



CLINICAL ALGORITHM FOR KETAMINE ADMINISTRATION FOR DEPRESSION

I. BACKGROUND

Depression is a common, severe, and potentially life-threatening syndrome. Several preclinical and clinical studies suggest that the glutamatergic system is involved in the mechanism of action of antidepressants. The non-competitive NMDA antagonist ketamine has been shown to have a rapid (hours) therapeutic effect in unipolar depression, treatment-resistant depression, and bipolar depression. Intravenous (IV), intramuscular, sublingual, or oral administration of subanesthetic doses of ketamine results in rapid, robust and relatively sustained antidepressant effects including the rapid resolution of suicide ideation (1-16).

The following clinical algorithm was developed to implement and ensure the safe use of ketamine for the treatment of moderate to severe, treatment resistant depressive symptoms including suicidal ideation (SI) at University Hospital (UHS). This guideline is based on an extensive review of the literature as well as the combined collaborative experience of physicians using ketamine for the treatment of depression in the Departments of Anesthesiology and Psychiatry at UTHSCSA. Given the safety, high degree of flexibility in the administration route of subanesthetic doses of ketamine (1-16), and the diverse hospital settings in which ketamine will be used at UHS, this guideline provides a set of broad and flexible recommendations that can be implemented as recommended by the psychiatrist working in consultation with anesthesia (Pain Consult Team) to best fit specific cases, with the goal of reducing patient length of stay and/or readmissions to the hospital and thus overall health costs.

Ketamine administration for depression will follow UHS guidelines for Moderate Sedation/Analgesia (Conscious Sedation), Policy No: 9.12 (effective Date: 04/03/12). Under this guideline, Conscious Sedation is defined as a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually not impaired.

II. GENERAL REQUIREMENTS

The administration of ketamine for the treatment of depressive symptoms including SI at UHS will be under the constant supervision of a physician with rapid access to a specialized resuscitation team by calling a "Code Blue."

Determination of the Need for Treatment: As depicted in the attached flow sheet/algorithm, any psychiatry attending can suggest that a patient be evaluated to receive ketamine as a form of treatment, however, only a psychiatrist authorized to do so¹ will make the determination of which patients can receive ketamine for the treatment of their depressive symptoms. Specifically, a psychiatrist authorized to recommend the administration of ketamine (henceforth *authorized*

¹ Authorization is given by the Department of Psychiatry Chair for Psychiatrists in the faculty that complete the requirements described in this clinical guideline.



psychiatrist) will work together with the Anesthesia-Pain Consult team to ultimately recommend ketamine treatments. If patients are admitted to the Inpatient Psychiatric Service (IP), the authorized psychiatrist will work with the IP attending to make the decision to use ketamine for any given patient.

A. Candidates

1. Adult patients who are American Society of Anesthesiologists (ASA; see *Ketamine Worksheet*) PS 1 or 2 are usually considered appropriate candidates for moderate or deep sedation (Policy No: 9.12) and they will be considered ideal candidates for ketamine administration. Patients with ASA PS 3 and 4 can be considered for ketamine administration but they will require additional precautions (see below). ASA scores will be determined by the authorized psychiatrists' team working with the Anesthesia-Pain Consult Service and the physician in charge of the patient.
 2. Adult patients reporting moderate to severe depressive symptoms who have failed to respond to at least 2 adequate treatment trials, those reporting acute suicidal ideation with a history of depression, and patients with co-morbid depressive symptoms and pain who cannot receive standard oral antidepressant therapy due to medical problems affecting their PO intake.
 3. Adult patients without contraindications for ketamine treatment including active psychotic symptoms or history of a primary psychotic disorder (e.g., schizophrenia or schizoaffective disorder), manic symptoms, hypersensitivity to the drug or its components, history of severe, ongoing alcohol or substance dependence (including ketamine), and ASA PS 5 and 6.
- B. Facility: Similar to the conscious sedation guidelines (Policy No: 9.12), the room or facility where sedation is performed must have the personnel and equipment available to manage emergency situations or have rapid access to the specialized resuscitation team.

C. Personnel

1. Patient Monitor: A qualified medical provider (e.g., attending or resident physician), mid-level provider (Nurse Practitioner-NP or Physician Assistant-PA), or registered nurse (RN), who observes, assesses, and documents the patient's response during ketamine administration. The *Patient Monitor* must have current credentials in basic life support (BLS) and be competent in the administration of medications. Similar to the conscious sedation guidelines (Policy No: 9.12), RNs acting as *Patient Monitor* must have completed Staff-Nurse core competencies including medication administration and rhythm recognition competency.
2. Medical Provider: Similar to the conscious sedation guidelines (Policy No: 9.12) this is a person privileged to practice medicine under the UHS Medical Staff Bylaws.



Faculty or fellowship-level providers initiating ketamine administration at the level of conscious sedation must be permitted by law, and privileged by UHS to prescribe medications, with current UHS clinical privileges to administer moderate or deep sedation (Policy No: 9.12). Providers in residency training must be monitored and supervised for the entire event by a faculty or fellowship-level physician with current UHS clinical privileges to administer moderate or deep sedation (Policy No: 9.12).

- D. Documentation: Information documenting the need for treatment with ketamine including depression rating scale scores, appropriateness of the candidate by meeting eligibility criteria, personnel available to administer and monitor ketamine administration, and assessment and recommendation of the *authorizing psychiatrist* will be included in a *Psychiatry Consult Note* generated prior to treatment. The *authorizing psychiatrist* must complete and/or sign this note. Information about the procedure itself will be recorded using the *Ketamine Worksheet* (see Appendix A) and completed by the *Medical Provider* administering the ketamine. The completed worksheet will be included in the patient's chart and subsequently scanning by medical records. Vitals signs will be recorded in the flow sheet section of the electronic chart in Sunrise by the *Patient Monitor*. A follow-up Psychiatry Consult Note will summarize outcomes from the ketamine treatment to include any adverse side effects and changes in depressive symptoms. The *authorizing psychiatrist* must complete and/or sign this note.

III. PROCEDURES

- A. Pre-treatment Consultation: The psychiatrist authorized to recommend ketamine will be consulted on the use of ketamine as a form of treatment for eligible patients. To make the determination of the need for treatment, the authorized psychiatrist's team will review the patient's chart and discuss the case with the physician in charge of the patient's care. Candidate patients' initial evaluation will also include an Anesthesia-Pain Consult.
- B. Eligibility: Patients are eligible to receive treatment with ketamine when they meet all of following criteria:
1. Adult, age ≥ 18
 2. ASA PS 1 or 2
 3. ASA PS 3 or 4 may be eligible for ketamine treatment with Anesthesia-Pain Consult recommendation documented in the anesthesia consult note as "the potential benefit outweighs the risk" and any possible safety concerns (e.g., a patient may require telemetry to safely receive ketamine).
 4. Moderate to severe symptoms of depression (including SI) objectively documented using mood/anxiety severity rating scale scores (MADRS ≥ 25 and BDI II ≥ 21) and Sunrises' DSM IV mood disorder criteria and Suicide risk score templates (see section E).



5. Patient's written informed consent for ketamine to include disclosure that use is off-label and not FDA approved for the treatment of depression (see C below)
 6. Completed H&P by physician in charge of patient's care
 7. Patient medically stable and cleared by physician in charge of care to receive ketamine
 8. No solid food for 6 hours prior to the administration of ketamine; no clear liquids for 2 hours prior. Requirements can be waived by the anesthesiologist in urgent situations with documentation on the consent form that patient has been informed of the increased risk of aspiration complications.
- C. Consent: Each subject must have capacity to make decisions about his or her medical treatment. However, a formal capacity evaluation as normally conducted by the Consult Psychiatry Team [following general evaluation guidelines (21, 22)] is not required unless a lack of capacity is suspected, in which case the patient will not be considered eligible for ketamine administration. The psychiatrist authorized to administer ketamine will inform the patient about the risks and benefits of the treatment as well as the fact that ketamine is not approved by the FDA for the treatment of depression. Therefore, the use of this medication will be off-label. Patient understanding and agreement will be documented by signing the medication administration consent form (appendix B), which will be added to the patient's chart.
- D. Exclusions
1. Active psychotic symptoms, manic symptoms, or a history of a primary psychotic disorder
 2. ASA PS 5 or 6, or uncontrolled hypertension
 3. Known hypersensitivity to ketamine or its components
 4. History of ketamine abuse or dependence; history of severe, ongoing alcohol or substance abuse or dependence
- E. Prior to Treatment Administration
1. The authorized psychiatrist's team will conduct a chart review (i.e., review of the active medical record serving as a health assessment with comment in the consult



note that the record has been reviewed for this purpose), discuss the case with the physician in charge of the patient’s care and physical exam findings, and review the Anesthesia-Pain Consult. In the psychiatry consult note, the authorized psychiatrist’s team will document the criteria for treatment eligibility including ASA class and the absence of any exclusions. On the *Ketamine Worksheet*, the authorized psychiatrist’s team will document pertinent medical/surgical history, allergies, current medications, pain score, and baseline vital signs (heart rate, blood pressure, respiratory rate, temperature, and oxygen saturation). The psychiatry consult note will include baseline scores for depression severity and suicidal ideation severity as documented in Sunrise screen captures below.

Figure 1. Sunrise DSM-IV mood disorders

The screenshot shows a web-based form for DSM-IV mood disorders. It includes sections for MAJOR DEPRESSIVE EPISODE, MAJOR DEPRESSIVE DISORDER, MANIC EPISODE, MIXED EPISODE, and BIPOLAR AFFECTIVE DISORDER. Each section contains a list of criteria with checkboxes and radio buttons for Yes/No responses.

Figure 2. Suicidal ideation severity

The screenshot shows a web-based form for suicidal ideation severity. It includes sections for Patient Current Suicide Risk Score, A. Current ideation, B. Reasons for Living/Dying, C. Desire to Make Active Suicide Attempt, D. Passive Suicidal Attempt, and Total Score. Each section contains a list of criteria with checkboxes and radio buttons for response options.

Clinician Rating For Suicide

Clinician Rating of Current Concern About Potential Suicide Behavior:

Note: The items below should serve as a guideline of minimum factors to be considered when determining your concern about the patient's potential risk for suicidal behaviors.

A. LONG-TERM FACTORS:

1. Any history of suicide attempt? Yes No

2. Any history of mental illness? Yes No

3. Any history of physical or sexual abuse? Yes No

4. Long-standing tendency to lose temper or become aggressive with little provocation? Yes No

5. Chronic severe pain or disabling illness? Yes No

6. Past suicidal behavior in family or associate? Yes No

B. RECENT EVENTS (within the past 3 months)

1. Recent significant loss? Yes No

2. Recent psychiatric admission or discharge? Yes No

3. Recent first diagnosis of any psychiatric disorder? Yes No

4. Recent worsening of depressive symptoms or increase in alcohol abuse? Yes No

C. CURRENT STATUS

1. Current preoccupation and plans for suicide? Yes No

2. Current psychomotor agitation or marked anxiety? Yes No

3. Current prominent feelings of hopelessness? Yes No

4. Currently living alone? Yes No

D. Clinician's Rating of the level of concern about potential suicidal behavior:

Lowest concern Some concern Moderate concern High concern Imminent concern

2. The psychiatry consult note will also include depression severity rating scores measured using clinician rated scales: Montgomery-Asberg Depression Scale (MADRS) and Bipolar Inventory of Signs and Symptoms Scale (BISS) -15 items; and patient rated scales Beck Depressive Inventory-II (BDI-II) and the Beck Anxiety Inventory (BAI).

3. The authorized psychiatrist's team will have the patient sign the medication consent form (appendix B) that will be added to the patient's chart.

4. Food and Fluid Intake Assessment: Similar to the conscious sedation guideline (Policy No: 9.12), prior to ketamine administration patients must be evaluated for intake of food and fluids. General guidelines are as follows: No solid food for 6 hours prior to the administration of sedation. Clear liquids may be taken up to two (2) hours prior to sedation. This information will be documented in the *Ketamine Worksheet*. Risks and benefits of sedation for the procedure must be considered in patients whose fasting status does not fall within the above guidelines or is unknown. The



anesthesiology provider in situations requiring urgent treatment may waive intake restrictions; however, the lightest degree of sedation possible should be considered with measures taken to protect the airway. Informed consent must make the patient aware of the increased risk of aspiration and subsequent complications if recommended fasting status is waived.

F. Treatment Administration

1. Ketamine will be administered in an pre-identified location where appropriate monitoring can be performed. Ideally, treatment will take place in the patient's hospital room. Psychiatric inpatients, however, will require transportation to a suitable location for the duration of the procedure.
2. Resuscitation (Crash Cart) and monitoring equipment (see below) appropriately sized to the patient must be available at the location and the recovery area. The location should be the quietest area possible. On medical floors and the IP if the patient is located in a private room, administration will take place in their room providing resuscitation and monitoring equipment is available. If the patient is not in a private room they will be transferred to a procedure room. Monitoring equipment must include blood pressure monitor, pulse-oximeter, wall source oxygen delivery system with suction, medications normally present in the Crash Cart and bag- valve-mask ventilation equipment also normally part of the Crash Cart.
3. The pharmacy will dispense the requested dose of ketamine; the order will be entered in Sunrise by the anesthesiologist (attending or fellow).
4. Supplemental oxygen is administered throughout the procedure and recovery period unless contradicted by the procedure (Policy No: 9.12) or deemed unnecessary by the authorized psychiatrist's team in consultation with anesthesiologist. If supplemental oxygen is contradicted, the reason for not administering oxygen must be documented in the patient's medical record. Oxygen saturation monitoring is continuous.
5. Ketamine administration: Ketamine dose of 2 mg/kg was determined based on the review of the literature [e.g., (2, 7, 9, 13-16)] as well as over 2 years of combined collaborative experience of physicians using ketamine for the treatment of depression and pain in UTHSCSA's Departments of Anesthesiology and Psychiatry.
 - a) The anesthesiologist (attending or fellow) will administer ketamine to the patient following the recommendation made by an authorized psychiatrist. These clinicians are highly qualified to administer conscious sedation, monitor patient outcomes, and recover the patient. The nursing staff or anesthesiologist will follow standard operating procedures to obtain intravenous access and intravenous fluid administration prior to ketamine administration. In many cases patients will already have readily available IV access. The



anesthesiologist (attending or fellow) will designate an appropriate *Patient Monitor* (see definition above).

b) IV dosing: A total ketamine dose of 2 mg/kg will be administered in 4 or more boluses (>4 if patient weight is >100 kg) given approx. 10 min apart. The maximum bolus dose for ketamine is 50 mg. Prior to administration of the first bolus, patients will receive midazolam 1 mg IV push. Two additional PRN midazolam 1 mg doses can be given to the minority of patients reporting symptoms or displaying signs of distress (about 5% in our experience) related to ketamine's dissociative effects.

G. Observation by *Patient Monitor* (from Policy No: 9.12)

1. Level of consciousness is monitored as evidenced by the patient's response to verbal or light tactile stimuli or the ability to answer questions or follow instructions.
2. Continuous ECG monitoring must be used for all patients of ASA score 3 or 4 in any patient with a history of cardiovascular disease or when arrhythmia is suspected or anticipated.
3. The *Patient Monitor* must immediately notify the medical provider of any adverse trends or assessment findings noted during recovery.
4. Patients receiving ketamine must have IV access maintained throughout the duration of the procedure and recovery phase and until discharge criteria for level of consciousness are met (see below).
5. The physician administering and supervising administration of ketamine (anesthesiology attending or fellow) must remain readily available for the entire duration of procedure in case the *Patient Monitor* notices any abnormalities. The rapid response team is always readily available if the *Patient Monitor* or supervising physician deems necessary to call a "Code Blue". The authorized psychiatrist or its team will be present and/or available for questions and documentation purposes.
6. The following will be recorded every 15 minutes on the *Ketamine Worksheet*: heart rate, blood pressure, respiratory rate, oxygen saturation and level of consciousness. Vital signs will also be entered in Sunrise in flow sheet section of Sunrise. After finishing the treatment administration, the *Ketamine Worksheet* will be added to the patient's chart to be scanned by medical records.
7. The anesthesiologist or the authorized psychiatrist's team will complete dissociation scales following administration of the ketamine treatment. Dissociation scales include the Clinician-Administered Dissociative States Scale (CADSS), the AOV (Altered States of Consciousness Scale), and the MEQ (mystical Experience Questionnaire). Ratings will be entered in the post-ketamine administration



psychiatry consult note. Worksheets are located in the Psychiatry Consult workroom or on the Psychiatry Services shared M drive.

H. Recovery and post-ketamine administration care: Patient monitor will observe the patient for 60-90 min after ketamine administration. This monitoring will be conducted in the same place where the treatment was administered. Similar to the conscious sedation guidelines (Policy No: 9.12), the patient must be monitored until recommended recovery criteria are met:

1. Cardiovascular function and airway patency are stable and oxygen saturation is at pre-procedure level
2. The patient is easily aroused; protective reflexes are intact and speech is appropriate for age and developmental level
3. The state of hydration is adequate
4. The modified Aldrete Score (see *Ketamine Worksheet* appendix A) has returned to baseline or pre-procedure levels. At time of discharge from the procedural area the patient should:
 - a) Be alert and oriented or at their baseline mental status
 - b) Have vital signs and pulse oximetry within acceptable limits and stable
 - c) Return to baseline ambulation status
5. For inpatients that have been transported to a procedure room for treatment, there must be demonstration of return to baseline status prior to transfer back to their room.
6. Recovery follow up by the *Patient Monitor* can be terminated after a minimum of 60 minutes when all of the following criteria have been met and the post ketamine infusion recovery criteria score is at least nine out of ten (See *Ketamine worksheet*).
 - a) Patient is able to move their extremities
 - b) Respiratory rate and effort are at baseline
 - c) Blood pressure is within 20% of baseline
 - d) Patient is fully awake
 - e) Oxygen saturation is greater than 94% on room air
 - f) Patient has minimal or no nausea and no emesis for at least 20 minutes



7. Recovery from the ketamine administration to pre-administration baseline must be documented. The physician responsible for the administration of ketamine must remain available until all applicable recovery criteria are met.

8. Post-infusion ratings will be recorded in the patient's psychiatry consult note which will include ratings for the scales mentioned above measuring mood symptom severity, suicidal ideation, psychosis, pain and adverse effects.

IV. AUTHORIZATION OF A PSYCHIATRIST TO RECOMMEND KETAMINE

A psychiatrist part of UTHSCSA's faculty with medical privileges at UHS is qualified to recommend the utilization of ketamine for the treatment of depression in the inpatient services at UHS only after completing the authorization process, which is signed by the Chair of the Department of Psychiatry. To obtain authorization the psychiatrist must complete the following three requirements, documented as part of the clinician request for authorization:

A. Successful completion of reading the *Ketamine for the Treatment of Depression Competencies Booklet*², and passing the *Ketamine for the Treatment of Depression Competency Test*³ which documents knowledge of the material.

B. Observation of a minimum of three antidepressant treatments with IV/IM ketamine with another psychiatrist authorized to recommend ketamine for the treatment of depression.

C. Knowledge and experience administering all the mood severity rating scales and dissociation scales described in the UHS Ketamine Administration Guideline.

²Ketamine Administration Competencies Booklet is an educational resource created for psychiatrists seeking to recommend ketamine use for the treatment of depression at UHS.

³The test is comprised of 20 multiple-choice questions out of which 15 must be answered correctly



APPENDIX A

KETAMINE WORKSHEET:

Identifying information

Name: _____ Date _____

Age: _____ Weight: _____ Height: _____ ASA PS: _____

Diagnosis: _____

Indication for ketamine treatment: _____

Pertinent medical/surgical history: _____

Allergies: _____

Current medications: _____

Medical clearance by: _____ Date/Time _____

Psychiatry assessment by: _____ Date/Time _____

Anesthesiology evaluation (attending/fellow): _____ Date/Time _____

ED Physician evaluation _____ Date/Time _____

Ketamine dose/route recommended: _____

Last intake of solids (hours): _____ Last-intake of clear liquids (hours) : _____

Location where the treatment will be provided: _____

Patient Monitor: _____

Medical provider administering IV/IM ketamine: _____

Medical provider ordering PO ketamine: _____

RN present during the treatment or given Ketamine PO: _____

Patient signed medication consent form: yes _____ No _____

| Time/*Date | HR | BP | RR | O Sat | Pain | Level of consciousness | Comments/medications ordered/side effects |
|------------------|----|----|----|-------|------|------------------------|--|
| *Screen baseline | | | | | | | Ratings <input type="checkbox"/> Start/Ratings <input type="checkbox"/> Fit for assessment <input type="checkbox"/> |
| +15 | | | | | | | |
| +30 | | | | | | | |
| +45 | | | | | | | |
| +60 | | | | | | | |
| +75 | | | | | | | |
| +90 | | | | | | | |
| +105 | | | | | | | |
| +120 | | | | | | | End/Ratings <input type="checkbox"/> |
| +135 | | | | | | | |
| +150 | | | | | | | |
| +165 | | | | | | | |
| +180 | | | | | | | |
| +195 | | | | | | | |
| +210 | | | | | | | Ratings <input type="checkbox"/> |
| +225 | | | | | | | |



+240

Transfer /DC

Discharge Criteria (modified Aldarete score):

| Score | 2 | 1 | 0 |
|--------------------------|--|---|---|
| Consciousness: | The patient is fully awake, able to answer questions and call for assistance. | The patient is drowsy but responds easily to verbal commands. | No response is elicited to verbal commands. |
| Respiration: | The patient is able to breathe deeply and cough. | The patient exhibits signs of dyspnea or has difficulty breathing and clearing secretions | The patient is apneic or requires assisted ventilation |
| Systolic Blood Pressure: | When the blood pressure reading is (+) or (-) 20 mm Hg the pre-Ketamine level. | When the blood pressure reading is (+) or (-) >20-35 mmHg of the pre- Ketamine level. | When the blood pressure reading is greater than (+) or (-) 35-50 mmHg of the pre- Ketamine level. |
| Oxygen Saturation: | Oxygen saturation is greater than 94% on room air | Oxygen saturation is greater than 94% on supplemental O2 | Oxygen saturation less than 94% on supplemental O2 |
| Activity: | The patient is able to move all 4 extremities or motor activity has returned to the patient's baseline | The patient is able to move only 3 extremities. | When the patient is able to move only 2 extremities. |

Patient must have a minimum score of 9/10 before ending recovery observation.

Modified Aldarete score: _____

Supervising Physician signature: _____

Patient Monitor: _____

American Society of Anesthesiologists Physical Status (ASA PS) Classification System

| ASA Physical Status (PS) Classification System* | | |
|---|---|---|
| ASA PS Category | Preoperative Health Status | Comments, Examples |
| ASA PS 1 | Normal healthy patient | No organic, physiologic, or psychiatric disturbance; excludes the very young and very old; healthy with good exercise tolerance |
| ASA PS 2 | Patients with mild systemic disease | No functional limitations; has a well-controlled disease of one body system; controlled hypertension or diabetes without systemic effects, cigarette smoking without chronic obstructive pulmonary disease (COPD); mild obesity, pregnancy |
| ASA PS 3 | Patients with severe systemic disease | Some functional limitation; has a controlled disease of more than one body system or one major system; no immediate danger of death; controlled congestive heart failure (CHF), stable angina, old heart attack, poorly controlled hypertension, morbid obesity, chronic renal failure; bronchospastic disease with intermittent symptoms |
| ASA PS 4 | Patients with severe systemic disease that is a constant threat to life | Has at least one severe disease that is poorly controlled or at end stage; possible risk of death; unstable angina, symptomatic COPD, symptomatic CHF, hepatorenal failure |
| ASA PS 5 | Moribund patients who are not expected to survive without the operation | Not expected to survive > 24 hours without surgery; imminent risk of death; multiorgan failure, sepsis syndrome with hemodynamic instability, hypothermia, poorly controlled coagulopathy |
| ASA PS 6 | A declared brain-dead patient who organs are being removed for donor purposes | |

*ASA PS classifications from the American Society of Anesthesiologists

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