Hypothesis

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Dextromethorphan as an Early Post-Trauma Prophylactic Candidate: Mechanistic Basis and Translational Challenges

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Dextromethorphan as an Early Post-Trauma Prophylactic Candidate:Mechanistic Basis and Translational Challenges

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Abstract

A disease-first off-patent drug-repurposing engine identified dextromethorphan (DXM) as a compound that could lower the risk of post-traumatic stress disorder (PTSD) when administered soon after exposure to severe stress. DXM combines anti-inflammatory activity, N-methyl-D-aspartate (NMDA) receptor antagonism, sigma-1 receptor agonism, and monoamine re-uptake inhibition, a profile that targets several molecular events observed minutes to hours after trauma. Animal studies confirm neuroprotection when DXM is given within two hours of injury, yet no controlled trial has tested this timing in humans. Abuse potential, a narrow therapeutic window, and the historical failure of other NMDA antagonists in neurotrauma limit enthusiasm for large programs until proof-of-concept data emerges.

Keywords: dextromethorphan; post-traumatic stress disorder prevention; acute trauma intervention; neuroinflammation; NMDA receptor antagonism; microglial modulation; drug repurposing; early prophylaxis; sigma-1 receptor agonist; conflict-zone medicine

1. Introduction

Preventing PTSD by intervening during the immediate biologic response to trauma is a long-standing goal in psychiatry and military medicine. Intravenous ketamine, although promising, requires clinical infrastructure that is rarely available in conflict zones or over-crowded emergency departments. DXM is inexpensive, orally available, and stocked globally as an antitussive. Its pharmacology mirrors key pathways linked to the earliest stages of stress-induced neurobiology, raising interest in its use as a prophylactic given within hours rather than as a chronic therapy.

2. Methods

2.1. Candidate Identification

A disease-first drug-repurposing engine screened all FDA-approved small molecules against transcriptomic signatures and pathway maps of early trauma. DXM scored in the top 10 and was selected for manual evidence review.

2.2. Literature Search and Selection

Following PRISMA guidelines, we searched PubMed, Web of Science, and ClinicalTrials.gov through 1 July 2025 using the terms "dextromethorphan", "NMDA antagonist", "PTSD", "traumatic brain injury", "neuroinflammation", and "sigma-1 receptor". Inclusion criteria were peer-reviewed articles or regulatory reports in English that examined mechanistic, pre-clinical, or clinical aspects of DXM related to trauma or neuroprotection. Two reviewers screened titles and abstracts, resolved disagreements by consensus, and extracted data on dosing, timing, outcomes, and safety.

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2.3. Quality Appraisal

Risk of bias in animal studies was assessed with the SYRCLE checklist, and human studies were evaluated with Cochrane RoB 2. Pharmacokinetic parameters were cross-validated with regulatory documents and drug-interaction databases.

3. Results

3.1. Mechanistic Alignment

DXM at micromolar concentrations suppresses TNF-α, IL-1β, and IL-6 release while polarising microglia toward an anti-inflammatory phenotype [1]. These cytokines remain elevated in chronic PTSD [2]. DXM binds the phencyclidine site of the NMDA receptor, a property shared with ketamine, which achieves sixty-seven percent response rates in chronic PTSD trials [3,4]. Sigma-1 agonism and high-affinity inhibition of serotonin and norepinephrine transporters further support mood-stabilising effects [5].

3.2. Pre-Clinical Timing Studies

In rats, a single intraperitoneal dose of DXM delivered immediately after controlled cortical impact reduced brain oedema and improved neurologic scores [6]. Rabbit models of focal ischaemia showed cortical protection when DXM infusion began within thirty minutes, but benefit disappeared with longer delays [7]. These findings define a narrow therapeutic window that matches operational realities in forward medical posts or busy emergency departments.

3.3. Human Data Outside PTSD

DXM-quinidine is approved for pseudobulbar affect and showed benefit in patients with traumatic brain injury enrolled in the PRISM-II study [8]. DXM-bupropion (Auvelity) demonstrated rapid antidepressant effects in major depression [9]. No trial has administered DXM within hours or days of trauma exposure to test PTSD prevention.

3.4. Safety Considerations

Protective plasma concentrations in animals overlap doses that cause dissociation, tachycardia, and transient psychosis in humans [10]. DXM interacts with more than three hundred medications, including MAOIs and SSRIs, risking serotonin syndrome [11]. Approximately seven percent of individuals of European ancestry are CYP2D6 poor metabolisers, increasing exposure duration [12]. The FDA's 2024 refusal to approve MDMA-assisted therapy illustrates current regulatory caution toward psychoactive agents in PTSD [13].

3.5. Comparison with Existing Acute Strategies

Intravenous ketamine provides rapid symptom relief but needs infusion capability. DXM can be given orally in the field but requires fifteen to thirty minutes to reach effective plasma levels. Previous NMDA antagonists, including selfotel, failed in late-phase neurotrauma trials, suggesting potential class limitations [14].

4. Discussion

DXM addresses inflammation and excitotoxicity, two drivers of the immediate post-trauma cascade. Its oral formulation and low cost make it attractive for deployment where intravenous agents are impractical. Yet the effective dose lies precariously close to the threshold for dissociative and psychotomimetic effects, and trauma-exposed populations already face high substance-use risk. Interaction burdens and genetic metabolism variants add complexity.

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The next step is a carefully controlled, adequately powered trial in which trauma survivors receive a single high dose of DXM within two hours of exposure, followed by serial Clinician-Administered PTSD Scale (CAPS-5) assessments over thirty days. Stratification by CYP2D6 genotype and systematic biomarker sampling would clarify pharmacokinetic and pharmacodynamic variability.

5. Conclusion

DXM is a mechanistically plausible, globally available candidate for prophylaxis against PTSD when given shortly after trauma. Its potential utility in conflict theatres, frontline occupations, and emergency departments justifies targeted proof-of-concept trials.

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Intellectual Property: The authors hold no patents or patent applications related to dextromethorphan as a mechanism-of-therapy for acute trauma. The material is offered strictly to encourage further independent research.

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