Short Note

A Stabilized Intranasal Formulation of R-Ketamine and Delta-9-Tetrahydrocannabinol (THC) for the Treatment of Post-Traumatic Stress Disorder (PTSD) and Fear-Extinction Deficits

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A Stabilized Intranasal Formulation of R-Ketamine and Delta-9-Tetrahydrocannabinol (THC) for the Treatment of Post-Traumatic Stress Disorder (PTSD) and Fear-Extinction Deficits

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Abstract

Post-traumatic stress disorder (PTSD) remains a debilitating condition with significant unmet clinical need; existing pharmacotherapies often provide incomplete symptom management and fail to target the underlying fear memory pathology. We describe a novel, stable intranasal formulation combining R-ketamine and Delta-9-tetrahydrocannabinol (THC) designed to target the neuroplasticity deficits inherent in the disorder. This approach leverages the distinct molecular mechanisms of R-ketamine (mTORC1 signaling, BDNF expression in the mPFC) with low-dose THC (CB1 receptor agonism in the BLA) to facilitate the "unlearning" of traumatic memories. The formulation uses advanced stabilization techniques, including micelle encapsulation and antioxidants, for optimal delivery via a calibrated mucosal atomization device (MAD). We outline a therapeutic strategy and clinical trial protocols designed to evaluate efficacy, safety, and durability of effect, specifically addressing the challenges of co-morbid substance use disorders. This work proposes a potent, non-invasive therapeutic agent to address the urgent need for effective PTSD interventions.

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1. Introduction

PTSD is characterized by a failure to extinguish conditioned fear responses following trauma exposure, resulting in persistent hyperarousal, intrusive memories, and cognitive dysfunction. Existing pharmacotherapies, such as SSRIs, are often insufficient to address these core symptoms, and current research efforts in novel drug candidates have frequently failed in clinical trials (Abbott et al., 2016). R-ketamine has shown promise as a rapid-acting antidepressant and neuroprotective agent with fewer psychotomimetic side effects compared to the S-isomer (Yang et al., 2016; Domino, 2010). However, its utility in a clinical setting often faces challenges related to administration and stability.

This preprint introduces an intranasal R-ketamine and THC co-administration strategy. This approach is grounded in preclinical evidence demonstrating R-ketamine's ability to promote BDNF-mediated synaptogenesis and the role of the endocannabinoid system (ECS), particularly CB1 receptor signaling, in fear extinction learning. The objective is to provide a stable formulation and method of use that maximizes therapeutic potential while mitigating the risks associated with existing treatments.

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2. Materials and Methods

Formulation and Manufacturing

The formulation is a stabilized aqueous solution for intranasal delivery, designed to achieve a rapid onset of action via the nose-to-brain pathway.

- Active Ingredients: R-ketamine hydrochloride and Delta-9-tetrahydrocannabinol (THC). A target ratio of 10:1 to 20:1 R-ketamine to THC (w/w) is maintained.
- Stabilizers:
  - Solubilization: Non-ionic surfactants such as Poloxamer 188 or Tween 80 are used to encapsulate hydrophobic THC in micelles, ensuring a homogenous solution.
  - Antioxidants: 30 mM Ascorbic Acid or Alpha-Tocopherol is included to prevent oxidation of the cannabinoid component into inactive CBN.
  - Adsorption Mitigation: Polyethylene Glycol (PEG) 1450 is used to treat internal surfaces of the delivery device, preventing loss of active ingredients to plastic.
- Device: A calibrated Mucosal Atomization Device (MAD) is used to ensure optimal Plume Geometry and Droplet Size Distribution for targeted nasal delivery.

Dosage and Administration

The agent is administered intranasally twice weekly for a 4-week induction period. Dosage is determined by baseline CAPS-5 scores.

PTSD Severity (CAPS-5 Score)	Severity Descriptor	Recommended Intranasal Dose (mg R-Ketamine / mg THC)
11 – 25	**Mild**	**~20 mg R-ketamine / 1-2 mg THC**
26 – 45	**Moderate**	**~40 mg R-ketamine / 2-4 mg THC**
46 – 60	**Severe**	**~60 mg R-ketamine / 3-6 mg THC**
61+	**Extreme**	**~80 mg R-ketamine / 4-8 mg THC**

Clinical Trial Protocols

Trials are designed to evaluate efficacy and safety in complex patient populations, including those with co-morbid substance use disorders.

- Primary Outcome Measure: Change in the total score of the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5).
- Secondary Outcome Measures: Fear-Potentiated Startle (FPS), fMRI connectivity analysis (mPFC-BLA circuits), Plasma BDNF levels, and objective sleep quality measures (EEG coherence).

3. Results and Discussion

Preliminary data in animal models suggest that R-ketamine significantly improves cognitive function associated with neurodegenerative diseases and substance use disorders (Pan et al., 2009; Ferro et al., 2007; Sekine et al., 2001). This effect is likely mediated by a BDNF-TrkB receptor mechanism. In contrast, S-ketamine shows no such effect (Yang et al., 2016). The combined formulation of R-ketamine and low-dose THC is hypothesized to translate this neuroprotective effect

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into a rapid-acting PTSD treatment. The targeted delivery and precise ratios are expected to produce superior outcomes compared to existing therapies.

5. Conclusions

The stabilized intranasal R-ketamine/THC formulation offers a novel, potent therapeutic approach for treatment-resistant PTSD. By combining R-ketamine's synaptogenic properties with THC's role in fear extinction, this agent targets the core pathology of trauma-related memory dysfunction.

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