Study Protocol

Official Title: Ketamine + Cognitive Training for Suicidality in the Medical Setting: Pilot

ClinicalTrials.gov ID (NCT number): NCT04154150

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Scientific Background

Rapidly acting pharmacological agents, such as subanesthetic ketamine, offer the promise of a new opportunity to address suicidal crises with the urgency they require, but this promise remains unfulfilled to date. Ketamine rapidly reduces suicidal thoughts as early as 2-24 hours after a single infusion, both in depressed patients and in transdiagnostic patients selected for high suicide risk, with some evidence suggesting effects on suicidality are statistically independent of antidepressant effects. Yet, a significant barrier to clinical adoption of this treatment approach is the lack of evidence for durability of these effects, raising concerns about illusory recovery and subsequent rebound of suicidality. Even if safe, effective pharmacological strategies to sustain ketamine's rapid effects are identified, the majority of depressed patients express preference for treatments involving a behavioral/learning component (e.g., up to 91% enrolling in drug trials.

Practical challenges in maintaining drug regimens over time further suggest that a diversity of approaches to achieve rapid, durable relief is likely to benefit the field; but efforts to extend ketamine's rapid effects nonpharmacologically remain in early stages.

In the proposed effectiveness pilot RCT, we posit that intravenous ketamine will induce a rapid shift towards greater plasticity and cognitive flexibility among patients with a recent suicide attempt, which can then be exploited in order to consolidate adaptive learning while neuroplasticity remains high. At the molecular level, depression and suicidality have been characterized as failures of neuroplasticity, including neuronal atrophy and synaptic depression in the prefrontal cortex (PFC) and hippocampus. At the neurocognitive level, suicidality is marked by impairments in experience-based learning, decision making, cognitive flexibility, and prefrontal inhibition, leading to inflexible negative biases in cognition and behavior, such as rigidly held "depressive selfschemas" (negative representations of self), a key risk factor for depression. Ketamine is posited to reverse the molecular signature of depression via

synaptogenic and neuroplasticity effects at the molecular level. We propose to leverage this shift to support adaptive learning. Thus, we hypothesize that we can extend and/or enhance rapid relief from suicidality during this window of opportunity by reinforcing adaptive self-representations through a novel form of cognitive training (CT) delivered by laptop computer. The past decade has seen growing interest in automated, mechanistic, dissemination-ready CT treatments, designed to modulate affective processing patterns directly in order to reduce symptoms. Though clinical effects show potential for reducing suicidal ideation in high-risk samples, the durability of such effects is currently limited. A critical gap in this literature, which this proposal will fill, is to initiate CT synergistically during a key clinical window of opportunity, when euthymic mood and enhanced plasticity are expected, to consolidate beneficial processing patterns and increase and prolong ketamine's rapid anti-suicidal effects.

This project will extend our research program wedding two previously unlinked areas of research: rapid pharmacology and automated CT. This synergistic approach is ideally suited to reaching individuals at imminent risk of suicide who may not otherwise engage effectively with mental health care: in this case, medical inpatients referred for psychiatric consultation/liaison immediately following a suicidal act. Patients will receive all study intervention procedures in a medical inpatient setting (e.g., during toxicology stabilization), and then will be followed as they transfer to psychiatric inpatient settings (as part of standard care), enabling us to quantify the impact of a single ketamine "pretreatment" on acute and long-term outcomes following a suicidal crisis. We will expand on our previous, replicated findings suggesting ketamine promotes rapid decreases in explicit suicidal thoughts, which are further linked to rapidly increased plasticity in implicit self-representations. In addition, we will pilot test a brief, highly efficient CT intervention designed to work synergistically within the brief window of opportunity ketamine provides in order to consolidate beneficial self-representations while neuroplasticity remains high.

Study Objectives

This project seeks to identify the acute and longer-term impact of a single dose of intravenous ketamine among suicidal patients referred for psychiatric consultation/liaison in the medical inpatient setting. We will then explore the feasibility of introducing helpful information delivered by a computer-based training protocol, designed to extend ketamine's rapid effects. This work could ultimately lead to the ability to treat suicidality more efficiently and with broader dissemination by rapidly priming the brain for helpful forms of learning.

Study Design & Methods

Medical inpatients will be enrolled through the psychiatric consultation/liaison service in a large Level 1 trauma hospital. In the context of ongoing standard care, participants will be randomized in a double-blind, parallel arm design to one of two groups: ketamine infusion followed by fully automated, computer-based CT or ketamine infusion followed by a sham variant of CT (a computer task that does not target suicide-relevant cognition).

Eligibility Criteria:

Inclusion Criteria:

Participants will:

1. be between the ages of 18 and 65 years
2. be a medical inpatient referred for psychiatric consultation/liaison due to suicidality
3. possess a level of judgment and understanding sufficient to agree to all procedures required by the protocol and must sign an informed consent document
4. be deemed an appropriate and reasonable medical candidate for intravenous ketamine by a physician authorized to prescribe medication to the patient during inpatient hospitalization

Exclusion Criteria:

1. Presence of current psychotic or autism spectrum disorder or current delirium
2. Use of a Monoamine Oxidase Inhibitor (MAOI) within the previous 2 weeks
3. Current pregnancy or breastfeeding
4. Reading level <5th grade as per WRAT-3 reading subtest
5. Past intolerance or hypersensitivity to ketamine
6. Patients taking any of the following medications: St John's Wort, theophylline, tramadol, metrizamide
7. Patients who have received ECT in the past 6 months prior to intake
8. Patients at risk for withdrawal related issues (e.g., delirium tremens, severe opiate withdrawal) or who present with substance-induced psychosis
9. Patients who, based on expressed preference and/or home geographic location, are deemed by the Psychiatric Consultation/Liaison service to be likely to receive inpatient psychiatric hospitalization at an alternate location outside of Western Psychiatric Institute & Clinic

Statistical Considerations and Statistical Analysis Plan

This is a pilot study, designed to develop novel study infrastructure and novel intervention methods, leading to small numbers of patients in each

treatment arm. Descriptive statistics (means, standard deviations) will be reported without statistical analysis to directly compare the two groups (active vs. sham CT), given the small number of patients within each group, which yields low statistical power for between-group comparisons.