutamate is released, paving the way for downstream plasticity [3].

### *Pharmacokinetic Extension*

Because DXM is rapidly cleared by the cytochrome P-450 2D6 pathway, the drug's window of action can be short. Potent 2D6 inhibitors such as fluoxetine or paroxetine slow metabolism by roughly an order of magnitude, keeping DXM concentrations in a therapeutically active range for most of the day [6]. This sustained exposure is thought to widen the plasticity window.

### *AMPA Potentiation*

A glutamate burst alone is insufficient; the signal must be captured postsynaptically. Piracetam, an inexpensive positive allosteric modulator at  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, heightens current flow and facilitates long-term potentiation. Animal work links this AMPA gain to rapid induction of the BDNF–mTOR cascade that drives dendritic spine formation [7,8].

### *Glutamate Replenishment*

Persistent stress depletes presynaptic glutamate pools, decreasing signal strength. Dietary l-glutamine restores these reserves and, in mouse trials, it decreases cytokine-related glutamate spikes hence reducing excitotoxic risk [9,10].

### *Integrated Perspective*

The four components—DXM for the NMDA "release," a CYP2D6 inhibitor for pharmacokinetic prolongation, piracetam for AMPA "capture," and glutamine for neurotransmitter resupply—collectively reproduce the NMDA-to-AMPA shift credited for ketamine's rapid synaptogenic and behavioural effects. Preliminary imaging after ketamine shows restored prefrontal–limbic connectivity [11]; the oral stack seeks to evoke the same circuit repair without intravenous delivery or dissociation.

## Clinical Evidence from Case Observations

### *Four-Patient Series*

The largest informal data set comes from a four-case report that followed two adults and two adolescents with differing trauma histories [5]. In the first vignette, a young man diagnosed with somatic-dominant PTSD, whose presentation centred on incapacitating cervico-thoracic pain and daily flashbacks, began nightly dextromethorphan combined with morning fluoxetine; within three months both the pain and the intrusive imagery had abated and he resumed full-time employment. The same stack, augmented with piracetam and delivered alongside bupropion rather than fluoxetine, was given to a bereaved nurse who was tormented by vivid replay of her mother's suicide; her nightmares and daytime intrusions subsided sufficiently to allow a return to ward duties. A third case involved a thirteen-year-old whose ruminative guilt and fear of renewed bullying had produced severe school impairment; twelve days after starting dextromethorphan, fluoxetine, and piracetam she reported "quiet" evenings, improved sleep, and re-engagement with choir practice. Finally, a woman with complex PTSD layered upon bipolar II disorder, ADHD, and borderline traits showed

a clear fall in trauma-focused rumination and better affect regulation on the fluoxetine–dextromethorphan backbone; subsequent addition of piracetam appeared to consolidate these gains.

### *Additional Reports*

Isolated case studies add breadth to this preliminary picture. A patient troubled by chronic derealisation and fugue-like "blank outs" experienced full resolution of dissociative spells after six weeks on the regimen [4]. Another individual with long-standing C-PTSD secondary to repeated bullying demonstrated a slower but steady decline in somatic anxiety and benzodiazepine reliance over four months when bupropion-potentiated dextromethorphan was paired with piracetam and l-glutamine [4]. In a separate retrospective series of adolescents and young adults with trauma-linked depression and active suicidality, Patient Health Questionnaire-9 scores fell into the mild range within two to four weeks, again without reports of dissociation, manic switching, or hypertensive episodes [4]. Across these heterogeneous presentations the common signature is rapid symptom relief—typically days to a few weeks—followed by functional re-engagement at school or work, all in the absence of the cardiovascular or psychotomimetic adverse effects that often limit intravenous ketamine.

## Advantages and Limitations

Oral delivery, generic pricing, and familiarity of each ingredient favour widespread adoption, especially where ketamine infusions are impractical. Night-time DXM dosing and low starting doses seem to limit daytime sedation or serotonin-syndrome risk.

Limitations encompass retrospective designs, small sample sizes, concurrent medications, and the lack of gold-standard PTSD scales (e.g., CAPS-5). Also, placebo effects cannot be ruled out. Developmental safety below puberty remains uncertain because excess excitatory drive might impair synaptic pruning [4].

## Conclusions

By coupling NMDA antagonism, CYP2D6 inhibition, AMPA facilitation, and glutamate support, the Cheung regimen offers a coherent, low-cost route to the plasticity changes credited for ketamine's rapid efficacy. Consistent case-level results justify prospective trials that use structured trauma scales, neuroimaging, and direct comparisons with Auvelity or ketamine.

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