ClinicalTrials.gov ID: NCT03395314

Title: A Randomized Active Placebo Controlled Trial of Ketamine in Borderline Personality Disorder

Document: Protocol with SAP

Date: 10/19/2021

HIC 2000021457

HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2016-1)

Protocol Title: Ketamine in Borderline Personality Disorder

Principal Investigator: Sarah Kathryn Fineberg

Version Date: October 10, 2021

(*If applicable*) Clinicaltrials.gov Registration #: NCT03395314

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

APPROVED BY THE YALE UNIVERSITY IRB 10/19/2021

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

Overall Aim:

To test the potential of the rapid-acting anti-depressant ketamine to decrease suicidality in Borderline Personality Disorder.

People with Borderline Personality Disorder (BPD) are plagued by chronic suicidal ideation(1), make repeated suicide attempts (2) (3), and complete suicide at nearly 50-fold the rates of people in the general US population (4). BPD patients have low rates of functional recovery (60% in a 16-year follow up study) (5). The BPD patients who go on to complete suicide are often these patients who, after several years, have not recovered (6). There is little role for currently-available medications in BPD: none are FDA-approved, and they may do more harm than good (7).

Rapid symptom reversal with sub-anesthetic dosing of the NMDA-antagonist drug ketamine is being used in community practice for depressive symptoms based on positive experimental data in people with Major Depressive Disorder (MDD). Ketamine facilitates rapid (within hours) relief of depressive symptoms with duration of approximately 2 weeks (reviewed in (8)). Of particular note, these ketamine administration protocols can specifically decrease suicidal ideation in MDD (9). However, as ketamine has become more widely available for this indication, patients have been treated by non-psychiatrists without detailed diagnostic clarification. Anecdotal data suggests that people with BPD are receiving ketamine treatment in the community without any evidence base about safety, tolerability, or efficacy.

Pre-clinical data suggests that ketamine may increase neuroplasticity – opening a window during which new learning can occur (10). This may be relevant in BPD, where negatively-biased social interpretations impede meaningful recovery (11) and increase suicide risk over time. A post-ketamine neuro-plastic window may provide an opportunity for revisions of rigid social attributions.

We propose the first controlled experiment of ketamine in people with Borderline Personality Disorder. We aim to establish safety, tolerability, and efficacy. We will test two target mechanisms by which ketamine may reduce the frequency of suicide in BPD: suicidal ideation and social cognition.

Aim 1. To test the tolerability of ketamine in suicidal patients with BPD.
Hypothesis 1: Intravenous ketamine will be well-tolerated by people with BPD.

Aim 2: To test the impact of ketamine on suicidal ideation in people with BPD
Hypothesis 2: Intravenous ketamine will rapidly reverse suicidal ideation in BPD.

Aim 3. To test the impact of ketamine on a contributing factor to suicide in BPD: social dysfunction.
Hypothesis 3a: Intravenous ketamine will normalize quantifiable laboratory measures of social functioning in BPD.
Hypothesis 3b: Intravenous ketamine will improve real-world social functioning on self-report scales in BPD.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

10 years

5 **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Borderline Personality Disorder:

BPD is a common condition characterized by symptoms that flare in the context of interpersonal triggers. Patients experience affective (e.g. labile mood, depression, anxiety), cognitive (e.g. quasi-psychotic, dissociative), impulsive (e.g. self-injury, binge-eating or drinking, etc…), and interpersonal (e.g. profound fears of abandonment, black-and-white understanding of others). People who suffer from BPD often have sustained symptom remissions (decrease to fewer than 5 of the 9 DSM criteria); more than one-third of people in a sample of patients first diagnosed in the psychiatric hospital remitted within two years, and 90% had experienced at least a 2 year remission within 10 years (5). However, despite symptomatic remission rate growing to 99% by 16 years after diagnosis, 40% of the group had not attained functional recovery (return to or attainment of work or relationships) (5). These patients who continue to suffer with some symptoms, and with isolation from societal roles, are at high risk of multiple suicide attempts. Studies have found 5-10% of people with BPD go on to complete suicide (2, 5).

Currently available treatment for suicidality in BPD:

BPD was initially described in the literature to explain a group of patients who were not helped by traditional psychotherapies. Newer approaches to psychotherapy have been quite effective in reducing suicide threats and self-harming acts in BPD. Dialectical Behavioral Therapy, in particular, has a strong evidence base (REF), however given the expert clinicians and intensive time commitment required, there remain many patients who cannot access it. Gunderson and colleagues at McLean Hospital have put forward a manual (Good Psychiatric Management) for non-expert mental healthcare providers based on a related approach, “General Psychiatric Management,” which decreased suicidality when implemented by experienced therapists (12). There are no FDA-approved medications for BPD; efficacy data for pharmacotherapy in BPD is so weak that British guidelines recommend against using medications at all [3].

Ketamine for depression and suicidality:

In depression (10) and PTSD (13), a single sub-anaesthetic dose of intravenous ketamine provides transient relief from depressive symptoms and suicidality. Symptomatic improvements endure 2-14 days in patients who respond, and repeat dosing schedules hold promise for extending the duration of the effect (10). While anecdoctal evidence suggests that people with BPD are being treated for depression and suicidal thinking with ketamine in the community, there is no evidence base to describe safety or treatment response in this population.

Ketamine effects on neuroplasticity:

Pre-clinical studies suggest that the mechanism of action of ketamine may be through the opening of a window of synaptic plasticity 24-72 hours after infusion. In a rat model of depression, ketamine stimulated new synapse formation in the prefrontal cortex. Ketamine-induced synaptogenesis was dependent on signaling in the mammalian target of rapamycin (mTOR) pathway (14), and had downstream effects including increased brain-derived neurotrophic factor (BDNF) (15). Of interest here, Borderline Personality Disorder symptom severity has been linked to changes in BDNF expression and methylation (16) (17). Ketamine may hold promise for targeting a pathway known to be dysregulated in BPD.

We have hypothesized that BPD is maintained by inflexible social cognitive models that drive extreme views of others and negatively-skewed social attributions (18). We predict that a window of ketamine-induced neuroplasticity will offer an opportunity for revision of these rigid models in BPD patients, promoting functional recovery.

6 **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

Write here

Overview: We propose a 5-week double-blind midazolam-controlled trial to assess safety and efficacy of intravenous ketamine in people with BPD and suicidality.

Medical assessment:
During the screening process, we will obtain vital signs, relevant physical exam findings, and clinical laboratory tests (i.e. CBC with differential, complete metabolic panel [including electrolytes, LFTs, BUN, creatinine and glucose], TFTs, and routine urinalysis). EKG results will also be required to rule out any cardiac abnormalities. For most participants, we will obtain records from a recent physical (within the past year), including bloodwork. If otherwise unavailable, we may perform these screenings.

Prior to infusion, a urine drug screen will be given to all participants, and a pregnancy test will be given to all biologically female participants enrolled in the study. If the urine drug screen or the pregnancy test is positive, the subject will not be able to participate in the protocol. Results of lab tests for illicit drugs will be destroyed after the decision to include or exclude each subject. We will not maintain copies of illicit drug test results.

Subject preparation:
Subjects will fast for 6 hours prior to the infusion. Infusions will take place atthe Yale New Haven Hospital Research Unit, the Church Street Research Unit, or the CMHC Clinical Neuroscience Research Unit (CNRU) under the direct supervision of a medical doctor experienced in the administration of IV ketamine. The study MD and a research nurse will be present for the entire procedure.

Ketamine administration:
Ketamine or active placebo (midazolam) will be prepared by the YNHH research pharmacy and the subject and study personnel will remain blind to drug identity. Dosing will be through peripheral intravenous access, with low dose ketamine (0.5 mg/kg) or placebo (0.045 mg/kg midazolam) delivered over 40 minutes.

The Yale Department of Psychiatry has been safely using ketamine in adult research studies with psychiatric patients for over 20 years (8) (19). Common side-effects include vital sign changes (increased BP, P, RR), injection site reaction, and transient psychiatric symptoms. Other serious but rare side-effects can include increased intra-ocular pressure, allergic reaction, laryngospasm, hypertensive crisis, and subsequent substance abuse (19). An important benefit of the intravenous route of ketamine administration is that most side-effects clear within a few minutes of stopping the infusion. Subjects will be monitored throughout the infusion and for three hours afterward, then assessed for medical and psychiatric safety before being allowed to leave in the presence of a companion to return home. Subjects will agree not to drive or operate heavy machinery for 24h after infusions.

This protocol includes two arms: active placebo (0.045 mg/kg midazolam over 40 min), and low-dose ketamine (0.5 mg/kg ketamine over 40 min). Previous dose-response trials with ketamine for depressive symptoms in Major Depressive Disorder suggest that doses from 0.1-0.5 mg/kg can reduce depressive symptoms, however the frequency and intensity of significant response is greater at higher dose (3) (4).

We will compare outcomes in the placebo and low dose groups using repeated-measures ANOVA to examine the effects of condition and time and condition x time for the primary outcome measures of depressive symptoms (MADRS score) and suicidality (C-SSRS score), and secondary outcomes related to subjective and objective social functioning (self-reports, social distance task, trust game). We will also measure change on exploratory outcomes from tasks related to emotional intelligence and implicit associations.

During the infusion, we will collect 30ml of blood (three timepoints, maximum of 10 ml at each timepoint) for the assessment of plasma ketamine levels.

Midazolam: We selected midazolam as an active control for this trial because it has similar subjective and objective characteristics to the active study medication, ketamine. It is similar to ketamine in that it is a short-acting anesthetic agent with rapid onset of action. It induces subjective sedation and disorientation, which helps to maintain the blind for researcher and patient (1).

We selected the dose of 0.045 mg/kg midazolam to be infused over 40 minutes, as this dose has been found by others to be closest in potency to 0.5 mg/kg ketamine over 40 minutes (the planned high dose for this study) (2).

Double-blind placebo-controlled design: In order to hone in on ketamine-specific effects, we plan a double-blind placebo-controlled dose response pilot study. Each subject will undergo infusion on a single occasion with one of two possible substances: active placebo (midazolam) or low-dose (still sub-anaesthetic) ketamine. Subjects and experimenters will be blinded during the study. Symptom raters will be experimental staff who are not present during the infusion itself to avoid potential guessing of treatment identity based on side-effects of the infusion. The overview of study flow is outlined in **Figure 1,** see details in **Figure 2**. Importantly, each subject will be assessed during the expected times for maximum anti-depressant effect (1 day after infusion) and effects of neuro-plastic window (1 week after infusion). Subjects will also be followed for a full month after infusion to assess for change in outcome measures and for tolerability during the expected time period for ketamine effects to wane.

ACTIVITY / TIME	phone screen	consent	verify in-/ex-clusion criteria	demographics + psychiatric interview	ketamine or placebo infusion	SUICIDALITY MEASURES *	SYMPTOM MEASURES **	SOCIAL MEASURES ***	brief check-in ****	study completion
# completed participants expected	175	88			66					45
~ Day -14 phone screen	X									
~ Day -7 in person screen		X	X	X		X	X	X		
Day 0					X	X	X			
Day1 - office						X	X	X		
Day 2 -phone									X	
Day3 - office						X	X	X		
+1week - office						X	X	X		
Day 10- phone									X	
+ 2 wks - office						X	X	X		
+ 3 wks - phone									X	
+ 4 wks -office						X	X	X		

* SUICIDALITY MEASURES: Columbia Suicide Severity Scale focusing on current and last 7 days of symptoms, MADRS-SI

** SYMPTOM MEASURES: MADRS, BDI, BAI, ZAN-BPD

*** SOCIAL MEASURES: Preferred social distance, Trust game, Self-report of real world functioning

**** Brief check-in: abbreviated assessment of suicidality and social functioning with follow-ups as needed

Figure 2. Study procedures

Electroencephalogram (EEG) will also be measured at baseline and after ketamine infusion to test for changes in brain connectivity and regional activation in response to ketamine or midazolam. The EEG measurements are safe and non-invasive. Electrodes are placed on the scalp and face to record electrical signals from brain activity. The EEG does not transmit stimuli to the patient; it only records electrical activity from the patient.

The aim of EEG measurement here is to establish neural changes with ketamine in people with BPD, and to explore the ability of resting state EEG signal to predict ketamine response.

<u>Optional second infusion and follow-up period:</u>

Each participant in the study going forward will be offered the opportunity to participate in a second infusion with open-label ketamine. This will ensure that each person who agrees to participate in the study has the opportunity to have at least one ketamine infusion if they have persistent depressive or BPD symptoms (3+ criteria on ZAN-BPD scale). The added phase will also allow us to test the impact(s) of open-label versus double blind design on treatment response. The second infusion will be offered to occur at a timepoint when the effects of the first

infusion are expected to be negligible (5+ weeks after first infusion date). Following the second infusion, procedures will be exactly the same as those described above after the first infusion.

We may invite any past participants who have completed participation and have current BPD symptoms (3+ criteria on ZAN-BPD scale) to reconsent and receive a second infusion. We will verify that subjects have been agreed to be re-contacted at the time of original consent before re-contacting them.

Outcome measures:
Aim 1 measures tolerability/safety. We will measure tolerability by patient's subjective reports and nurse/MD observations during the infusion, as well as focused review of systems on the same day and 3 days and weekly for 4 weeks to report interval symptoms.

Aim 2 measures efficacy for the reduction of suicidal ideation. For this primary outcome measure, we will monitor change from baseline score on the Montgomery-Asberg Depression Rating Scale – Suicide subscale (MADRS-SI).

As secondary outcome measures, we will also measure interval change at each in-person visit on self-report scales including these symptom measures:
1. Depression: Beck Depression Inventory (BDI)
2. Depression: Montgomery-Asberg Depression Rating Scale (MADRS)
3. BPD: (ZAN-BPD) self-report.
4. Pain: The Brief Pain Inventory (BPI) (20)

Interviews may be audio-recorded for measures of inter-rater reliability, for later re-scoring, and for language analysis.

Aim 3 focuses on changes in social cognition. We will employ two laboratory-based quantitative measures which have been shown to reveal differences between BPD and control subjects. Importantly, both of these two assays measure social functioning in an interactive setting – the specific arena of difficulty in BPD.

Social distance task: Ralph Adolphs' group found that when 2 people stand face to face, an amygdala-lesioned patient comfortably tolerated a much smaller interpersonal space than did control subjects (**Figure 3A**), and that with decreasing distance, control subjects showed specific amygdala activation in fMRI (**Figure 3B**) (21). Given profound social dysfunction and previous reports of amygdala hyperactivity in BPD, we repeated this task in women with BPD and non-psychiatric controls. As predicted, BPD subjects preferred greater interpersonal distance (**Figure 3C**) and preferred distance correlated with BPD symptom burden (**Figure 3D**). We predict that at our post-ketamine assessments (1, 2, and 4 week follow-ups), revised social attributions will be evident in decreased preferred social distance (versus pre-ketamine measurement). We may implement a computerized version of this task for remote-only visits.

Trust game The "trust game" is a 10-round economic game with an investor and a trustee. Investments are tripled en route to the trustee, who then decides how much to return. Players repeat this investment and return cycle 10 times. When investments are low, control trustees increase returns to "coax" the investor to invest

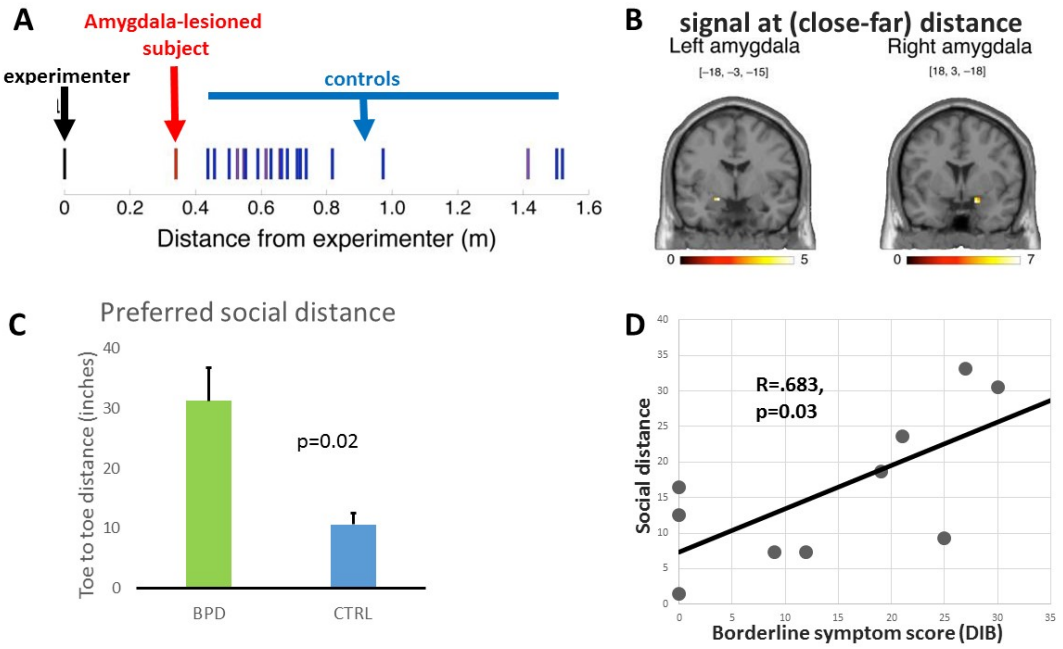
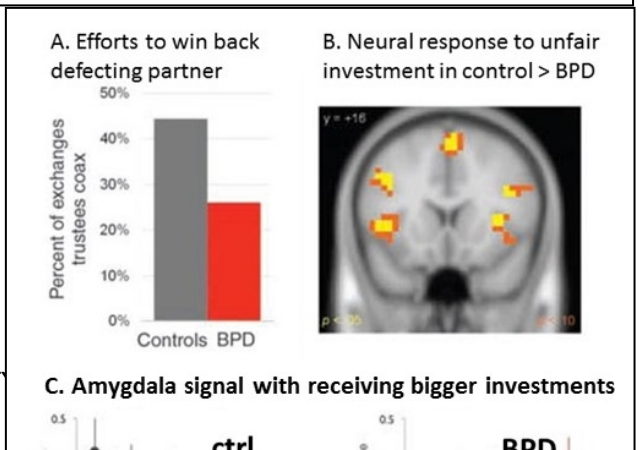


Figure 3. Social distance task The subject and experimenter stand facing one another and the experimenter slowly approaches the subject until the subject says to stop. A) Figure adapted from Kennedy et al. 2009. Control subjects prefer a roughly 1m social distance; an amygdala-lesioned subject prefers a much smaller distance. B) Also from Kennedy et al. Close vs. far distance leads to bilateral amygdala activation. C,D) Our preliminary data in 5 subjects/group suggests that BPD subjects prefer a much greater distance (C), and that this effect correlates with BPD symptom burden (D).

more. BPD trustees coax less ((22), **Figure 4**). We predict that ketamine will increase coaxing during ketamine administration, and on follow-up assessments (after window of increased neuroplasticity).



Subjects will also complete the canonical social cognition task "Reading the Mind in the Eyes" and self-report measures of social cognition and implicit associations. These are brief computer-based surveys.

Subjects will be interviewed with audio recording to discuss body modifications. We aim to test the hypothesis that people with BPD may modify respond to aberrant sense of self by modifying their bodies in non-self harming ways in addition to the canonical self-harm that is known to be frequent in BPD. Subjects will be invited to have body modifications, including hairdos, tattoos, piercings, makeup, etc documented by photography as part of this interview. Photographs will be closeups of the specific modification with blurring of facial features to avoid potential identification of any specific subject.

We will also record spontaneous fluctuations of the pupillary diameter prior to EEG recordings, since fluctuations in autonomic activity and arousal are a promising biomarker for neuropsychiatric disease states. We will use a commercially available system for recording pupillary diameter over time during five-minute epochs. These experiments will be conducted prior to behavioral testing while the individual fixates on a location, without any task. We will determine whether spontaneous fluctuations of the pupillary diameter are increased after ketamine administration.

Study visits may also be conducted by secure audiovisual messaging platform, such as the Yale Zoom product, and participants may complete surveys using secure survey platforms such as Qualtrics and RedCap, and may complete computer-based tasks delivered through internet platforms. Consent will be collected in one of two methods: (1) either through online/electronic (e-Consent) format using Epic or REDCap or (2) remotely obtained consent in which a consent form will be mailed or email to individual research participants who will then sign a printed or electronic version of the consent form and fax/scan/email/send a picture of the signed consent form. After obtaining participants' consent, video-conference visits may be recorded for quality assurance and training purposes.

As a precautionary measure due to conversations about suicidality, every participant in our study will receive a paper copy of resources for people who may feel suicidal or need urgent mental health support

Data analysis:

Placebo-controlled studies of ketamine in adult depression report effect sizes (Cohen's d in two-group design) of 1.5 (23, 24). Based on those results, we predict Cohen's $f^2 > 0.3$ (medium effect size in ANOVA) with a sample size of 15 subjects in each of 2 groups to detect a difference at the □=0.05 level. For the primary outcome of suicidal ideation, repeated-measures ANOVA will be used to compare MADRS-SI score between treatment conditions and over multiple time points. A similar approach will be employed to look for differences between conditions (active placebo, low-dose ketamine) on symptom scales and interactive social measures.

Participants will be contacted upon unblinding to disclose their treatment assignment. We will phone or text them to arrange their preferred method of contact (email or postal mail), and will send them the attached letter template. The unblinding letter will include a personalized graph with enough data to help subjects interpret how they did in the study.

Data coordination with Esterlis Lab:

Data sharing is planned between two studies (Esterlis protocol HIC # 1101007933 and Fineberg protocol HIC # 2000021457). We aim to examine the relationship of neuroimaging markers to clinical ketamine

response. Subjects who enroll in either study and may be eligible will be invited to be screened for the other study.

7 Genetic Testing N/A ☒

8 **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

Write here

We will include 66 subjects aged 21-60 who have BPD and suicidal ideation but no imminent suicidal intent. Suicidal intent will be measured by the subject's responses on the Columbia Suicide Severity Scale, and by the study MD to provide further assessment as needed. Diagnosis will be verified by semi-structured interview and scores on BPD screening interview. Baseline assessment of current and past suicidality will be done using the Columbia Suicide Severity Rating Scale. Medications must be stable for one month prior to study initiation and during the study. Subjects may continue to engage in any ongoing psychotherapy, and will be required to be engaged with mental health treatment. Exclusion criteria will be psychotic diagnosis in self or 1st degree relative, current substance dependence, history of NMDA-antagonist abuse (ketamine, PCP, etc…), history of opiate abuse, current prescription of topiramate, lamotrigine, or lithium, history of major medical illness especially neurologic or cardiovascular condition. All potential subjects will undergo urine drugs of abuse screening, which must be negative on the day of study infusion; pregnancy tests will be administered to all female subjects, which must also be negative for participation. Results of testing for illicit drugs will be destroyed after inclusion/exclusion decision for each subject.

Subjects will be recruited from the community, including local mental health practitioners and from previous study subjects who agreed to be re-contacted for future studies.

9 **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

10 **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Write here

Inclusion Criteria:
Age 21-60
Meets criteria for BPD based on Diagnostic Interview for BPD, Diagnostic Interview for Personality Disorder BPD questions, and psychiatrist interview.
Has history of suicidal ideation.
Fluent in English

Has a current mental health treater, and signs bi-directional release of information to that treater

Exclusion Criteria:
Current suicidal intent (these subjects will be identified by Columbia Suicide Scale, and will be referred for emergency treatment by study MD).
Med changes in last 4 weeks.

Any ketamine in any context in the last one year.
Current prescription for topiramate, lamotrigine, or lithium.
Psychotic disorder in self or first-degree relative.
Current substance dependence including alcohol dependence.
Any history of NMDA-antagonist abuse (ketamine, PCP, etc…).
Any history of opiate abuse.
History of major medical illness especially neurologic or cardiovascular condition, or any other medical contra-indication to ketamine administration at the discretion of the study MD.
Positive urine test for drugs of abuse on day of ketamine administration.
Positive pregnancy test on day of ketamine administration.
At the discretion of study staff.

Note of clarification: unmedicated patients will be allowed to participate in this trial.

11 How will **eligibility** be determined, and by whom? Write here

By study team with approval from study PI, Dr. Fineberg

12 **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

The Yale Department of Psychiatry has been safely using ketamine in adult research studies with psychiatric patients for over 20 years (8) (19). Common side-effects include vital sign changes (increased BP, P, RR), injection site reaction, and transient psychiatric symptoms. Other serious but rare side-effects can include increased intra-ocular pressure, allergic reaction, laryngospasm, hypertensive crisis, and subsequent substance abuse (19). An important benefit of the intravenous route of ketamine administration is that most side-effects clear within a few minutes of stopping the infusion. Subjects will be monitored throughout the infusion and for three hours afterward, then assessed for medical and psychiatric safety before being allowed to leave in the presence of a companion to return home. Subjects will agree not to drive or operate heavy machinery for 24h after infusions.

Ketamine is a medication approved by the Food and Drug Administration to be used as an anesthetic. It is a dissociative anesthetic that has been used in humans since the late 1960's. Despite extensive experience here at Yale and elsewhere there is no clear evidence of long-term toxicity associated with ketamine administration. However the acute behavioral side effects of this medication warrant particular attention. Krystal et al, administered ketamine to approximately 30 healthy subjects at the West Haven VAMC. The first study showed that ketamine produces dose-related effects at sub-anesthetic effects in healthy subjects. At 0.1 mg/kg administered over 40 minutes, the low dose in the VA protocol, ketamine produced little more than a tingling in the extremities and a "little buzzing in the head". At 0.5 mg/kg, the VA study's high dose, and the dose proposed in this protocol, ketamine transiently elicited both the positive and negative symptoms of schizophrenia, dissociative symptoms, attentional impairments, a preferential impairment in delayed over immediate recall, increased perseverative errors on the Wisconsin card sort test, and decreased verbal

fluency. In the sub-anesthetic dose utilized in this study, perceptual changes dissipate within 10-20 minutes following the termination of ketamine infusion. Ketamine also increased prolactin and cortisol, while blunting a test day decline in plasma HVA. Ketamine increased systolic and diastolic blood pressure by approximately 10-15 mm Hg, without a clear effect on pulse. Ketamine did not produce gross disorientation, as evidenced by complete absence of an effect on the MMSE and the successful completion of all categories on the Wisconsin card sort test. There have been no medical complications of ketamine administration to date. There have not been adverse psychological reactions in any of the healthy subjects. There is no doubt that ketamine has clear and, in some cases, dramatic effects upon cognitive function. Some people find these effects pleasant or interesting and others find these effects frightening. In prior studies, all subjects have been thoroughly prepared for possible ketamine response prior to testing and debriefed at the end of each test day. As a result, only two subjects terminated their participation in either study prematurely. No subject has had adverse or lingering responses to ketamine following a test day. Also, none of the subjects experienced "flashbacks" to their ketamine experiences following a test day. These findings are very consistent with the earlier work of Domino and his colleagues. Thus, ketamine appears to be safe and, despite the intensity of its short-term behavioral effects, well tolerated. The extent to which the effects of ketamine are perceived as unpleasant is context dependent and can be reduced by preparing individuals in advance for the possible responses to ketamine, which we will do carefully here as part of the consent process.

None of the patients or healthy subjects receiving ketamine in Yale studies to date has had any *long-term* adverse consequences as a result of ketamine administration. This impression is supported by follow-up data up to 2 years on 132 healthy subjects participating in ketamine studies at Yale University and at Washington University at St. Louis (unpublished data). Researchers examined follow-up assessments collected in a sub-sample of 132 healthy subjects who returned for subsequent testing over a duration of 1 week to 2 years. These subjects completed a similar battery of assessments when they reappeared as they completed in their earlier testing. In this analysis, no significant changes occurred in any measure between their initial and follow-up assessment.

Blood drawing/intravenous placement: Bruising or thrombosis can occur with placement of the intravenous line. A total of 30cc may be drawn at baseline in case recent labs are not already available to ensure subject health before entering the study, and a total of 30cc will be drawn on infusion day to quantify circulating ketamine levels. The total blood drawn for the whole study will not exceed 60 ml. The risks of blood draws include brief pain at the time of needle insertion, bruising, swelling at needle site and rarely, fainting or infection. The amount drawn is considerably less than 500 cc, the amount approved by the Red Cross.

Electroencephalogram (EEG): EEG is a safe procedure with no risk of electric shock. One risk is minor skin irritation on the scalp due to application of electrode gel which can be mitigated by immediate removal of gel with cloth.

Psychiatric evaluation, rating scales and questionnaires: These are all non-invasive, should add no risk, and have been used without difficulty or adverse events in previous studies with a similar population. The major disadvantage is the time taken to complete them.

Clinical Deterioration: There is a risk that a participant may experience an increase in BPD or depressive symptoms due to the natural course of the illness or poor response to ketamine administration. Because subjects will be asked to refrain from changing any psychotropic medication over the course of the study,

clinical progress will be monitored closely with frequent symptom ratings and frequent contact with clinic personnel. The following are criteria for evaluation and possible pharmacological and/or non-pharmacological treatments: (1) An increase of 25% in depression or BPD symptom score at any time over the course of treatment (lasting beyond acute administration studies), (2) new-onset of suicidal intent or an increase in passive suicidal ideation.

Risks of Ketamine:
The experimental drug, ketamine, is approved by the U.S. Food and Drug Administration (FDA) for use as an anesthetic (a medication that is used to block sensations, pain or consciousness/awareness) for procedures, but ketamine is not approved for the treatment of BPD so not all risks or side effects are known. While you are receiving ketamine through the IV tube in your vein, you may notice that ketamine affects the way you think, making you feel detached from your surroundings and reducing your concentration. It may also make you feel like you are in a dream, with colors or sounds seeming brighter or duller than usual. Your body may also feel different, for example you may feel that you are floating. You may also notice having blurred vision, and you may feel a little sleepy. Other behavioral effects of ketamine can include decreased pain, increased anxiety, feeling high, confusion, and hallucinations (hearing or seeing things that are not really there). Other effects of ketamine administration that you may experience include sweating, increased blood pressure, increased heart rate, rash, nausea or vomiting. Nausea is one of the most common side effects of ketamine. The risks of vomiting are minimized by asking you to refrain from eating anything on the morning of the test session. These are possible effects from getting ketamine that you may or may not experience. Generally, noticeable effects are gone within 30-60 minutes of completing the ketamine administration. The risks of participating in the optional second infusion are similar to the risks of the single-dose protocol.

The most serious possible risks or side effects of ketamine are:

1) Severe respiratory depression and apnea (problems breathing).
2) Substance abuse/dependence.
3) Elevations in intraocular pressure (eye pressure) that could lead to vision problems.
4) Allergic reactions to ketamine are possible. Serious allergic reactions can be life-threatening.
5) Elevation in blood pressure that could result in stroke, heart problems and death.

The most common side effects of ketamine are:

1) Elevated blood pressure, breathing rate, and pulse rate.
2) Local pain at injection site and temporary rash.
3) A variety of temporary psychological symptoms including, but not limited to anxiety sadness, disorientation, insomnia, flashbacks, hallucinations, and psychotic symptoms. These types of reactions have occurred in approximately 12% of participants given higher doses of ketamine when used for anesthesia. These symptoms usually last no more than a few hours.

Less common side effects are:

1) Respiratory depression.
2) Enhanced skeletal muscular tone resulting in tremors (shakiness) and jerking movements.

Rare side effects are:

1) Changes in heart rhythm
2) Severe respiratory depression and apnea

3) Recurrences of psychological side effects such as hallucinations, disorientation and anxiety up to 24 hours after the anesthetic dose administration.
4) Substance abuse/dependence:

You should know that there is the potential for people to abuse ketamine. It is unclear whether exposure to ketamine in the laboratory can result in ketamine use or abuse. Thus, if you are concerned about this possibility, you should not participate in this study. Also, if at any point after completing this study you become aware of a desire to use or abuse ketamine, you should contact us immediately. We will refer you to an appropriate treatment facility if necessary. In our experience doing research with ketamine, we are unaware of individuals abusing ketamine as a result of study participation.

We are also taking a number of precautions to help reduce the chance of having an unpleasant response to ketamine or to reduce the severity of any lingering medication effects. These precautions include:

1) A research clinician will be present throughout the study to offer support and to help clarify the progress of the test day in case the medication causes feelings of confusion. A research doctor will also be available.
2) Medications are available to relieve distress related to the behavioral effects of ketamine.
3) We will ask you to remain at the research unit until the behavioral effects of ketamine have worn off.
4) We will review the test day with you to deal with your feelings and reactions before you leave.
5) We will ask you to contact us at any time if any unpleasant effects occur.
6) We will ask you not to engage in demanding work in the day following the test session and we will work with you to schedule your test day accordingly.
7) If you have any lingering medication effects, such as sedation, work with you to assess and respond to these side effects.
8) If you develop psychiatric symptoms, we may admit you to the hospital. This may be involuntary if you are in imminent danger of harming yourself or others.
9) We may also invite you to stay in the psychiatric hospital at the Connecticut Mental Health Center before or after the testing day to facilitate your travel and participation in the study.
10) We will also talk with you on the phone or in person on days 1, 2, 3, 7, 10, 14, 21, and 28 days/weeks/months after the test day for safety checks and research visits.

Risks to pregnant women and fetuses are unclear, and female participants must have negative pregnancy tests at screening and the infusion visit, and must agree to use a reliable form of birth control during the study.

Risks of Midazolam:

The placebo medication (midazolam) is an FDA-approved medication that is in the class of benzodiazepine type medications. It is FDA approved at higher doses for anaesthesia, and is also approved for pre-procedure management of anxiety. If used frequently, it can lead to chemical dependence.

The most common risks (occurring in 1-10% of people) of the placebo medication (midazolam) are:

Breathing becoming too slow or too shallow or stopping
Low blood pressure
Drowsiness or even severe sedation
Headache
Hiccups
Nausea or vomiting
Nystagmus (unusual eye movements)
Agitation

Write here

13 Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.
As described above, potential subjects will be carefully prepared for the possible side-effects of ketamine administration and monitored by trained personnel (including experienced research nurse and MD) during administration, and through frequent study contacts thereafter as scheduled and as needed. All subjects will be required to be in active mental health treatment during the course of the study.

With regard to medical risk of ketamine administration, all subjects will undergo medical screening to include baseline bloodwork, EKG, and physical exam at baseline to ensure good physical health before beginning the study. Subjects will be monitored during and for 1 hour after ketamine or placebo infusion for changes in vital signs or physical problems.

With regard to the psychiatric evaluation and the completion of scales, subjects will be provided a comfortable quiet environment to complete them whenever possible to reduce the potential annoyance of working on them, and will be offered the opportunity to take breaks in case of strong or upsetting emotions that may arise due to clinical questions.

Each subject will be assessed by Dr. Fineberg to determine that (s)he is safe to go home at the end of the infusion visit. This evaluation will include, but is not limited to, a brief neurologic evaluation including assessment of gait and alertness, and a brief psychiatric evaluation including assessment of current mood and safety at the time of discharge.

With regard to potential for clinical deterioration, subjects' symptom scales will be reviewed before the subject departs from the clinic at each visit and, as discussed above, subjects will meet with the study psychiatrist to discuss clinical status as well. For any subject who becomes unstable by the criteria listed above, the study psychiatrist will assess whether emergency resources are needed. If they are needed, standard clinical practice is to request ambulance transport to the emergency room for emergency psychiatric evaluation, and to give verbal and written signout to the emergency personnel about the reason for evaluation. If emergency evaluation is not needed, but clinical deterioration is detected, the study PI will meet with the patient to assess for the need to discontinue the study and to assess for the need to do further safety planning, including such avenues as making a written safety plan, contacting supportive others, contacting the subject's clinical team, etc. We may also offer voluntary admission to the Clinical Neuroscience Research Unit (CNRU) at the CMHC.

If a subject experiences a clinical deterioration during a study visit, the subject will be assessed by Dr. Fineberg to determine the appropriate next steps, which may include reassurance, revised safety planning, involving the outpatient treatment team (n.b. having an outpatient mental health provider is an inclusion criterion for this study), voluntary admission to the Clinical Neuroscience Research Unit, and/or referral to the Emergency Department for further assessment. If you become agitated or very anxious during the infusion, we may offer you an oral dose of medication to help you feel calmer.

Given our interest in studying the safety and tolerability of ketamine in Borderline PD, we will continue to follow anyone who unfortunately does experience clinical deterioration during the study.

14 Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)

a. What is the investigator's assessment of the overall risk level for subjects participating in this study? moderate

b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? n/a

c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for

   i. Minimal risk
   ii. Greater than minimal

Greater than minimal Risk DSMP

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency which must be conducted at a minimum of every 6 months (including when re-approval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator or the IRB have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed moderate for the following reasons: (choose those that apply)

1. We do not view the risks associated with the ketamine infusion as minimal.
2. Given the now established safety and validity of the current dose of ketamine in our prior work, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience

with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:
Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator (Sarah Fineberg MD PhD) according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

1. is life-threatening OR
2. results in in-patient hospitalization or prolongation of existing hospitalization OR
3. results in persistent or significant disability or incapacity OR
4. results in a congenital anomaly or birth defect OR
5. results in death OR
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, OR
7. adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting Reportable Adverse Events and other unanticipated problems involving risks to subjects or others to the IRB

The principal investigator will report the following types of events to the IRB: a) adverse events that are serious or life-threatening AND unanticipated (or anticipated but occurring with a greater frequency than expected) AND possibly, probably or definitely related to the drug/device/intervention; and b)other unanticipated problems involving risks to subjects or others.

These adverse events or unanticipated problems involving risks to subjects or others will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website.

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), and funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

X All Co-Investigators listed on the protocol.

X Food and Drug Administration

The principal investigator (Sarah Fineberg, MD PhD) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A

i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?
ii. What provisions are in place for management of interim results?
iii. What will the multi-site process be for protocol modifications?

d. For multi-site studies for which the Yale PI serves as the lead investigator:
n/a

15 Statistical Considerations: Describe the statistical analyses that support the study design.

Write here

Data analysis:

Placebo-controlled studies of ketamine in adult depression report effect sizes (Cohen's d in two-group design) of 1.5 (23, 24). Based on those results, we predict Cohen's $f^2 > 0.3$ (medium effect size in

ANOVA) with a sample size of 15 subjects in each of 2 groups to detect a difference at the α=0.05 level. For the primary outcome of suicidal ideation, repeated-measures ANOVA will be used to compare MADRS-SI score between treatment conditions and over multiple time points. A similar approach will be employed to look for differences between conditions (active placebo low-dose ketamine) on symptom scales and interactive social measures.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

1. Name of the radiotracer: *Write here*

2. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

3. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use)

B. DRUGS/BIOLOGICS ☐N/A

Ketamine
Midazolam

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☒
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☒
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☒
4. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☒
5. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☒

Regarding Exemption Category 1 item 3:

--Ketamine has now been tested in a large number of people with treatment-resistant depression and suicidal ideation (Wilkinson et al., Am J Psychiatry, 2018, vol. 175(2): 150-8) and posttraumatic stress disorder (e.g. Feder et al., JAMA Psychiatry, 2014, vol. 71(6): 681-8) without report of serious adverse events. Of particular note is a report of safety and stability of cognitive outcomes over several years after multiple infusion protocols from the Yale Psychiatric Hospital in 2018 (Wilkinson et al., J Clinical Psychiatry, 2018, vol. 79(4)).

--Also, an intranasal formulation of ketamine has been recently approved by the FDA. This medication “Spravato” is esketamine, the left-handed enantiomer of ketamine. Please find this spring 2019 FDA approval documentation in attachments to protocol.

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):

☐ Blood grouping serum
☐ Reagent red blood cells
☐ Anti-human globulin

☐ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. Background Information: Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Ketamine is a medication approved by the Food and Drug Administration to be used as an anesthetic. It is a dissociative anesthetic that has been used in humans since the late 1960's. Despite extensive experience here at Yale and elsewhere there is no clear evidence of long-term toxicity associated with ketamine administration. However the acute behavioral side effects of this medication warrant particular attention. Krystal et al, administered ketamine to approximately 30 healthy subjects at the West Haven VAMC. The first study showed that ketamine produces dose-related effects at sub-anesthetic effects in healthy subjects. At 0.1 mg/kg administered over 40 minutes, the low dose in the VA protocol, ketamine produced little more than a tingling in the extremities and a "little buzzing in the head". At 0.5 mg/kg, the VA study’s high dose, and the dose proposed in this protocol, ketamine transiently elicited both the positive and negative symptoms of schizophrenia, dissociative symptoms, attentional impairments, a preferential impairment in delayed over immediate recall, increased perseverative errors on the Wisconsin card sort test, and decreased verbal

fluency. In the sub-anesthetic dose utilized in this study, perceptual changes dissipate within 10-20 minutes following the termination of ketamine infusion. Ketamine also increased prolactin and cortisol, while blunting a test day decline in plasma HVA. Ketamine increased systolic and diastolic blood pressure by approximately 10-15 mm Hg, without a clear effect on pulse. Ketamine did not produce gross disorientation, as evidenced by complete absence of an effect on the MMSE and the successful completion of all categories on the Wisconsin card sort test. There have been no medical complications of ketamine administration to date. There have not been adverse psychological reactions in any of the healthy subjects. There is no doubt that ketamine has clear and, in some cases, dramatic effects upon cognitive function. Some people find these effects pleasant or interesting and others find these effects frightening. In prior studies, all subjects have been thoroughly prepared for possible ketamine response prior to testing and debriefed at the end of each test day. As a result, only two subjects terminated their participation in either study prematurely. No subject has had adverse or lingering responses to ketamine following a test day. Also, none of the subjects experienced "flashbacks" to their ketamine experiences following a test day. These findings are very consistent with the earlier work of Domino and his colleagues. Thus, ketamine appears to be safe and, despite the intensity of its short-term behavioral effects, well tolerated. The extent to which the effects of ketamine are perceived as unpleasant is context dependent and can be reduced by preparing individuals in advance for the possible responses to ketamine, which we will do carefully here as part of the consent process. None of the patients or healthy subjects receiving ketamine in Yale studies to date has had any long-term adverse consequences as a result of ketamine administration. This impression is supported by follow-up data up to 2 years on 132 healthy subjects participating in ketamine studies at Yale University and at Washington University at St. Louis (unpublished data). Researchers examined follow-up assessments collected in a sub-sample of 132 healthy subjects who returned for subsequent testing over a duration of 1 week to 2 years. These subjects completed a similar battery of assessments when they reappeared as they completed in their earlier testing. In this analysis, no significant changes occurred in any measure between their initial and follow-up assessment.

Midazolam is a benzodiazepine class medication that is FDA approved for anaesthesia and procedure-associated anxiolysis. It has been used in major ketamine research settings as an active control condition, such as in the group of NIMH intramural researcher Carlos Zarate, and Mt Sinai researcher James Murrough. The main risks of benzodiazepine class medications are, as listed above, sedation and depressed respiratory drive.

3. Source: Identify the source of the drug or biologic to be used. YNHH Investigational Drug Pharmacy

   a) Is the drug provided free of charge to subjects? ☒YES ☐NO
   If yes, by whom? Infusion provided during study visit at the YNHH Research Unit.

4. Storage, Preparation and Use: Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.
   Storage and preparation of drugs will be arranged by the YNHH Investigation Drug Pharmacy.

Check applicable Investigational Drug Service utilized:

☒ YNHH IDS ☐ CMHC Pharmacy ☐ West Haven VA
☐ PET Center ☐ None
☐ Other:

Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

5. Use of Placebo: ☐Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.
This is not a treatment study and placebo is not replacing treatment. There are behavioral treatments available to address suicidality in BPD, including Dialectical Behavioral Therapy. Subjects may be enrolled in DBT during this study, and they will be made aware of this alternative. Some people with BPD are also prescribed medications such as Lithium and Clozapine to decrease suicidality, and this may have benefit for some of them. Mood stabilizer medications are not allowed in this study.

b) State the maximum total length of time a participant may receive placebo while on the study.
One single infusion will be given to each subject.

c) Address the greatest potential harm that may come to a participant as a result of receiving placebo.
Placebo is not replacing treatment. Midazolam is a benzodiazepine class medication, and it carries risk of sedation, respiratory suppression, and more rarely, agitated delirium. Anterograde amnesia has associated with benzodiazepines.

d) Describe the procedures that are in place to safeguard participants receiving placebo.
All research subjects' medical history and physical exam will be assessed by the study MD. The subjects will be closely monitored including continuous pulse monitoring and frequent BP monitoring during the study infusion.

6. Continuation of Drug Therapy After Study Closure ☐Not applicable to this project

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. *Write here*

☒ NO If no, explain why this is acceptable. This infusion is not meant to provide an alternative to treatment for these subjects, but rather primarily to assess the short-term effects of ketamine infusion in this study population. Subjects will continue in the primary evidence-based treatment for BPD as they otherwise would: this is psychotherapy.

B. DEVICES ☒N/A

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol: Maximum of 500 subjects. However, when the study was revised to have two arms instead of three, a minimum number of completers was revised to 30 subjects (15 in each arm). The maximum number of completers is 66.
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: n/a

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers
☒ Posters
☐ Letter (via JDAT)
☐ Medical record review*
☒ Departmental/Center newsletters
☒ YCCI Recruitment database
☒ Other: YCCI Recruitment Call Center

☒ Internet/web postings
☒ Mass email solicitation
☒ Departmental/Center website
☒ Departmental/Center research boards
☒ Web-based clinical trial registries
☒ Social Media (Twitter/Facebook):

☐ Radio
☒ Telephone
☐ Television
☐ Newspaper
☒ Clinicaltrails.gov

* Requests for medical records should be made through JDAT as described at http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

- Provider Referrals
- Study Team Members
- Existing registries, studies, and websites where participants have previously provided informed
- consent or a request to be contacted for research utilizing their preferred method of contact
- when known.
- Joint Data Analytics Team (JDAT)

b. Describe how potential subjects are contacted.

Patients who agree to be contacted will be phoned by study staff to initiate discussion about possible participation.
Clinical trial registries will be used to identify eligible patients and contact them with IRB approved materials by phone, email, or traditional mail (letter), since this category of patients has already given their consent to be contacted for potential trials. Furthermore, participants will be recruited through the YCCI website/registry/Help Us Discover and ClinicalTrials.gov website. Study personnel will use MyChart, traditional mail, telephone, or email of patients recruited through this method. If the EPIC registration module provides a preferred method of contact, that method will be utilized.

Recruitment through JDAT:
The Joint Data Analytics Team (JDAT) will be used to query eligible patients in EPIC based on the following eligibility criteria and diagnosis codes:

INCLUDE people with any of the following:
borderline personality disorder (F60.3)
depressive disorder (F32)
depressive disorder, recurrent (F33)
persistent mood disorders (F34)
bipolar disorder (F31)
self-injurious behavior (X71-X83)
suicidal ideation (R45.851)
suicide attempt (T14.91)

EXCLUDE people with any of the following:

opiate use disorder (F11)
methadone maintenance therapy (HZ81, HZ91)
age < 21 years
age > 60 years
ischemic heart diseases (I20-I25)
cerebrovascular diseases (I60-I69)
epilepsy

JDAT will identify and send a study communication to potential participants based on these criteria as of September 1, 2013.

Potential participants who do not use MyChart will receive a paper mailing including information about the study.

JDAT will not identify the potential participants to the researchers, and therefore the researchers will receive no identifiable information from JDAT.

Messaging to Study Participants:
The following wording will be used in the letter or MyChart message patients receive via JDAT describing the study and inviting them to participate:

"You are receiving this notification because you may qualify and be interested in a study looking at an investigational medication for people who experience frequently changing moods, impulsivity, and difficulty in relationships.
The Yale New Haven Health electronic health record system has searched medical conditions to find people who may be good matches for research studies. No one has looked at your record and no information has been shared with any research doctor or research team member. Just because you received this message does not mean that you are in a research study or that you have to decide to be in this or any study.
You may be interested and eligible to participate in a research study conducted by Yale University investigators to better understand these experiences and how to best treat them.
To opt-out of research, including opting out of receiving future messages about research studies, please email optout@yale.edu or call 1-877-978-8348 and select option #3.
Title of study, Phase or type of study: Ketamine in Borderline Personality Disorder, Interventional Study, Pilot phase
Principal Investigator: Sarah Fineberg MD PhD
Phone# 203-974-7265

The message/mailing to potential study participants will also include the following information, regardless of who sends it:
"You are receiving this notification because you may qualify and be interested in a study looking at a novel investigational medication for people with frequently changing moods, impulsivity, and difficult relationships.

Description of Study:
This clinical trial primarily tests the impact of ketamine on suicidal thoughts in Borderline Personality Disorder (BPD). It also tests the impact of ketamine on symptom intensity (for mood, BPD, and pain symptoms), social cognition, and neuroplasticity in people with BPD.

Suicidal ideation and action are too common in BPD, occurring at rates similar to those in people with depression or schizophrenia. Intensive psychotherapy helps, but many people with BPD do not have access to that treatment, and not everyone responds to psychotherapy if they do get access. No medication is FDA-approved for BPD, and no medication has been shown to decrease suicidality in BPD. Ketamine is a promising medication for this problem. It is a FDA-approved for use as an anesthetic medication with N-methyl D-aspartate activity. Sub-anesthetic doses of ketamine decrease suicidality and have been shown to improve mood in people with Major Depressive Disorder (MDD). This effect is rapid, with symptom improvement within hours that endures approximately two weeks. People with BPD can have symptoms that overlap with those of MDD, however, the effective treatments for BPD and MDD differ. This clinical trial will test if ketamine, which is has been shown to be effective in MDD, is also effective in BPD.

The investigators will use semi-structured interviews and self-report questionnaires to measure suicidal ideation and clinical symptoms (adverse events, mood symptoms, BPD symptoms, and pain). Social cognition will also be measured using both interviews/questionnaires and cognitive psychology tasks.

Confidentiality and Privacy: Any personal health, financial data, and other information gathered in the study will remain [anonymous or confidential] and will be stored on a password-protected computer, only accessed by study personnel. When the results of the research are published or discussed, information will be included that would reveal your identity. We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you would like to learn more about participating in this study, please contact Dr. Fineberg at sarah.fineberg@yale.edu or 203-974-7265.

Possible Benefits: This research may not benefit you directly. However, knowledge gained from the results may help us to better understand treatment of Borderline Personality Disorder. Participation in this study is completely voluntary. You are free to decline to participate, to end participation at any time for any reason, or to refuse to answer any individual question at any time. Refusing to participate will involve no penalty or Joss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). The benefit to participation in the substudy is that participants will be certain they received a dose of ketamine. Ketamine has been demonstrated to help with mood and suicidiality in people with Major Depressive Disorder.

Questions: If you have any further questions about this study, you may contact the investigator, Sarah Fineberg MD PhD, at 203-974-7265. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation' Committee at (203) 785-4688."

c. Who is recruiting potential subjects? All research team members as well as the individuals listed above (JDAT, referring providers, etc.).

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects

☒Yes, some of the subjects

☐No

If yes, describe the nature of this relationship. Some subjects may be CMHC patients who have clinical relationships with Dr. Fineberg, study PI. Some subjects may have clinical contact with the psychiatry residents on the study team.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)
   Choose one:
   ☐ For entire study
   ☒ For recruitment/screening purposes only
   ☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

   i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:

   ii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: For brief phone screening, we aim to identify subjects who are potentially eligible (and exclude those who are certainly ineligible) before inviting subjects into the lab for lengthier full screen. When subjects are invited to the lab, they will complete the consent process before any further study procedures occur.

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
   After phone screen, eligible subjects will be invited to come to the CMHC for consent. A member of the research team will describe the study to potential subjects (including description of study rationale, procedures, potential benefits, alternative options, potential risks, and specific discussion of expected side-effects of ketamine). After this discussion, including verification that the subject can articulate these points in her/his own words, and an opportunity to review the written consent form and to ask further questions, then oral and written/electronic consent will be obtained before beginning any further study procedures. Subjects who wish to take the form home or have it emailed to consider it further before providing consent will have the option to do so. They may telephone study staff later to arrange a follow-up visit if they wish to consent to the study.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

Study staff will ask subjects to describe in their own words each of: -study rationale- study procedures- potential risks and potential side-effects of ketamine administration- potential benefits of the study- alternative treatments- option to discontinue participation in the study at any time.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.
n/a

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☐

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐Not Requesting any consent waivers

☒Requesting a waiver of signed consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☐

OR

- Does the research activity pose greater than minimal risk? YES ☐ NO☒
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☒

☐ Requesting a waiver of consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☐ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☐
- Why would the research be impracticable to conduct without the waiver? Need to phone screen potential subjects to determine basic eligibility criteria.
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *na*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research? Mental health diagnoses and symptoms. Medical results including test results and physical exam findings. Identifiers will include name, age, gender, telephone number, email address, home address.

2. How will the research data be collected, recorded and stored? Information will be collected at the CMHC and at the HRU. Each patient will be assigned a unique code for the study. A paper record connecting individual identifying information will be kept in a locked filing cabinet in a locked office. The filing cabinet will be accessible only to study personnel. The study data will be entered into computer files and printed for back-up paper copy, but will identify subjects only by their unique code.

Data sharing is planned between two studies (Esterlis protocol HIC # 1101007933 and Fineberg protocol HIC # 2000021457). Password protected files including identifying information will be shared between studies for initial coordination, then going forward, unique subject identifiers will be used to link data sets and permit future de-identification for analysis.

3. As part of participation in a study using HRU resources, each subject will have research participation information entered into the YNHH electronic medical record.

4. The HIC understands that all subjects who enroll in studies conducted at the HRU, such as this study, will have a medical record created for them at YNHH. In addition, the researchers and HRU staff will have access to records of any prior admissions to YNHH, including the details of those admissions.

5. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☒ Laptop Computer ☐Desktop Computer ☐Other

6. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study? The information we collect will be de-identified at the earliest reasonable time after we receive it, meaning we will replace identifying information with a code that does not directly identify the subject. Photographs will be edited to blur faces and only edited blurred files will be saved for later data analysis and reporting. The principal investigator will keep a link that connects identified subjects to coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify an individual subject will remain confidential. Data and research materials will be stored in locked cabinets and in password-protected files on a computer. The research team will only give coded information to others to carry out this research study.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

7. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured. The data and identifiers will remain in separate locked cabinets at the CMHC as described above. The digital data will be identified only by unique codes, and no PHI will be in digital form, other than the data entered into the YNHH Epic system for medical management of the study visit or the DMHAS electronic medical record for management of CMHC research visits. The link to personally identifiable information will be kept for a maximum of 10 years after the study is closed to recruitment, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

8. If appropriate, has a Certificate of Confidentiality been obtained?

n/a

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

Some participants (2/3 of them) will be exposed to a medication (ketamine) which has the potential to improve mood and decrease suicidality. The benefit to participation in the substudy is that participants will be certain they received a dose of ketamine. Ketamine has been demonstrated to help with mood and suicidiality in people with Major Depressive Disorder.

Participants will receive a comprehensive psychological assessment during the course of this study, and feedback will be provided to participants about their mental health. If the participant chooses, s/he may request that this diagnostic information be provided to their outpatient clinicians, at no charge to the

patient, which may help to enhance the quality of care they receive. (If the participant does not wish to have this information released to his/her clinician, it will of course be kept confidential).

Participants who are not already in specific treatment for Borderline Personality Disorder (some participants may be in a general mental health treatment that is not focused on BPD) will be provided with referrals to mental health professionals as needed, which may help them to gain access to focused treatment that they would not otherwise receive. In terms of benefits to society, we hope that this study will increase our understanding of the social neuroscience of trust in borderline personality disorder, which may help to refine treatments for these disorders.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?
   Treatment as usual with psychotherapy and/or medication management. There are behavioral treatments available to address suicidality in BPD, including Dialectical Behavioral Therapy. Some people with BPD are also prescribed medications such as Lithium and Clozapine to decrease suicidality.
   .
2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   Participants will be compensated $20 per study visit. Participants may also earn up to $5 bonuses for performance on the "Trust Game," totaling $50 total ($5 x 10; 5 timepoints for each infusion).

   At the PI's discretion, the lab may cover costs of travel including transportation and hotel fees.

3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   Study participation costs nothing other than time and potential inconvenience. Participants will be asked to provide information from a recent (within one year) physical, including bloodwork, with their primary healthcare provider. If they have not had a physical within the past year, we will ask them to obtain a physical prior to participating in the study. A physical exam with their own primary healthcare provider would be at the participant's (or the participant's insurance) cost.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

Will medical treatment be available if research-related injury occurs?

If subjects sustain injury or have adverse events that require ongoing assessment or treatment after post-infusion observation period, appropriate referrals will be made. The study will not pay for this further assessment or treatment.

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ☐ No ☐

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the specific procedure that you will perform? Yes ☐ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises

must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

1. Wedig MM, Frankenburg FR, Bradford Reich D, Fitzmaurice G, Zanarini MC. Predictors of suicide threats in patients with borderline personality disorder over 16 years of prospective follow-up. Psychiatry Res. 2013;208(3):252-6. doi: 10.1016/j.psychres.2013.05.009. PubMed PMID: 23747235; PMCID: PMC3876888.
2. Paris J, Zweig-Frank H. A 27-year follow-up of patients with borderline personality disorder. Compr Psychiatry. 2001;42(6):482-7. doi: 10.1053/comp.2001.26271. PubMed PMID: 11704940.
3. Boisseau CL, Yen S, Markowitz JC, Grilo CM, Sanislow CA, Shea MT, Zanarini MC, Skodol AE, Gunderson JG, Morey LC, McGlashan TH. Individuals with single versus multiple suicide attempts over 10years of prospective follow-up. Comprehensive psychiatry. 2013;54(3):238-42. doi: 10.1016/j.comppsych.2012.07.062. PubMed PMID: 22995448; PMCID: PMC3541431.
4. Pompili M, Girardi P, Ruberto A, Tatarelli R. Suicide in borderline personality disorder: a meta-analysis. Nord J Psychiatry. 2005;59(5):319-24. doi: 10.1080/08039480500320025. PubMed PMID: 16757458.
5. Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G. Attainment and stability of sustained symptomatic remission and recovery among patients with borderline personality disorder and axis II comparison subjects: a 16-year prospective follow-up study. The American journal of psychiatry. 2012;169(5):476-83. PubMed PMID: 22737693; PMCID: 3509999.
6. Paris J. Managing suicidality in patients with Borderline Personality Disorder. Psychiatric Times. 2006 July 1 2006.
7. Bateman AW, Gunderson J, Mulder R. Treatment of personality disorder. Lancet. 2015;385(9969):735-43. doi: 10.1016/S0140-6736(14)61394-5. PubMed PMID: 25706219.
8. Krystal JH, Sanacora G, Duman RS. Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. Biological psychiatry. 2013;73(12):1133-41. doi: 10.1016/j.biopsych.2013.03.026. PubMed PMID: 23726151; PMCID: PMC3671489.
9. Ballard ED, Ionescu DF, Vande Voort JL, Niciu MJ, Richards EM, Luckenbaugh DA, Brutsche NE, Ameli R, Furey ML, Zarate CA, Jr. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J Psychiatr Res. 2014;58:161-6. doi: 10.1016/j.jpsychires.2014.07.027. PubMed PMID: 25169854; PMCID: PMC4163501.
10. Abdallah CG, Sanacora G, Duman RS, Krystal JH. Ketamine and rapid-acting antidepressants: a window into a new neurobiology for mood disorder therapeutics. Annu Rev Med. 2015;66:509-23. doi: 10.1146/annurev-med-053013-062946. PubMed PMID: 25341010; PMCID: PMC4428310.
11. Sadikaj G, Moskowitz DS, Russell JJ, Zuroff DC, Paris J. Quarrelsome behavior in borderline personality disorder: influence of behavioral and affective reactivity to perceptions of others. Journal of abnormal psychology. 2013;122(1):195-207. doi: 10.1037/a0030871. PubMed PMID: 23231460.
12. McMain SF, Guimond T, Streiner DL, Cardish RJ, Links PS. Dialectical behavior therapy compared with general psychiatric management for borderline personality disorder: clinical outcomes and functioning over a 2-year follow-up. Am J Psychiatry. 2012;169(6):650-61. doi: 10.1176/appi.ajp.2012.11091416. PubMed PMID: 22581157.
13. Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, Saxena S, Kirkwood K, Aan Het Rot M, Lapidus KA, Wan LB, Iosifescu D, Charney DS. Efficacy of intravenous ketamine for treatment

of chronic posttraumatic stress disorder: a randomized clinical trial. JAMA psychiatry. 2014;71(6):681-8. Epub 2014/04/18. doi: 10.1001/jamapsychiatry.2014.62. PubMed PMID: 24740528.

14. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science. 2010;329(5994):959-64. Epub 2010/08/21. doi: 10.1126/science.1190287. PubMed PMID: 20724638; PMCID: 3116441.

15. Bjorkholm C, Monteggia LM. BDNF- a Key Transducer of Antidepressant Effects. Neuropharmacology. 2015. doi: 10.1016/j.neuropharm.2015.10.034. PubMed PMID: 26519901.

16. Koenigsberg HW, Yuan P, Diaz GA, Guerreri S, Dorantes C, Mayson S, Zamfirescu C, New AS, Goodman M, Manji HK, Siever LJ. Platelet protein kinase C and brain-derived neurotrophic factor levels in borderline personality disorder patients. Psychiatry research. 2012;199(2):92-7. doi: 10.1016/j.psychres.2012.04.026. PubMed PMID: 22633012; PMCID: PMC4128317.

17. Wagner S, Baskaya O, Dahmen N, Lieb K, Tadic A. Modulatory role of the brain-derived neurotrophic factor Val66Met polymorphism on the effects of serious life events on impulsive aggression in borderline personality disorder. Genes, brain, and behavior. 2010;9(1):97-102. doi: 10.1111/j.1601-183X.2009.00539.x. PubMed PMID: 19817874.

18. Fineberg SK, Steinfeld M, Brewer JA, Corlett PR. A Computational Account of Borderline Personality Disorder: Impaired Predictive Learning about Self and Others Through Bodily Simulation. Front Psychiatry. 2014;5:111. doi: 10.3389/fpsyt.2014.00111. PubMed PMID: 25221523; PMCID: PMC4145581.

19. Perry EB, Jr., Cramer JA, Cho HS, Petrakis IL, Karper LP, Genovese A, O'Donnell E, Krystal JH, D'Souza DC, Yale Ketamine Study G. Psychiatric safety of ketamine in psychopharmacology research. Psychopharmacology. 2007;192(2):253-60. doi: 10.1007/s00213-007-0706-2. PubMed PMID: 17458544.

20. Biskin RS, Frankenburg FR, Fitzmaurice GM, Zanarini MC. Pain in patients with borderline personality disorder. Personal Ment Health. 2014;8(3):218-27. doi: 10.1002/pmh.1265. PubMed PMID: 25044742; PMCID: PMC4129454.

21. Kennedy DP, Glascher J, Tyszka JM, Adolphs R. Personal space regulation by the human amygdala. Nature neuroscience. 2009;12(10):1226-7. doi: 10.1038/nn.2381. PubMed PMID: 19718035; PMCID: PMC2753689.

22. King-Casas B, Sharp C, Lomax-Bream L, Lohrenz T, Fonagy P, Montague PR. The rupture and repair of cooperation in borderline personality disorder. Science. 2008;321(5890):806-10. doi: 10.1126/science.1156902. PubMed PMID: 18687957.

23. Salvadore G, Cornwell BR, Colon-Rosario V, Coppola R, Grillon C, Zarate CA, Jr., Manji HK. Increased anterior cingulate cortical activity in response to fearful faces: a neurophysiological biomarker that predicts rapid antidepressant response to ketamine. Biological psychiatry. 2009;65(4):289-95. doi: 10.1016/j.biopsych.2008.08.014. PubMed PMID: 18822408; PMCID: PMC2643469.

24. Zarate CA, Jr., Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Archives of general psychiatry. 2006;63(8):856-64. doi: 10.1001/archpsyc.63.8.856. PubMed PMID: 16894061.