Statistical Analysis Plan for the Effect of Ketamine and Etomidate During RSI on Long Term Outcomes (RSI-LTO)

NCT06179485

May 26, 2026

1. Administrative Information

Title	Effect of Ketamine and Etomidate During RSI on Long-Term Outcomes (RSI-LTO)
Registration	https://clinicaltrials.gov/study/NCT06179485
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2. Introduction

This serves as the formal Statistical Analysis Plan (SAP) for the Effect of Ketamine and Etomidate During RSI on Long Term Outcomes (RSI-LTO) study. RSI-LTO compares long-term outcomes at 3 and 12 months between ketamine vs etomidate among patients in the Randomized trial of Sedative choice for Intubation (RSI), the short-term outcomes of which were registered separately (NCT05277896) and have been published separately.[1] This SAP was finalized before the completion of the long-term follow-up. The RSI-LTO study was registered at: https://clinicaltrials.gov/study/NCT06179485.

3. Background and Rationale

Approximately 13 million critically ill adults undergo emergency tracheal intubation annually worldwide.[2,3] Among survivors, up to 34% experience symptoms of post-traumatic stress disorder (PTSD) months to years after the critical illness.[4] Symptoms of PTSD can negatively affect quality of life and ability to maintain employment.[5-8] Finding treatments that prevent or improve PTSD symptoms and other mental health outcomes in intensive care unit (ICU) survivors, especially for those who receive mechanical ventilation, is urgently needed.[9,10]

Ketamine and etomidate are the two most commonly used medications for the induction of anesthesia for emergency tracheal intubation in the emergency department (ED) and ICU.[11,12] The choice between these two medications has been hypothesized to affect the development of symptoms of PTSD after critical illness. The development of PTSD following a hospitalization in the ICU is thought to be attributed to frightening memories and distressing experiences, such as delusions and hallucinations, experienced during the ICU stay.[4] Ketamine may reduce the burden of PTSD by antagonizing the N-methyl-D-aspartate (NMDA) receptor,[13] which inhibits the brain's glutamatergic system.[14] This

system mediates stress responsivity and resiliency, and inhibiting it may mitigate the formation of distressing memories, which are responsible for PTSD development.[15]

In adult outpatients with chronic PTSD, a single dose of intravenous ketamine (0.5mg/kg) has been shown to reduce PTSD symptoms for up to 2 weeks.[16,17] Therefore, it is possible that a single dose of intravenous ketamine (1-2 mg/kg) given for emergency tracheal intubation could similarly reduce the development of PTSD symptoms related to intubation or subsequent mechanical ventilation during critical illness. In a recent observational study of 141 adult patients who were intubated in the ED or ICU, receipt of ketamine was associated with significantly decreased symptoms of PTSD at 12 months, compared to receipt of etomidate.[18] However, the effect of induction medications such as ketamine and etomidate on symptoms of PTSD has not been rigorously evaluated in a randomized trial.

4. Objective

We sought to compare the effect of use of intravenous ketamine versus etomidate for induction of anesthesia during tracheal intubation on symptoms of PTSD at 12 months among participants in the RSI randomized trial.

5. Trial Design

The RSI trial was a multicenter, randomized trial comparing intravenous ketamine vs etomidate for the induction of anesthesia during emergency tracheal intubation of critically ill adults in the ED and ICU.[1] The RSI trial was approved by the institutional review board at Vanderbilt University Medical Center and the US Food and Drug Administration (IND 141424) and conducted with Exception from Informed Consent Requirements for Emergency Research (EFIC). The current RSI-LTO study compares symptoms of PTSD and other outcomes at 3 and 12 months among participants in the RSI randomized trial. Patients or their surrogates provided informed consent to participate in the RSI-LTO study.

6. Study Population

The RSI trial and the current RSI-LTO study were conducted at 14 sites (6 EDs and 8 ICUs) in 6 medical centers across the United States. Patients were included in the RSI trial if they were ≥ 18 years old and undergoing tracheal intubation with the use of a medication to induce anesthesia. Patients were excluded if they were known to be pregnant, were known to be a prisoner, were presenting with a primary diagnosis of trauma, or had an immediate need for tracheal intubation that precluded randomization. Patients were also excluded if the treating clinicians determined that the use of ketamine or etomidate was either necessary or contraindicated.

RSI-LTO had a small number of additional exclusions. Patients were excluded if they were deaf, aphasic or non-verbal, unable to follow simple commands prior to index hospitalization, or non-English speaking. In addition to these exclusion criteria, patients were not enrolled in RSI-LTO if they did not have access to a telephone because the

follow-up assessments at 3 and 12 months were completed by telephone and patients without access to a telephone would have been unable to complete the assessments.

7. Randomization

In the RSI trial, patients were randomly assigned in a 1:1 ratio to receive either ketamine or etomidate for induction of anesthesia during tracheal intubation. Randomization was performed with the use of permuted blocks of variable size, stratified by trial site. Trial-group assignments were placed in sequentially numbered, opaque envelopes and remained concealed until after enrollment. Clinicians and research personnel were aware of trial-group assignments after randomization. However, the outcome assessors were blinded to treatment group assignment.

8. Trial Interventions

For patients assigned to the ketamine group in the RSI trial, clinicians administered ketamine intravenously to induce anesthesia. A nomogram provided a list of doses of ketamine (in milligrams) that was based on patient weight, which corresponded to a full dose (2.0 mg per kilogram of body weight), an intermediate dose (1.5 mg per kilogram), or a reduced dose (1.0 mg per kilogram). Clinicians selected the dose of ketamine to administer.

For patients assigned to the etomidate group in the RSI trial, clinicians were instructed to administer etomidate intravenously to induce anesthesia. A nomogram provided a list of doses of etomidate (in milligrams) that was based on patient weight, which corresponded to a full dose (0.3 mg per kilogram), an intermediate dose (0.25 mg per kilogram), or a reduced dose (0.2 mg per kilogram). Clinicians selected the dose of etomidate to administer.

9. Outcomes

The short-term outcomes of the RSI trial were registered separately (NCT05277896) and have been reported previously.[1] This SAP addresses the outcomes of RSI-LTO. In RSI-LTO, trained neuropsychological raters, blinded to treatment group assignment, conducted long-term follow-up at 3 and 12 months after randomization using a telephone battery.

9.1 Primary Outcome for RSI-LTO

The primary outcome for RSI-LTO is symptoms of PTSD at 12 months after randomization, as assessed using the PTSD Checklist for the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (PCL-5), anchored to the intubation and mechanical ventilation events.[19] The PCL-5 is a widely used 5-10 minute patient survey validated to characterize the severity of PTSD symptoms. Patients rate 20 items corresponding to the DSM-5 criteria for PTSD on a 5-point Likert scale ranging from 0 (not bothersome) to 4 (extremely bothersome). Total scores range from 0 to 80, with higher scores indicating more severe symptoms of PTSD.[19]

We chose the PCL-5 over the Clinician Assessment of Post-Traumatic Stress Symptoms for the DSM-5 (CAPS-5), which is considered the reference standard for PTSD diagnosis,[20] because the CAPS-5 takes 60 minutes to complete, placing a significant burden on easily-fatigued ICU survivors and increasing the risk of incomplete data. Despite its shorter length, the PCL-5 is highly correlated with the CAPS-5 (r=0.94); a score on the PCL-5 >30 is 94% sensitive and 94% specific for PTSD, as diagnosed by the CAPS-5.[20] We chose PTSD symptoms rather than PTSD diagnosis as the primary outcome (1) to increase statistical power and (2) because patients who have PTSD symptoms that do not meet full diagnostic criteria for PTSD still have difficulty living productively,[21] and experience high rates of comorbid psychiatric illnesses and poor quality of life.[22,23] PCL-5 scores > 30 were indicative of possible PTSD.[20] We chose to measure PTSD symptoms at both 3 and 12 months while prioritizing the 12-month assessment because PTSD symptoms tend to be the most severe at 1-3 months and then improve 6-12 months after the traumatic event.

9.2. Additional Outcomes for RSI-LTO (Table 1)

Name	Measure	Time point
PTSD Symptoms at 3 months	PCL-5 ranges from 0 (no PTSD symptoms) to 80 (most severe PTSD symptoms). The PCL-5 will be anchored to the intubation and mechanical ventilation events.[20]	3 months
Vital Status	Date and location of death will be assessed from enrollment until 12 months after enrollment by trial personnel using review of electronic health records, telephone calls with families, and state or national death indices.	3 and 12 months
Depression	The Patient Health Questionnaire-9 is a multiple-choice inventory used to measure the severity of depression. Scores range from 0 (no depression) to 27 (severe depression).[24]	3 and 12 months
Anxiety	Generalized Anxiety Disorder-7 is a multiple-choice inventory used for measuring the severity of anxiety. Scores range from 0 (no anxiety) to 21 (severe anxiety).[25]	3 and 12 months
Quality of life	EQ-5D-5L quantifies quality of life by characterizing mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and global health status.[26] EQ-5D-5L scores will be summarized using the index value validated for the US population. Index scores range from -0.573 (quality of life worse than death) to 1.000 (perfect quality of life).[27]	3 and 12 months
Cognition	MoCA-Blind assesses naming, immediate recall, attention, language, abstraction, delayed recall, and orientation. Scores range from 0 to 22, with higher scores indicating better cognition.[28,29]	3 and 12 months
Executive function	Oral Trail Making Test – Patient counts from 1 to 25 and then alternates between numbers and letters (i.e., 1-A-2-B-3-C, etc). Lower scores indicate better executive function.[30]	3 and 12 months
Employment	Patients are asked what their employment status is prior to the acute illness and at follow-up. Patients will be considered to have lost employment if they go from: (1) full to partial employment, (2) full to no employment, or (3) partial to no employment.	3 and 12 months
Physical Disability	Duke Activity Status Index (DASI) is an 11-item survey that assesses the patient's current ability to perform various physical activities. Scores range from 0 (poor physical function) to 58.2 (excellent physical function).[31]	3 and 12 months
Awareness of paralysis	Determined by a semi-structured interview using ICU Memory Tool[32,33] and modified Brice Questionnaire.[34]	3 months
Threat perception	This 7-item questionnaire assesses the patient's perception of feeling threatened during the intubation experience. Scores range from 0 (none at all) to 21 (extremely threatened).	3 months
The presence of factual, delusional, and emotional memories	Determined by a semi-structured interview using ICU Memory Tool.[32,33]	3 months
Coma-and-delirium free days (CDFD)	Days alive and free of coma and delirium are based on local delirium assessment and level of consciousness assessment during the first 28 days after randomization. If the patient died before day number 28, they were assigned a CDFD of 0 days	Hospitalization

Table 1. Additional outcomes to be collected at 3 and 12 months via telephone follow-up. Telephone follow-up was conducted by trained neuropsychological raters blinded to treatment assignment.

10. Statistical Analysis

10.1. Analytic Principles

To characterize the study sample, demographic, clinical, and lab data will be described by treatment group, overall and among patients with data for the primary outcome of RSI-LTO. Categorical variables will be described using frequencies and proportions; continuous variables will be described using medians and interquartile ranges (IQR).

10.2. Analysis of the primary outcome of RSI-LTO

Our primary analysis will be an intention-to-treat comparison of symptoms of PTSD at 12 months, as measured by the PCL-5, between those who were randomized to ketamine and those randomized to etomidate. Because a value for the PCL-5 score will not exist for patients who die prior to assessment, our primary analysis will use a composite endpoint approach, in which we will assign patients whose PCL-5 could not be assessed because they died a value of 81 (higher than the worst value on the PTSD symptom scale). We will consider death a worse outcome than being alive with severe PTSD because: [1] 60-80% of patients with PTSD eventually experience full recovery[35] and [2] our patient partners with PTSD unanimously felt that, despite their symptoms, it was still better to have survived. Among patients who are alive at 12 months, PCL-5 scores will be treated as missing if the score is unavailable because the patient was lost to follow-up, declined the assessment, or was unable to complete the assessment because of severe cognitive impairment or non-verbal status at the time of the assessment. Our primary analysis will use "complete case" analysis, excluding patients who have completely missing PCL-5 assessments or information about death. As described below, we will use multiple imputation for patients who partially completed the PCL-5 score. Our primary analysis will compare the PCL-5 at 12 months between patients randomized to ketamine vs patients randomized to etomidate using a partial proportional odds model to permit separate estimates of the effect of ketamine vs etomidate on (1) death and (2) symptoms of PTSD. The partial proportional odds model is a flexible regression model that estimates the treatment effect separately for each of the ordinal outcome categories (i.e., relaxes the proportional odds assumption). For the partial proportional odds model, the PCL-5 scores will be categorized to create the ordinal outcome variables as in the following groupings of values: 0, 1-5, 6-10, 11-15, 16-20, 21-25, 26-30, 31-35, 36-40, 41-45, 46-50, 51-80, and death. The reason for groupings of 5 values is that serial changes in individuals of ≥5 on the PCL-5 total score are considered reliable.[36] The reason for grouping all values of 51-80 is that few patients (<5%) will have values in this range.

The main scientific objective is to determine whether the intervention demonstrates an effect in the settings where it was actually implemented. Accordingly, the primary analysis focuses on statistical inference about the effects of the intervention conditional on the observed study sites and other realized levels of clustering. Because inference about effects generalized beyond the observed sites requires additional assumptions regarding correlation and heterogeneity, we will conduct sensitivity analyses (**Section 10.3)** using alternative variance estimators and correlation structures, including cluster-robust standard errors and mixed-effects models, to assess the robustness of conclusions to assumptions required for generalization to a broader population of sites

and other clustering units. These sensitivity analyses are intended to quantify the extent to which conclusions depend on assumptions required for generalization to all possible sites/clusters, rather than to identify a single preferred variance estimator.

10.3. Sensitivity Analyses for Primary Outcome

We will perform additional sensitivity analyses to evaluate the robustness of our findings.

First, we will compare the outcome between trial groups using an unadjusted Wilcoxon Rank Sum Test.

Second, we will repeat the primary analysis using cluster-robust standard errors for the primary estimand, where trial sites are treated as the clustering variables.

Third, we will perform a proportional odds mixed effects model with a random effect for site and fixed effects for trial group and the following pre-specified covariates in order of importance:

1) Age
2) Neighborhood disadvantage as characterized by the Area Deprivation Index[37]
3) Rurality as characterized by the Rural-Urban Commuter Index[38]
4) Elixhauser comorbidity index[39]
5) Pre-enrollment history of PTSD
6) Pre-enrollment history of depression
7) Pre-illness history of bipolar disorder
8) Pre-illness history of anxiety
9) Severity of illness, as characterized by the APACHE II score[40]
10) Race
11) Ethnicity
12) Sex

Fourth, we will repeat the primary analysis in patients who have fully completed the PCL-5.

Fifth, we will compare PTSD symptoms between groups in a survivors-only analysis, both unadjusted and adjusted for the above variables, plus baseline measures of traumatic experiences (Life Events Checklist for DSM-5 [LEC-5]) and resilience (Brief Resilient Coping Scale), financial strain,[41] social network using a survey from the Midlife Development in the United States (MIDUS) study,[42,43] and social support from the ENRICHD Social Support Instrument.[44,45]

Sixth, we will perform Survivor Average Causal Effect (SACE) analysis. We will estimate the principal stratum causal effect, often referred to as the SACE, defined as the average causal effect among a subset of subjects who would survive under either treatment.[46]

Seventh, we will compare possible PTSD diagnosis between trial groups using a generalized linear model. A possible PTSD diagnosis will be defined as a PCL-5 score > 30.[20]

For the multivariable models, non-linear continuous variables will be modeled using splines. Collinearity will be assessed, and if two variables are highly correlated, the lesser priority covariate will be removed. Post-randomization covariates (e.g., interventions provided during hospitalization) will not be adjusted for because they may potentially be affected by the randomized intervention and be on the causal pathway. Multiple imputation for missing covariates based on predictive mean matching will be performed. As with our previous studies, multiple imputation will also be performed for missing scores secondary to partially completed PCL-5s.[47-49]

10.4. Heterogeneity of Treatment Effects for the Primary Outcome

Heterogeneity of treatment effect is nonrandom variation in the magnitude or direction of the effect of a treatment on an outcome across levels of a baseline covariate. We will apply two complementary approaches to analysis of heterogeneity of treatment effect described in the Predictive Approaches to Treatment Effect Heterogeneity Statement:[50] (1) traditional one-variable-at-a-time subgroup analyses and (2) an effect-modeling approach, as described in detail in the statistical analysis plan for the RSI trial[51] (the results of which may be reported separately from the remainder of the RSI-LTO analyses).

Our subgroup analyses will examine whether prespecified baseline variables modify the effect of trial group assignment on the primary outcome of symptoms of PTSD using a formal test of statistical interaction in proportional odds model with the primary outcome of symptoms of PTSD as the dependent variable, a random effect for trial site, and independent variables of trial group, the proposed effect modifier, and the interaction between the effect modifier and trial group for each of the following prespecified baseline variables:

1) Age
2) Sex
3) Neighborhood disadvantage
4) Rurality
5) Pre-enrollment history of PTSD
6) Pre-enrollment history of depression
7) Pre-illness of bipolar disorder
8) Pre-illness history of anxiety
9) Severity of illness
10) Encephalopathy (altered mental status) as the induction for intubation
11) Neuromuscular blocking agent

We selected pre-illness mood disorders (PTSD, depression, bipolar disorder, and anxiety) as potential effect modifiers because of their high prevalence in the general population and their association with increased vulnerability to developing PTSD after trauma exposure.[52-55]

10.5. Analyses for Additional Outcomes

Additional outcomes will be compared between trial groups using an unadjusted Chi-square test for categorical variables, an unadjusted Wilcoxon Rank Sum Test for continuous or ordinal variables, and Kaplan-Meier survival analysis for survival to 12 months. In the analysis of survival, patients who are lost to follow-up will be censored when they were last known to be alive and a log-rank test will be performed to determine if there is a significant difference (two-tailed p-value < 0.05) between trial groups. All functional outcomes (non-mortality outcomes) at 3 and 12 months will be compared between trial groups in survivors only. No adjustments will be made for multiple comparisons.

10.6. Power and Sample Size

Primary Analysis for the Primary Outcome of RSI-LTO

Based on our prior trials, during the design of the RSI trial and RSI-LTO, we estimated that of the 2,364 patients planned to be enrolled in RSI, 1,756 patients would have complete data on symptoms of PTSD or death at 12 months, required for the primary analysis of the primary outcome of RSI-LTO. We estimated statistical power with a simulation-based method using the observed distribution of PCL-5 scores at 12 months from a recent trial in a similar patient population.[56] Our sample size calculation used a partial proportional odds model to test for an intervention effect where the dependent variable was an ordinal outcome that combined PCL-5 scores and death (with death being the worst possible outcome).

The minimum clinically important difference (MCID) in PCL-5 is generally considered to be 10 points,[57] with MCIDs ranging from 5.7 to 18 points in the literature.[36,58,59] For our primary analysis, we conservatively used a detectable difference of a 5-point improvement in the PCL-5 score,[58] which is also considered the minimum reliable change.[59] Using simulation repeated 1000 times with the null hypothesis that the intervention has no effect for any category, we calculated that with complete data on **1,756 patients**, we would have **98% statistical power** to detect a significant intervention effect in the primary analysis of the primary outcome of RSI-LTO.

Survivors-Only Analysis of Symptoms of PTSD

In addition to the power calculation performed during the design of the trial for the primary outcome of RSI-LTO (symptoms of PTSD in which death is included as the worst value on the ordinal scale – a 'composite outcome' approach to handling truncation by death), at the time of the writing of this SAP, we added a description of the difference in PCL-5 score between trial groups that would be detectable across a range of total numbers of patients with complete data on the PCL-5 score. Assuming the PCL-5's standard deviation (SD) to be 17.85 points[18] and a two-sided alpha of 0.05, the difference between trial groups (effect size)

Effect Size	Sample size for 90% power
10	136
9	166
8	210
7	274
6	370
5	532

Table 2. Sample size calculations to detect differences in PCL-5s with 90% power.

that could be detected with 90% statistical power at each corresponding number of patients with complete data on PCL-5 is displayed in **Table 2**. These calculations demonstrated that even a sample size as small as 136 total patients with complete data on PCL-5 would allow the detection of a 10-point difference in PCL-5 scores between the ketamine and etomidate groups with 90% statistical power. A half a standard deviation (SD) of that particular test has also been used to define the MCID.[60-63] Based on our preliminary study,[18] the MCID, based on half an SD, would be 8.93 points; a total of 166 patients would be needed to detect this difference with 90% power. Because the number of the 2,365 patients who were enrolled in the RSI trial who will survive to 12 months and provide complete data on the PCL-5 is unknown, these calculations provide information on the range of possible detectable differences depending on the final number of patients with PCL-5 values in the survivors-only analysis.

11. Software Details

R version 4.5.3 or above will be used for all analyses. Versions of specific packages used for analysis will be noted in the analysis report. The checkpoint package will be used to preserve R package versions throughout the manuscript submission and review process.

12. References

1. Casey JD, Seitz KP, Driver BE, et al. Ketamine or Etomidate for Tracheal Intubation of Critically Ill Adults. *N Engl J Med*. Dec 9 2025;doi:10.1056/NEJMoa2511420
2. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. *Lancet*. Oct 16 2010;376(9749):1339–46. doi:10.1016/S0140-6736(10)60446-1
3. Jivraj NK, Hill AD, Shieh MS, et al. Use of Mechanical Ventilation Across 3 Countries. *JAMA Intern Med*. Aug 1 2023;183(8):824–831. doi:10.1001/jamainternmed.2023.2371
4. Parker AM, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. *Critical care medicine*. May 2015;43(5):1121–9. doi:10.1097/CCM.0000000000000882
5. Smith MW, Schnurr PP, Rosenheck RA. Employment outcomes and PTSD symptom severity. *Ment Health Serv Res*. Jun 2005;7(2):89–101. doi:10.1007/s11020-005-3780-2
6. Davydow DS, Desai SV, Needham DM, Bienvenu OJ. Psychiatric morbidity in survivors of the acute respiratory distress syndrome: a systematic review. *Psychosom Med*. May 2008;70(4):512–9. doi:10.1097/PSY.0b013e31816aa0dd
7. Kapfhammer HP, Rothenhausler HB, Krauseneck T, Stoll C, Schelling G. Posttraumatic stress disorder and health-related quality of life in long-term survivors of acute respiratory distress syndrome. *The American journal of psychiatry*. Jan 2004;161(1):45–52. doi:10.1176/appi.ajp.161.1.45
8. Jackson JC, Pandharipande PP, Girard TD, et al. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. *Lancet Respir Med*. May 2014;2(5):369–79. doi:10.1016/S2213-2600(14)70051-7
9. Mikkelsen ME, Still M, Anderson BJ, et al. Society of Critical Care Medicine's International Consensus Conference on Prediction and Identification of Long-Term Impairments After Critical Illness. *Critical care medicine*. Nov 2020;48(11):1670–1679. doi:10.1097/CCM.0000000000004586
10. Spruit MA, Holland AE, Singh SJ, Tonia T, Wilson KC, Troosters T. COVID-19: Interim Guidance on Rehabilitation in the Hospital and Post-Hospital Phase from a European Respiratory Society and American Thoracic Society-coordinated International Task Force. *Eur Respir J*. Aug 13 2020;56(6)doi:10.1183/13993003.02197-2020
11. Driver BE, Semler MW, Self WH, et al. Effect of Use of a Bougie vs Endotracheal Tube With Stylet on Successful Intubation on the First Attempt Among Critically Ill Patients Undergoing Tracheal Intubation: A Randomized Clinical Trial. *JAMA*. Dec 28 2021;326(24):2488–2497. doi:10.1001/jama.2021.22002
12. Sivilotti ML, Filbin MR, Murray HE, Slasor P, Walls RM, Investigators N. Does the sedative agent facilitate emergency rapid sequence intubation? *Acad Emerg Med*. Jun 2003;10(6):612–20. doi:10.1111/j.1553-2712.2003.tb00044.x
13. Newcomer JW, Farber NB, Olney JW. NMDA receptor function, memory, and brain aging. *Dialogues Clin Neurosci*. Sep 2000;2(3):219–32.

14. Krystal JH, Abdallah CG, Averill LA, et al. Synaptic Loss and the Pathophysiology of PTSD: Implications for Ketamine as a Prototype Novel Therapeutic. *Curr Psychiatry Rep*. Aug 26 2017;19(10):74. doi:10.1007/s11920-017-0829-z
15. Nair J, Singh Ajit S. The role of the glutamatergic system in posttraumatic stress disorder. *CNS Spectr*. Jul 2008;13(7):585–91. doi:10.1017/s1092852900016862
16. Feder A, Parides MK, Murrough JW, et al. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA psychiatry*. Jun 2014;71(6):681–8. doi:10.1001/jamapsychiatry.2014.62
17. Feder A, Costi S, Rutter SB, et al. A Randomized Controlled Trial of Repeated Ketamine Administration for Chronic Posttraumatic Stress Disorder. *The American journal of psychiatry*. Feb 1 2021;178(2):193–202. doi:10.1176/appi.ajp.2020.20050596
18. Wollenman LC, Tipold AM, Semler MW, et al. Association Between Receipt of Ketamine vs Etomidate for Emergency Tracheal Intubation and Symptoms of Posttraumatic Stress Disorder at 12 Months. *CHEST Crit Care*. Jun 2025;3(2)doi:10.1016/j.chstcc.2025.100136
19. Blevins CA, Weathers FW, Davis MT, Witte TK, Domino JL. The Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5): Development and Initial Psychometric Evaluation. *J Trauma Stress*. Dec 2015;28(6):489–98. doi:10.1002/jts.22059
20. Geier TJ, Hunt JC, Nelson LD, Brasel KJ, deRoon-Cassini TA. Detecting PTSD in a traumatically injured population: The diagnostic utility of the PTSD Checklist for DSM-5. *Depress Anxiety*. Feb 2019;36(2):170–178. doi:10.1002/da.22873
21. Friedman MJ, Schnurr PP, McDonagh-Coyle A. Post-traumatic stress disorder in the military veteran. *Psychiatr Clin North Am*. Jun 1994;17(2):265–77.
22. Chen C, Salim R, Rodriguez J, et al. The Burden of Subthreshold Posttraumatic Stress Disorder in World Trade Center Responders in the Second Decade After 9/11. *The Journal of clinical psychiatry*. Jan 21 2020;81(1)doi:10.4088/JCP.19m12881
23. Mota NP, Tsai J, Sareen J, et al. High burden of subthreshold DSM-5 post-traumatic stress disorder in U.S. military veterans. *World Psychiatry*. Jun 2016;15(2):185–6. doi:10.1002/wps.20313
24. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. Sep 2001;16(9):606–13.
25. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of internal medicine*. May 22 2006;166(10):1092–7. doi:10.1001/archinte.166.10.1092
26. Johnson JA, Coons SJ, Ergo A, Szava-Kovats G. Valuation of EuroQOL (EQ-5D) health states in an adult US sample. *Pharmacoeconomics*. Apr 1998;13(4):421–33.
27. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Aug 2019;22(8):931–941. doi:10.1016/j.jval.2019.02.009
28. Pendlebury ST, Welch SJ, Cuthbertson FC, Mariz J, Mehta Z, Rothwell PM. Telephone assessment of cognition after transient ischemic attack and stroke: modified telephone interview of cognitive status and telephone Montreal Cognitive Assessment

versus face-to-face Montreal Cognitive Assessment and neuropsychological battery. *Stroke; a journal of cerebral circulation*. Jan 2013;44(1):227–9. doi:10.1161/STROKEAHA.112.673384
29. Jennings LA, Araujo KLB, Meng C, Peduzzi P, Charpentier P, Reuben DB. Utility of a short, telephone-administered version of the Montreal Cognitive Assessment. *Journal of the American Geriatrics Society*. Oct 2021;69(10):2741–2744. doi:10.1111/jgs.17318
30. Mrazik M, Millis S, Drane DL. The oral trail making test: effects of age and concurrent validity. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists*. May 2010;25(3):236–43. doi:10.1093/arclin/acq006
31. Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol*. Sep 15 1989;64(10):651–4. doi:10.1016/0002-9149(89)90496-7
32. Jones C, Griffiths RD, Humphris G, Skirrow PM. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. *Critical care medicine*. Mar 2001;29(3):573–80. doi:10.1097/00003246-200103000-00019
33. Samuelson KA, Lundberg D, Fridlund B. Stressful memories and psychological distress in adult mechanically ventilated intensive care patients - a 2-month follow-up study. *Acta anaesthesiologica Scandinavica*. Jul 2007;51(6):671–8. doi:10.1111/j.1399-6576.2007.01292.x
34. Brice DD, Hetherington RR, Utting JE. A simple study of awareness and dreaming during anaesthesia. *British journal of anaesthesia*. Jun 1970;42(6):535–42. doi:10.1093/bja/42.6.535
35. Rosellini AJ, Liu H, Petukhova MV, et al. Recovery from DSM-IV post-traumatic stress disorder in the WHO World Mental Health surveys. *Psychological medicine*. Feb 2018;48(3):437–450. doi:10.1017/S0033291717001817
36. Marx BP, Lee DJ, Norman SB, et al. Reliable and clinically significant change in the clinician-administered PTSD Scale for DSM-5 and PTSD Checklist for DSM-5 among male veterans. *Psychological assessment*. Feb 2022;34(2):197–203. doi:10.1037/pas0001098
37. Kind AJH, Buckingham WR. Making Neighborhood-Disadvantage Metrics Accessible - The Neighborhood Atlas. *The New England journal of medicine*. Jun 28 2018;378(26):2456–2458. doi:10.1056/NEJMp1802313
38. Agriculture UDo. Rural-Urban Commuting Area Codes. Accessed February 3, 2026. https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/
39. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Medical care*. Jan 1998;36(1):8–27.
40. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Critical care medicine*. Oct 1985;13(10):818–29.
41. Osborn CY, Kripalani S, Goggins KM, Wallston KA. Financial strain is associated with medication nonadherence and worse self-rated health among cardiovascular patients. *J Health Care Poor Underserved*. 2017;28(1):499–513. doi:10.1353/hpu.2017.0036

42. Brim OG, Ryff CD, Kessler RC. *How healthy are we? : a national study of well-being at midlife*. John D and Catherine T MacArthur Foundation series on mental health and development Studies on successful midlife development. University of Chicago Press; 2004:ix, 687 p.
43. Donato KM, Leon-Perez G, Wallston KA, Kripalani S. Something Old, Something New: When Gender Matters in the Relationship between Social Support and Health. *Journal of health and social behavior*. Sep 2018;59(3):352–370. doi:10.1177/0022146518789362
44. Mitchell PH, Powell L, Blumenthal J, et al. A short social support measure for patients recovering from myocardial infarction: the ENRICHD Social Support Inventory. *J Cardiopulm Rehabil*. Nov–Dec 2003;23(6):398–403. doi:10.1097/00008483-200311000-00001
45. Vaglio J, Jr., Conard M, Poston WS, et al. Testing the performance of the ENRICHD Social Support Instrument in cardiac patients. *Health Qual Life Outcomes*. May 13 2004;2:24. doi:10.1186/1477-7525-2-24
46. Tchetgen Tchetgen EJ. Identification and estimation of survivor average causal effects. *Stat Med*. Sep 20 2014;33(21):3601–28. doi:10.1002/sim.6181
47. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *The New England journal of medicine*. Oct 3 2013;369(14):1306–16. doi:10.1056/NEJMoa1301372
48. Little RJA, Rubin DB. *Statistical analysis with missing data*. 2nd ed. Wiley series in probability and statistics. Wiley; 2002:xv, 381 p.
49. Groenwold RH, Donders AR, Roes KC, Harrell FE, Jr., Moons KG. Dealing with missing outcome data in randomized trials and observational studies. *American journal of epidemiology*. Feb 01 2012;175(3):210–7. doi:10.1093/aje/kwr302
50. Kent DM, Paulus JK, van Klaveren D, et al. The Predictive Approaches to Treatment effect Heterogeneity (PATH) Statement. *Annals of internal medicine*. Jan 7 2020;172(1):35–45. doi:10.7326/M18-3667
51. DeMasi SC, Imhoff B, Lewis AA, et al. Protocol and Statistical Analysis Plan for a Multicenter Randomized Trial of Ketamine vs Etomidate for Emergency Tracheal Intubation. *CHEST Crit Care*. Sep 2025;3(3)doi:10.1016/j.chstcc.2025.100177
52. Xue C, Ge Y, Tang B, et al. A meta-analysis of risk factors for combat-related PTSD among military personnel and veterans. *PloS one*. 2015;10(3):e0120270. doi:10.1371/journal.pone.0120270
53. Spinhoven P, Penninx BW, Krempeniou A, van Hemert AM, Elzinga B. Trait rumination predicts onset of Post-Traumatic Stress Disorder through trauma-related cognitive appraisals: A 4-year longitudinal study. *Behav Res Ther*. Aug 2015;71:101–9. doi:10.1016/j.brat.2015.06.004
54. Kountanis JA, Muzik M, Chang T, et al. Relationship between postpartum mood disorder and birth experience: a prospective observational study. *Int J Obstet Anesth*. Nov 2020;44:90–99. doi:10.1016/j.ijoa.2020.07.008
55. Kleim B, Ehlers A, Glucksman E. Early predictors of chronic post-traumatic stress disorder in assault survivors. *Psychological medicine*. Oct 2007;37(10):1457–67. doi:10.1017/S0033291707001006
56. Mart MF, Semler MW, Jenkins CA, et al. Oxygen-Saturation Targets and Cognitive and Functional Outcomes in Mechanically Ventilated Adults. *American*

journal of respiratory and critical care medicine. Apr 1 2024;209(7):861–870. doi:10.1164/rccm.202310-1826OC
57. PTSD Checklist for DSM-5 (PCL-5). VA National Center for PTSD, US Department of Veterans. Accessed February 7, 2026. https://www.ptsd.va.gov/professional/assessment/adult-sr/ptsd-checklist.asp
58. Stefanovics EA, Rosenheck RA, Jones KM, Huang G, Krystal JH. Minimal Clinically Important Differences (MCID) in Assessing Outcomes of Post-Traumatic Stress Disorder. *Psychiatr Q*. Mar 2018;89(1):141–155. doi:10.1007/s11126-017-9522-y
59. Blanchard BE, Johnson M, Campbell SB, et al. Minimal important difference metrics and test-retest reliability of the PTSD Checklist for DSM-5 with a primary care sample. *J Trauma Stress*. Dec 2023;36(6):1102–1114. doi:10.1002/jts.22975
60. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*. May 2003;41(5):582–92. doi:10.1097/01.MLR.0000062554.74615.4C
61. Norman GR, Sloan JA, Wyrwich KW. The truly remarkable universality of half a standard deviation: confirmation through another look. *Expert Rev Pharmacoecon Outcomes Res*. Oct 2004;4(5):581–5. doi:10.1586/14737167.4.5.581
62. Copay AG, Subach BR, Glassman SD, Polly DW, Jr., Schuler TC. Understanding the minimum clinically important difference: a review of concepts and methods. *Spine J*. Sep–Oct 2007;7(5):541–6. doi:10.1016/j.spinee.2007.01.008
63. Katz P, Morris A, Trupin L, Yazdany J, Yelin E. Disability in valued life activities among individuals with systemic lupus erythematosus. *Arthritis Rheum*. Apr 15 2008;59(4):465–73. doi:10.1002/art.23536