Safety of Intranasal Ketamine for Reducing Uncontrolled Cancer Related Pain

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A. SIGNIFICANCE:

There are about 11.9 million Americans affected with cancer; of these, 53% of patients with cancer experience pain at all stages of cancer. The number rises to 58 to 69% in those with advanced cancer [1]. Depression often co-exists with cancer pain. Patients with cancer pain often require high dosages of opioids that make them too sedated to effectively participate in day-to-day activities and have a good quality of life. Occasionally, even after high dose opioids their pain remains uncontrolled in the setting of opioid tolerance or opioid unresponsive pain. An epidemiological study revealed that 10 to 15% of these patients fail to achieve acceptable pain relief with opiates alone or in combination with conventional adjuvant analgesics [5-7]. Opioid medications are associated with numerous side effects such as: 1) Most commonly- constipation, sedation, nausea and vomiting, respiratory depression, urinary retention, and pruritus. [8-11], 2) Tolerance, causes loss of treatment effectiveness forcing the increase of dosage, which simultaneously entails a greater risk for ADRs [12] , 3) Increased pain sensitivity, also known as hyperalgesia, can appear during opioid treatment, despite increasing dosage of opioids or steady state of disease[13], 4) Immunosuppression leading to significant infections has been demonstrated for opioids in experimental studies [14], 5) Hypogonadism caused by the central suppression of hypothalamic secretion of gonadotropin releasing hormone [15] 6) Hyperglycemia by decreasing the insulin secretion through the sympathetic nervous system [16] and 7) "Stress cardiomyopathy", also known as Takotsubo cardiomyopathy (transient left ventricular dysfunction, usually triggered by intense emotional or physical stress), could appear when withdrawing opioid [17].

The need to identify and evaluate new evidence-based interventions, including pharmacologic agents, to address cancer pain is a priority for the NIH as well as global public health agencies. The NIH Pain Consortium was established in 1996 to enhance pain research and promote collaboration among investigators across the NIH. Currently, the research interests of 21 NIH Institutes, Centers, and Offices are represented in the Consortium. In 2011, the Institute of Medicine (IOM) released its landmark report, *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*, which outlines the state of the science of pain prevention, care, training, and research, and provides a guide intended to transform pain care in the United States. NIH, in response, set forth a program of research funding for all conditions, including cancer, for which pain is a prominent component. The Cochrane Pain, Palliative and Supportive Care Group has urged the generation of evidence for effective, well-tolerated

pain interventions. Despite these efforts, the understanding and treatment of cancer pain remains inadequate.

A1. Background:

In the search for improved therapies for chronic cancer pain, medications with novel mechanisms of action have been sought. One such promising pharmacologic approach is ketamine.

Ketamine is an FDA approved anesthetic with amnesic, analgesic, dissociative, and sedative properties. It is unique among anesthetic agents in that it does not depress cardiovascular and respiratory systems. Ketamine is a noncompetitive, antagonist of *N*-methyl-D-aspartate (NMDA) receptors that blocks the NMDA channel in the open state by binding to the phencyclidine (PCP) site located within the lumen of the channel. Antagonism of NMDA receptors produces antinociception of persistent or neuropathic pain in animal models and analgesia in pain states in humans. The NMDA receptor is believed to play a role in the development of opioid tolerance and ketamine has been shown in a rat model to prevent fentanyl-induced hyperalgesia and subsequent acute morphine tolerance [18]. Ketamine also interacts at a number of other receptor sites to block pain. Some of these sites include voltage-sensitive calcium channels, depression of sodium channels, modulation of cholinergic neurotransmission, and inhibition of uptake of serotonin and norepinephrine. Ketamine also interacts with kappa and mu opioid receptors; however, in humans, naloxone, an opioid antagonist, does not antagonize the analgesic effects of ketamine. Safety and efficacy of ketamine as an anesthetic and analgesic agent is well documented [2-4]. Ketamine is not labeled by the FDA as an analgesic agent. Low (subanesthestic) doses of ketamine have minimal adverse impact upon cardiovascular or respiratory function but produce analgesia and modulate central sensitization, hyperalgesia, and opioid tolerance. Cancer pain, especially in end stages, can be very complicated and is mediated by a variety of pathways: visceral, nociceptive, neuropathic and central. If ketamine can be utilized for pain in end stage cancer patients, this could provide them with superior analgesia and better quality of life, without the risk of significant respiratory depression associated with opioid medications.

One of the challenges that we face with ketamine is the route of administration. The most common route is intravascular or intramuscular. Although it has been given orally and rectally, the bioavailability of ketamine when given via these routes is limited to 20-30%. Intranasal (NAS) administration represents a promising route because of:

1) Potential method of ketamine maintenance therapy as an outpatient;
2) Ease of access as a needle-free, patient-friendly route of administration;
3) Higher bioavailability compared to oral route due to absence of hepatic first pass effect; and

4) Large surface area, uniform temperature, high permeability and extensive vascularity of the nasal mucosa facilitate rapid systemic absorption of intranasal administered drugs [19].

Intranasal ketamine has been shown to be effective in controlling breakthrough pain in a double blind randomized control trial (DBRCT) performed by Carr in 2003, as well as help with depression in a DBRCT by Lapidus in 2014 [20,21]. Both studies were NIH funded. The Carr study was a DBRCT in 20 patients with breakthrough pain and noted pain relief within 10 min, lasting up to 60 minutes with 10-50 mg of intranasal ketamine (2.65 point average decrease on NPRS scale). The pain scores were only recorded until 60 minutes after the drug administration and the patients were allowed to determine the dose themselves, without precise description for this in the study. Lapidus study was performed in 20 patients with major depression and noted significant improvement in depressive symptoms (7.6 point average decrease on MADRS scale) in 44% of patients at 24hrs with 50mg of intranasal ketamine. There are limited data regarding the use of ketamine as an adjuvant to opioids for the management of *cancer* pain[22]. We seek to obtain preliminary data on safety, feasibility, and utility of this novel technique for the treatment of uncontrolled cancer pain. Ketamine is a scheduled III medication. Intranasal ketamine can be ordered by a physician from a compounding pharmacy.

A2. Pharmacokinetics:

Ketamine has a rapid onset and relatively short duration when administered as a single intravenous dose. Onset of action for intravenous dose is 30 seconds; distribution half-life 10 minutes; elimination half-life 2-3 hours. Oral bioavailability is poor (20-25%) possibly due to the hepatic first pass effect/GI tract effect. Ketamine undergoes rapid demethylation to norketamine via cytochrome P450 (CYP) conversion, with CYP3A4 being the principle pathway, with minor and clinically insignificant contributions from CYP2B6 and CYP2C9. [50] Bioavailability of intranasal ketamine was found to be 50% in children aged 2-9 year old in a study done by Malinkovsky et al. in 1996 [2]. However this study was done in children and the subjects did not serve as their own controls. In a study by Yanagihara et al. in 2002 the bioavailability of intranasal ketamine was found to be 45%. In this study the subjects served as their own controls, however, the number of subjects was limited to 3. The time for maximum concentration after *intranasal* ketamine administration was found to be 22.5(+- 9.6) min for ketamine and 120(+- 52) min for its metabolite norketamine. The $T_{1/2\beta}$ (elimination half-life) of *IV* ketamine is reported to be 126.8(+-47.4) min by Yanagihara et al [23]. Elimination half-life of intranasal ketamine has not been reported. Ketamine has high lipid solubility and crosses the blood-brain barrier quickly, and exhibits high hepatic clearance and a large volume of distribution. It undergoes extensive hepatic metabolism by the cytochrome P-450 system to form the

active metabolite, norketamine. Norketamine is one-third to one-fifth as potent as Ketamine. Norketamine is eventually conjugated to form more inactive metabolites that are excreted by the kidneys.

A3. Preliminary Data:

To date, we have collected data on two cases of cancer patients to whom ketamine was delivered palliatively for pain unresponsive to usual interventions:

Case 1. A 38 year old female with squamous cell cancer of the tongue with bone and lung metastases and cord compression had back/spinal pain rated as 9-10/10 on NPRS. Increasing opioid medications paradoxically increased her pain, representing opioid-induced hyperalgesia. She had failed antineuropathic medications and was admitted for the neurological symptoms secondary to cord compression. Intravenous ketamine was initiated. On day 1, her pain score reduced to 8-10/10 and on day 2 went to 4-7/10. On day 2 she was switched to intranasal ketamine (10 mg BID), so it could be continued after discharge at home. On day 3, her pain score decreased to 2-6/10, and she was slowly titrated to 20 mg BID. Her pain score reduced further to 0-7/10 on day 5, however, she developed complications from her primary disease and could not be discharged. Throughout her stay she received intranasal ketamine without reported side effects except for one episode of bloody mucus discharge after blowing her nose when she first started.

Case 2. A 74 year old female with multiple myeloma in remission had developed severe peripheral neuropathy and chronic diarrhea secondary to adverse effects of multiple myeloma therapy. She had multiple osseous lesions in pelvis and right femur s/p radiation therapy. However, she complained of pain in her right sacrum radiating to the front of her groin. Although she had full motor strength, she remained bedridden secondary to pain and peripheral neuropathy causing imbalance. She had failed multiple medications including opioids and interventions such as steroid injections. She remained on morphine extended release, and was started on ketamine IV while in the hospital and appeared to respond, although she still reported high pain scores. When ketamine was stopped, she went into a pain crisis again. The decision was thus made to continue NAS ketamine 10mg BID at home. She tolerated this dose and did not report any side effects. She maintained good pain control and required no further pain related hospital visits. Based on these limited preliminary data, a formal clinical pharmacology and efficacy study is indicated to evaluate intranasal ketamine in cancer-related pain.

B. INNOVATION:

Although ketamine has been used as an adjunct to opioid medication for pain, there is no data on intranasal ketamine for cancer-related pain. If studied extensively, this could potentially provide physicians with a simple option and unique adjunct to treat pain. Ketamine could also modulate central sensitization and hyperalgesia which are some of the mechanisms involved in development of chronic pain. This could potentially help decrease the severity of pain in general. Depression often coexists with cancer, and intranasal ketamine has the potential to improve depressive symptoms when used chronically.

Intravenous ketamine is used by pain physicians to control pain not responding to opioid medications in the hospital setting. However, it is not continued as an outpatient therapy as absorption of oral ketamine is limited to 25%. Intranasal ketamine, if feasible, will provide clinicians with an option to continue ketamine chronically. There is also lack of long term studies regarding use of ketamine for pain. Future long term studies with intranasal ketamine for pain control can be designed based on data obtained from the current proposed study.

The route of administration can be limited in terminally ill patients as many suffer from nausea and vomiting (limiting the oral route) and have dehydration making it difficult to find veins for intravenous route. A study, focusing on the effects of chemotherapy on Chemotherapy Induced Nausea Vomiting (CINV), and the effect of CINV on daily life found that 36% of all patients reported emesis and 60% reported nausea. Intranasal route is underutilized for medication administration, especially pain medications in cancer patients. If successful, this study will open new horizons of medication delivery and pain control in this population.

Objectives

Overall Goal: To determine the safety, feasibility, and utility of intranasal (NAS) ketamine in persistent uncontrolled cancer related pain.

Specific Aims:

Primary Outcomes

1. **To conduct a clinical trial of NAS ketamine in a sample of patients with cancer related pain.**

   1a. To measure pharmacokinetics of NAS ketamine through analysis of ketamine and its metabolite norketamine to determine pharmacokinetic variables including peak concentration after each dose and route (C_{max}), time to peak concentration (t_{max}), total area under-the-concentration-time curve (AUC_{0-t}), half-life ($t_{1/2}$), and clearance (Cl).

2. **To evaluate (pharmacodynamic) effects of NAS ketamine on Patient Reported Outcomes (PROs), such as pain scores, side effects, depression, health-related quality of life, and functional status.**

    2a. To assess PROs as measured by the Numerical Pain Rating Score (NPRS), Side Effect Rating Scale for Dissociative Anesthetics (SERSDA), Montgomery Asberg Depression Rating Scale (MADRS), and Edmonton Symptom Assessment (ESAS), Eastern Cooperative Oncology Group (ECOG) and Patient-Reported Outcomes Measurement Information System (PROMIS) scales.

Secondary Outcomes

3. **To determine opioid sparing effect of NAS ketamine.**

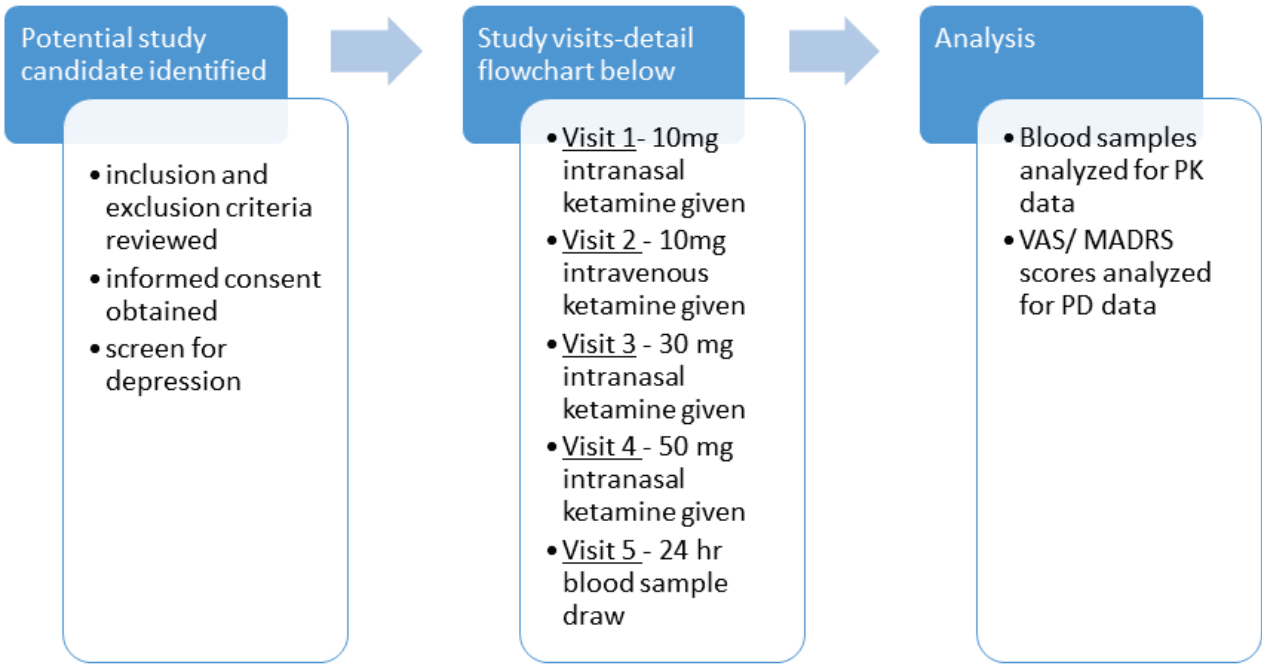
    3a. To document use of rescue medications prior to and during the study

    3b. To evaluate total opioid consumption prior to and during the study.

If intranasal ketamine can be utilized for pain control in cancer patients, this could provide them with superior analgesia and better quality of life, without the risk of significant respiratory depression associated with opioid medications. We seek to obtain preliminary data via a clinical trial addressing safety, feasibility, and utility of this novel technique for the treatment of persistent uncontrolled cancer pain. These findings would be an important initial step towards testing the effectiveness of intranasal ketamine as a non-opioid medication for cancer pain used as potential maintenance outpatient therapy. These initial findings would be applied to a subsequent trial to determine the effectiveness and associated toxicities of ketamine in a larger sample of cancer patients, and address the compelling need to identify new, successful management therapies for cancer pain.

C.APPROACH:

C.1 Study design and methods:



C.2 Methods:

This is a prospective clinical trial to investigate the use of intranasal ketamine in patients with uncontrolled pain related to cancer or cancer treatment. The trial will be conducted in the Phase 1 Unit of the Winship Cancer Institute (WCI).

Intranasal ketamine will be prepared from a 100 mg/mL vial to be delivered nasally with a nasal atomizer. We will deliver 0.1 ml to provide 10 mg of atomized ketamine. Alternating nares will be used to deliver 0.1 ml at a time until the full dose is delivered. In the intranasal ketamine study for breakthrough pain by Carr et al., 10 to 50 mg of intranasal ketamine was given regardless of the patient's weight. IV ketamine analgesic doses are >100 ng/ml [24]. Lapidus et al. found the mean ketamine plasma concentration to be 72 ng/mL at 20 min and 84 ng/mL at 40 min when 50 mg of intranasal ketamine was given over 25 min [21]. IV bioavailability is 93%, with oral bioavailability of 16.5%[25]. Intranasal bioavailability is estimated to be 45%-50% from prior studies[23, 26, and 27]. Studies from Kyle Christensen et al. have shown safety with

intranasal doses of ketamine at 10 mg, 30 mg and 50 mg [28]. Therefore, for study purposes 10mg, 30 mg and 50mg of intranasal ketamine will be administered. Each visit will be two to seven days apart to avoid any accumulation of study doses. Subjects will be recruited at the supportive oncology clinic, oncology clinics, the pain clinic and Acute Pain Service at Emory. Subjects may be identified and contacted via telephone with information about the study prior to their next clinic appointment in order to allow time for them to consider the study. After informed consent has been obtained, study eligibility will be confirmed (see Table of Assessments). An appointment will be made for the Phase I Unit at Winship. A family member/friend must transport the patient home following drug administration, as driving for 24 hours post drug administration is discouraged. Written informed consent will be obtained prior to performance of study procedures, either while recruiting prior to study visit one or during the first study visit, prior to beginning the study. Subjects must meet all study eligibility criteria on Visit 1 prior to study treatment. Patients will be asked to return to the Phase 1 Unit for a total of 5 study visits. All study visits to the clinic will take place within six weeks or less. A telephone call visit will occur 14 days after the last dose of medication administered to follow any ongoing adverse events that occurred during the study period. If there are no ongoing adverse events at the end of visit five, the subject's participation will end at that time. Subjects may be reconsented if withdrawn early, at the discretion of the investigator, provided all eligibility requirements are met.

Table of Assessments

Assessments	Screening	Visit One	Visit Two	Visit Three	Visit Four	Visit Five	Telephone Call
Review of Inclusion/Exclusion	X						
Informed Consent	X						
Med Hx/Demographics	X						
Hemoglobin (if none within 3 months of Visit One)		X					
Urine pregnancy test-within one week of planned Visit (women of child bearing potential)		X	X	X	X	X	
PHQ9 Depression Screening	X	X[1]					
Completion of PROMIS Questionnaire		X				X	
ECOG score		X	X	X	X	X	
ESAS		X	X	X	X	X	
MADRS[2,3]		X	X	X	X	X	
Height		X					
Weight		X	X	X	X	X	
IV access		X	X[4]	X	X		
Study Medication Administration		X	X	X	X		
Vital Signs(HR[5], BP, RR, Pulse Oximetry[6])		X[7]	X[7]	X[7]	X[7]	X[8]	
Blood Samples (PK)		X[9]	X[9,10]	X[9,10]	X[9,10]	X[10]	
Hepatic Function test		X				X	
Urinalysis		X				X	
Pain Scores (NPRS)		X[7]	X[7]	X[7]	X[7]	X[8]	
RASS scale		X[11]	X[11]	X[11]	X[11]	X[8]	
CAM ICU Scale for RASS score between +4 to -3		X	X	X	X	X	
SERSDA scale		X[11]	X[11]	X[11]	X[11]	X[8]	
Olfactory assessment- pre and post drug		X	X	X	X		
Adverse Events		X	X	X	X	X	X[12]
Rescue medication use details		X	X	X	X	X	
Pain Diary[13]		X	X	X	X	X	
Opioid Pill Count		X	X	X	X	X	

[1]If not previously recorded during screening visit or within 3 months of planned visit one and no history of depression
[2]If screened positive for depression, questionnaire to be administered before medication given
[3]Questionnaire to be repeated between 180 and 240 minutes after medication given
[4]Two IV's needed Visit two: one for study medication, one for blood draw
[5] Monitoring will occur continuously for a minimum of 30 minutes post drug administration
[6]Pulse oximetry monitoring will occur continuously for a minimum of 30 minutes post drug administration
[7]To be recorded at baseline, 5, 10, 15, 30 (+/- 5), 45(+/- 5), 60 (+/- 5), 120(+/- 15), 180(+/- 15) and 240(+/- 15) minutes after medication administration
[8]On arrival for study visit

[9]Samples will be obtained at 2, 30(+/-5), 60(+/-5) and 240(+/- 15) min after medication administration on visits 1 through 4.
[10]Baseline samples will be drawn on visits 2 to 5
[11]Assess at baseline, 30(+/-5), 60(+/-5), and 240 (+/- 15) minutes after medication administration
[12] Ongoing adverse events will be followed by a telephone call 14 days after the last day of study medication administration, plus or minus one day.
[13]Patient to record data throughout study enrollment, collected at final visit

Dose Finding. Escalating dosages of intranasal ketamine will be given during the study in order to find optimal analgesic dose without significant side effects. On the first study visit, after obtaining written informed consent, 10mg of intranasal ketamine will be given to make sure that the study patients are able to tolerate a small dose of NAS ketamine. On the second visit, 10 mg of IV ketamine will be given to help establish bioavailability of NAS ketamine, with patients serving as their own controls. On the third and fourth visit, higher doses of ketamine, 30 mg and 50 mg respectively, will be given, if the patients did not have severe adverse events with the smaller dosage. Licensed study personnel delegated to do so, will administer ketamine. The intranasal ketamine will be administered as follows: 1) Ensure mucosal atomization device (MAD) is primed and the appropriate dose loaded into the syringe. 2) Have patient sit in chair and clear sinuses using a tissue if needed. 3) Tilt the patient's head back. 4) Insert MAD into nostril and aim directly posterior, level with the floor of the nare, and slightly lateral. 5) Administer 0.1mL (10mg). 6) Have patient keep his head tilted back for 5 minutes, if tolerable, to ensure that the medication does not run out of nares. Make a note if medication is visibly noted to run out of nares or if patient reports feeling of medication trickling down his throat. 7) If more than 0.1mL (10mg) needs to be delivered, repeat steps 3-5 in the contralateral nare, alternating until the full dose is delivered. Ensure 30 seconds have passed before re-administration into the same nare. Patients may continue to take their usual pain medication as needed. Since most of the oral immediate release opioid medications peak between 30 to 90 minutes, ketamine will be given at least 120 minutes after the last dose of immediate release opioid medication so the reduction in pain score is not confounded with the results of immediate release opioid medications. Pain scores will be recorded on NPRS prior to and at 5, 10, 15, 30, 45, 60, 120, and 180 and 240 minutes after administration of test medication. NPRS is the most responsive tool to document pain intensity when compared to Visual Analogue Scale (VAS) and Visual Rating Scale (VRS) for measuring pain, [29] showing higher compliance rates, better responsiveness, ease of use, and good applicability relative to VAS/VRS[30]. In general, improvements of pain severity</=1.5 points on NPRS could be seen as clinically irrelevant [31-34]. Above that value, the cutoff point for "clinical relevance" depends on patients' baseline pain severity, and ranges from 2.4 to 5.3 [33-35]. Higher baseline scores require larger raw changes to represent clinically important differences [36].

Concomitant Opioid medications: As the study subjects will have uncontrolled pain it is likely that they might be on opioid medications during the study. Georgia prescription monitoring database will be searched by the investigators and an opioid pill count will be done at each visit to monitor opioid intake during the study.

Pharmacokinetics. Blood samples will be drawn at 2, 30, 60 and 240 minutes. Baseline blood samples will be drawn on visits 2 through 5. The specimen requirements for lab testing are 3 ml serum or plasma in EDTA containing vacuum tubes. We will draw 6 ml of blood per sample to allow for adequate serum/plasma sample. The total blood drawn during one visit would be 24 to 30 mL. Samples will be promptly centrifuged and serum or plasma will be separated into a plastic cryovial and frozen. The plastic containers will be preservative free. All samples will be sent within 3 months to National Medical Services. The samples are valid for 7 months at -20°C, 30 days when refrigerated or stored at room temperature. Samples will be destroyed immediately after analysis. A gas chromatography with mass spectrometry (GC/MS) analysis of the samples will be done for concentrations of ketamine and its metabolite, norketamine. Plasma concentration-time curves for ketamine and norketamine will be generated for each subject and compared within subjects for the variables of route and dose, with IV administration serving as the basis for comparison.

Additional Labs: Liver function test (LFT) and urinalysis (UA) will be done on visits 1 and 5.

Patient Reported Outcomes. Patients will maintain a pain diary(Appendix I-J) for the entire study period up until the 5th and final study visit and record how often they took their usual breakthrough medication during the trial.

At home, patients will log pain scores 3 times a day. 10 item PROMIS questionnaire will be filled out at first (baseline) and fifth (final) study visit to assess global health. Participants will fill out a PHQ-9 scale during the screening visit or the first study visit. PHQ-9 scale ranges from 0 to 27 and can be used for screening of depression. Patients who are on antidepressants or score more than 4 on PHQ-9 scale will be assessed for depression during the study. Depression will be assessed on the MADRS on each visit. *(See appendix 1 F)* This is a 10 item questionnaire designed to be particularly sensitive to treatment effects[37]. Higher MADRS score indicates more severe depression, and each item yields a score of 0 to 6. The overall score ranges from 0 to 60. Participants who screen positive for depression and are not on any treatment for depression, will be offered a psychiatry consult as a part of their routine healthcare, if interested. Performance status will be assessed on ECOG grading at baseline and throughout the study, which ranges from 0 to 5, where 0 is fully active and 5 is dead. ESAS will be used to assess 9 common symptoms (pain, tiredness,

nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath) experienced by cancer patients. Each symptom is rated from 0 to 10 on a numerical scale; with 0 meaning that the symptom is absent and 10 that it is the worst possible severity. Patient's study participation will end with the 5th and final study visit. Patients will be followed up in the pain or supportive oncology clinic for their routine care for pain management. They will be followed up more frequently if needed. Patients who benefit from intranasal ketamine would be offered this medication as an outpatient. The dosage and regimen will be decided on a case by case basis by the treating physician.

C.3 Monitoring and Documentation: ***(See appendix 1 for all scales)***

The following assessments will be documented in patient research study record:

1. Height and weight at the first study visit
2. Pain intensity on NPRS prior to and at 5, 10, 15, 30, 45, 60, 120, 180 and 240 minutes after medication is given
3. Vital signs including heart rate, blood pressure, respiratory rate and pulse oximetry at baseline, and 5, 10, 15, 30, 45, 60, 120, 180 and 240 minutes. Vital signs and pulse oximetry will be monitored continuously for a minimum of 30 minutes post drug administration. More frequent vital signs if they are unstable
4. ECOG and ESAS score at baseline on each visit
5. Sedation level on RASS scale prior to and at 30, 60 and 240 minutes after medication is given
6. If RASS score is between +4 to -3 then sedation/delirium assessment on CAM scale will be done prior to and at 30, 60 and 240 minutes after medication is given
7. Side effects on SERSDA scale prior to and at 30, 60 and 240 minutes after medication is given
8. An olfactory assessment will be performed pre and post study drug administration to determine if the study medication has impacted the sense of smell.
9. Rescue medication taken; if taken, was it taken at the usual interval or longer
10. Patient response to intervention if anything besides change in NPRS is reported
11. Patient and family education regarding maintaining pain diary and reviewing discharge instructions, including when to call study coordinator or report to emergency department
12. PROMIS functional scale on the first and last day of the study
13. Any change in health status during the duration of study
14. Opioid medication pill count at the beginning of each visit
15. Only for visits 1, 3, and 4: If the patient reports symptoms of a significant upper respiratory tract infection (e.g. rhinorrhea, congestion), the study visit will be canceled and re-scheduled at a later date.

16. If changes in sense of smell are noted, a study investigator will be notified, and additional olfactory assessments will be performed, with the frequency and amount of assessments at the discretion of the investigator.
17. The frequency of the assessments may be increased at the discretion of the investigator.

The study nurse will notify the attending physician if any of the following occur:

1. Baseline HR >100 or BP>160/100 or pain score </=3 on NPRS who will make the decision of whether or not to proceed with the study visit or cancel based on the inclusion/exclusion criterion
2. After the study medication is given, vital signs change more than 20% from baseline; HR<50 or >110, SBP<90 or >180, DBP<30 or >100, RR<8 or >24 or SaO2<90; Any side effects or unexpected results
3. Sedation on RASS scale between -1 and -5 at any time
4. Positive for delirium on CAM scale at any time
5. Presence of any possible side effects from the study drug administration

Patients will be deemed eligible for discharge after the 240 minute assessment if they meet the following:

- Vital signs are within 10% of baseline values
- RASS score is between +1 and -1
- Side effects as noted on the SERSDA scale are valued as 2 or less, or no more than 1 point greater than their baseline value. Investigator must be notified if value is greater than 2.

Should the patient not meet these criteria at the end of the 240 minute assessments, the study nurse will contact the research physician for further evaluation and assessment.

C.4 Potential Risks

Adverse effects are dose related. No serious side effects have been reported with intranasal ketamine doses of up to 50 mg.

Common side effects of ketamine: Include sedation, somnolence, sensory illusions, dissociative feelings, blurred vision, anorexia, abdominal pain [38, 39], feeling of insobriety [40, 41], and dream disturbances [42]. Dose-dependent side effects include hallucinations, agitation, nightmares, dizziness, and nausea [43]. At higher doses, side effects may include delirium, impaired motor function, amnesia, anxiety, panic attacks, mania, insomnia, and elevated blood pressure [43]. Rarely, hepatic failure[43] has been reported in participants with

underlying liver disease prior to ketamine administration. Additionally, chronic administration of ketamine has been associated with ulcerative or hemorrhagic cystitis, which usually resolves with cessation of ketamine administration [43]. However this was reported in ketamine abusers and dosage being used for this study are very low. Additionally, a LFT and UA will be done the day of or up to 24 hours before both visits 1 and 5 to monitor for rare side effects. If obtained as standard of care within this time frame, these will not need to be repeated for the study. Benzodiazepines and neuroleptics have been used to successfully minimize psychotomimetic effects, such as psychosis or delirium, when ketamine is used for the treatment of pain [44, 45].

C.5 Management of specific side effects

Side effects unique to intranasal route: Include transient change in taste, rhinorrhea and nasal passage irritation. If the patient reports that these changes to be persistent beyond the date of administration of study drug and are moderate to severe in intensity, then a formal ENT consult will be sought.

Cardiovascular effects: Potential effects include: increases in heart rate, systemic arterial pressure, systemic vascular resistance, pulmonary artery pressure, and pulmonary vascular resistance. In the absence of autonomic control, ketamine has direct myocardial depressant effect, usually overridden by central response. If >20% variation from baseline is noted in heart rate or blood pressure, study MD will be notified. Risk assessment will be done by the MD and appropriate medications will be given as deemed necessary. Patient will be admitted to inpatient medical oncology service for 23 hours observation if at the end of study visit a >20% variation persists despite treatment; HR >120; hypertensive urgency/emergence occurs. Hypertensive urgency is defined at SBP>180 or DBP>110. In hypertensive emergency signs or symptoms of end organ damage are noted such as blurry vision, headache, and chest pain.

Central nervous system effects: Include- tremors, increased intracranial pressure, floating sensation, hallucinations (auditory and visual), delirium, vivid dreams or illusions, confusion, restlessness, disorientation, dysphoria, dizziness, and sedation. After discontinuation of ketamine, recurrent illusions (flashbacks) can occur. Ketamine can lower the seizure threshold, especially in patients on aminophylline. Benzodiazepines such as midazolam 0.5 mg to 5 mg IV or lorazepam 0.5 mg to 5 mg IV or diazepam 0.5 mg to 10 mg IV or oral, etc. may be given to mitigate CNS side effects at the discretion of the study MD. Admission for 23 hours observation to the inpatient medical oncology service will be considered if at the end of a study visit either excessive sedation is noted or RASS score between -3 and -5 or if any severe psychological manifestations exist.

Gastrointestinal system effects: Include nausea, vomiting and increased salivation (due to increased salivary and tracheobronchial mucous gland secretions). Nausea and/or vomiting will be treated with

ondansetron 4 to 8 mg IV or PO depending upon severity. Diphenhydramine 6.25 to 25mg IV may be given, if no relief from ondansetron or if ondansetron is contraindicated. For increased salivation, not well tolerated by the patient, glycopyrollate 0.2mg IV may be given if deemed necessary by the study MD. Admit if unable to tolerate oral liquid at the end of visit.

Respiratory effects: Respiratory depression is rare (ventilator response to CO2 is maintained). Upper airway skeletal muscle tone is maintained; upper airway reflexes remain relatively intact. Respiratory depression can occur when ketamine is given in conjunction with other agents (e.g. opioids) or when given in large doses or rapid infusions. Treatment may include: decrease/stop opioids and other sedating medications. If respiratory depression (RR < 10/min, O2 sat < 90%) persists at the end of the study visit, the study MD will be notified and potential admission will be considered, the patient's will be admitted for 23 hour observation with the inpatient oncology service.

Ocular effects: Nystagmus (especially vertical nystagmus), diplopia, blurred vision and slight elevation in intraocular pressure are possible. If this happens at the end of the study visit, the study MD will evaluate for safeness for discharge vs 23 hrs observation.

Musculoskeletal effects: There is a possibility of increased skeletal tone or tonic-clonic movements. The study MD notified if this happens. This will be monitored and treated appropriately. Short acting benzodiazepines like IV midazolam may be considered.

Allergic reaction: Ketamine does not evoke histamine release; and, rarely, if ever causes allergic reaction. If an allergic reaction is suspected then the reaction will be treated based on the severity, with steroids and antihistamine allergic agents.

C.6 Benefits:

The patient may benefit from improved pain control and improved mood or depression control by participating in this research study.

C.7 Participant selection*:*

A sample size of 7 from a population of 20 (in the study done by Carr et al.) achieves 91% power to detect a NPRS difference of -2.7 between the null hypothesis mean of 0.0 and the alternative hypothesis mean of 2.7 with an estimated standard deviation of 1.9 and with a significance level (alpha) of 0.05000 using a two-sided Wilcoxon test assuming that the actual distribution is normal.

We need a sample size of 7 patients based on statistical analysis observed in the study done by Carr. We will include 10 patients to account for the possibility that the observed pain reduction in the current study may be different than the study done by Carr, as in this study patients were given ketamine for breakthrough pain,

as opposed to for baseline pain. We will enroll up to 25 patients in the study to account for potential dropouts. If a higher dropout rate is observed, then we will enroll more patients until we have at least 10 patients who complete the entire study.

Subject Replacement

Any subject who does not complete the IV dosing and at least one intranasal dose will be replaced and followed for safety as needed and/or via telephone call at 14 days.

Enrolled subjects who discontinue early will be replaced.

If a subject misses more than one treatment visit during the study period, the subject will be withdrawn and replaced to achieve a minimum of 10 subjects who are maximally treated with study medication (4 study visits).

The patients should meet the following inclusion and exclusion criteria.

C.8 Inclusion Criteria: Patients will be eligible to participate if they are:

1. Male and female subjects at least 18 years of age
2. Patients with uncontrolled pain related to cancer or cancer treatment. Uncontrolled pain will be defined as [46,47]
    i. pain which persists for more than 7 days and is rated >/=4 on NPRS
    ii. use of breakthrough medication more than 4 times in 24 hours or being treated with oral morphine equivalent of 50 mg/d or more
3. Patients who are[48] able to follow-up in person during the trial
4. Patient on stable analgesic regimen for >7 days without escalation during study period with rescue or immediate release medication every 3 hours or longer
5. Patients who are willing and able to maintain a daily pain diary
6. Patients who are able to understand written and verbal English
7. Patient weight >/= 50 kg

C.9 Exclusion Criteria: Patients will be excluded from the study if they have any of the following:

1. Transportation issues interfering with return study visits
2. Patients with high disposition of laryngospasm or apnea
3. Presence of severe cardiac disease

4. Presence of conditions where significant elevations in blood pressure would be a serious hazard.
5. Stage 2 hypertension or greater (systolic blood pressure > 160 and/or diastolic blood pressure >100)
6. Baseline tachycardia, HR >100
7. History of seizures, elevated ICP or CSF obstructive states(e.g. severe head injury, central congenital or mass lesions)
8. Conditions that may increase intraocular pressure (e.g. glaucoma, acute globe injury)
9. History of uncontrolled depression or other psychiatric comorbidity with psychosis
10. History of liver disease
11. History of interstitial cystitis
12. History of nasal or sinus anomalies or dysfunction e.g. allergic or infectious rhinitis.
13. Patients with lesions to the nasal mucosa
14. Pregnant women, nursing mothers and women of childbearing potential not using contraception known to be highly effective. Highly effective contraception methods include combination of any two of the following:
    i. Use of oral, injected or implanted hormonal methods of contraception or;
    ii. Placement of an intrauterine device (IUD) or intrauterine system (IUS);
    iii. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository;
    iv. Total abstinence;
    v. Male/female sterilization.
15. Illicit substance abuse within the past 6 months
16. Documented history of medication abuse/misuse (e.g. Unsanctioned dose escalation, broken opioid agreement etc.)
17. Clinical requirement for medications that are concurrent inducers or strong inhibitors of CYP3A4. CYP3A4 substrates are allowed. (Appendix II-D)
18. Porphyria (possibility of triggering a porphyric reaction)
19. Severe active anemia (a hemoglobin< 8 documented by labs drawn within 3 months of first study treatment)
20. History of difficult intravenous access
21. Intractable vomiting

C.10 Informed Consent Process*:*

Informed consent will be obtained by a research team member delegated to do so by the PI, prior to conducting any research procedures. This process will include a discussion of risks and benefits, as well as answering patient questions. If patients are able to provide their own medical history, they will be deemed capable of providing informed consent for research participation. The process will be free of coercion. Study patients will be paid a small amount to reimburse for travel expenses for each visit completed. They can withdraw at any time without penalty to their ongoing care.

C.11 Compensation for time and effort*:*

A compensation of $50 per visit will occur with each patient for each completed visit to reimburse for travel expenses to and from the institution.

C.12 Statistical analysis*:*

Study results will be analyzed as below to achieve the study objectives:

1. **Determine pharmacokinetics of intranasal ketamine.**

   Concentrations of ketamine and its metabolite norketamine will be analyzed to determine pharmacokinetic characteristics such as bioavailability, peak effect and elimination.

2. **Determine pharmacodynamics of intranasal ketamine in terms of Patient Reported Outcomes**

   i. Pain scores on NPRS will be analyzed by Wilcoxon signed-rank test as the study sample size is too small to be analyzed by paired –t test. Generalized Linear Model will be used to model any time trend for pain score change and to test if the trend is significant.

   ii. T-test will be used to compare any changes in depression severity on MADRS.

   iii. Chi-square test will be used to test presence/absence of any side effects. Wilcoxon signed rank test will be used to assess the severity of all the side effects (including SERSDA), if needed.

   iv. Paired T-test will be used to asses any changes in functional status on PROMIS scale.

   v. T-test will be used to compare any changes in ESAS and ECOG.

3. **Determine PK-PD relationships of NAS ketamine delivered**

Timing, degree and duration of change in pain scores will be compared with individual and group pharmacokinetic parameters to assess potential relationships between measures of exposure (C_{max}, and AUC_{0-t}) and pain relief. Multivariate modeling including patient-specific data (age, sex, weight, BMI, morphine equivalents) will be performed using initial PK parameters and goodness of fit analyses for compartmental model selection. If applicable, data from vital sign measurement changes will also be used as comparison with pharmacokinetic data.

4. **Determine opioid sparing effect of intranasal ketamine.**
   i. Chi-square test will be used to compare frequency of rescue medication use.
   ii. T-test will be used to compare total opioid consumption.

C.13 Data and Safety Monitoring and Reporting Plan:

1. This study will be followed by the Winship Cancer Institute Data Safety Monitoring Committee (DSMC) for local review and confirmation of proper study execution and safety measures. Initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects reviewed. Therefore, subsequent monitoring will occur in six month intervals if any subjects were accrued. The population continuing to receive intervention will be monitored as determined by the DSMC. At minimum, 10% of subjects accrued since previous monitoring will be reviewed. An additional subject (or subjects) may be selected based on previously noted monitoring deficiencies or at DSMC discretion. Continued monitoring will occur in six month intervals for the population continuing to receive intervention as determined by the DSMC.

The DSMC will review pertinent aspects of the study conduct including patient safety, protocol compliance, data collection, and efficacy. The PI or designee will be responsible for notifying the DSMC of patient accrual and status updates within two months of the planned review.

2. *Procedures to assure data integrity and protocol adherence:*

a) A monthly meeting of investigators, clinical research coordinators and regulatory personnel will be held to review the clinical data.

b) Adverse event reporting will utilize the Common Terminology Criteria for Adverse Events CTCAE) version 5.0. The grading scale for these adverse events is as follows:
Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

Grade 4 Life-threatening consequences; urgent intervention indicated

Grade 5 Death related to AE.

c) A serious adverse event (SAE) is an AE or suspected adverse drug reaction that fulfills one of the following:

- results in death
- is immediately life-threatening (life-threatening in the definition of SAE refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- requires in-subject **hospitalization** or prolongation of existing hospitalization
- results in persistent or significant **disability** or incapacity
- is a **congenital anomaly** or birth defect
- is an important medical event: important medical event in the definition of "serious refers to those events which may not be immediately life-threatening, or result in death, or hospitalization, but from medical and scientific judgment may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the other outcome listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization. Development of cancer or drug dependency or drug abuse will normally be considered serious by this criterion.

d) Study progress in terms of enrollment and activity of current patients will be reviewed during the monthly meeting of the investigators, clinical research coordinators and regulatory personnel. The PI may increase the frequency of this meeting if necessary.

e) Study specific training of all study personnel, including management of potential adverse events, will occur prior to initiating study enrollment using the final approved protocol and study specific standard operating procedure document. Training of the Phase I staff will be conducted by the team clinical research coordinator prior to study enrollment. Completion of training will be documented on a study training log and stored in the regulatory binder. Investigators will complete CITI training as well as any additional training required by the Emory Office for Clinical Research.

3. Clinical monitoring will occur as previously described (Study Methods).

4. As the IND sponsor-investigator, unexpected fatal or life threatening suspected adverse reactions will be reported using the Medwatch FDA form 3500A via FedEx to the FDA no later than 7 calendar days after the initial receipt of information (21CFR 312.32(C)(2)). Additionally, serious, unexpected suspected adverse reactions and a clinically important increase in the rate of a serious suspected adverse reaction will be reported to no later than 15 calendar days after determining the information qualifies for reporting (21 CFR 312.32 (C) (1)) in paper format using FDA form 3500A. Finally, an annual progress report will be provided within 60 days of the anniversary date that the IND became active , January 20, 2017, (21 CFR 312.33).

5. Patient data will be evaluated by the PI on an ongoing basis during the study visits to observe for any trends in adverse effects of the study treatment, to ensure continued subject safety and to ensure the scientific validity of the trial. Adverse events (AE) will be recorded. An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or study treatment and that does not necessarily have a causal relationship with this administration. An AE can therefore be any unfavorable and unintended sign (including any abnormal laboratory findings), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Adverse events will be captured from the time of the first study drug administration through the fifth study visit. Ongoing adverse events at the fifth visit will be followed with a telephone call visit 14 days (plus or minus 1 day) after the last medication administration. AEs will be reported to the PI by Emory email or telephone. All adverse events will be documented in an AE log. The reporting policy of the Emory IRB will be followed.

6. The study will be stopped after a hospitalization that is related to study drug administration for a formal review by the PI and the DSMC. When a hospitalization related to study drug administration occurs, the study will be put on hold. The PI or delegated person will communicate the event details to the DSMC for their review and determination of approval to continue the study. The study will be ended if there is more than one hospitalization related to the study drug administration.

7. The Emory University School of Medicine Department of Anesthesiology will conduct this study according to national rules, regulations and guidelines governing human clinical research. In addition,

procedures cited by the US Code of Federal Regulations (Title 21) will be followed as these apply to the principles of Good Clinical Practice and approval by the Emory University Institutional Review Board (IRB).

Confidentiality*:* The privacy of the research subjects will be ensured through the standard procedures for securing research data. All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available. Subjects will be identified by a study number. If the results of the study are published, the subject's identity will remain confidential.

C.14 Potential Pitfalls:

Lack of blinding/Lack of placebo arm. There is enough evidence to support an analgesic effect of ketamine. Since the study is being conducted in cancer pain patients and involves blood draws and transport, a placebo arm is considered to be unethical in these circumstances. The possibility exists that **ketamine might have long term effects beyond its duration of action** and the pain scores might be significantly lower than the compared to at the beginning of the study. In this case **change in pain score may not be significant during the later study visits**. However, overall this would be a good effect for pain control and can future studies can be designed to account for this effect. As cancer pain can be evolving and changing, the decision was made to finish all the study visits in the least possible duration of time, as possible. Once feasibility and safety is established with this study, the aim of future studies will be allow patients to take this medication at home for maintenance. **Lack of standard opioid regimen** among patients could be problematic in terms of comparison of outcomes.

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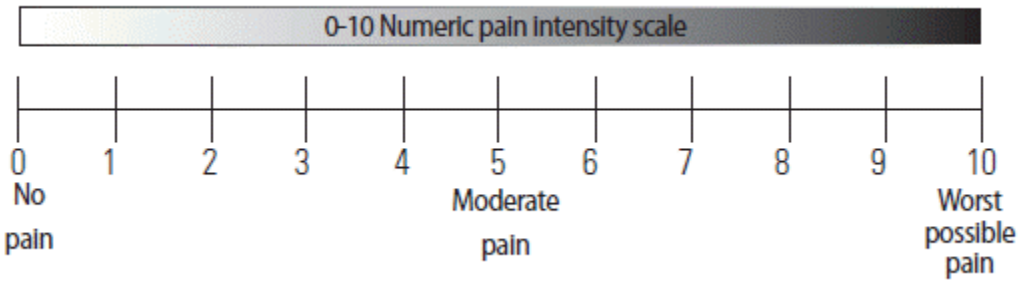
Appendix I: Assessment scales used in the study (click on files G, H, and I to open the files).

A. Numerical pain rating scale.



B. SERSDA –Side Effects Rating Scale for Dissociative Anesthetics[20, 40]

Side effects	Severity of side effects scale
Fatigue	0, no change
Dizziness	1, weak
Nausea	2, modest
Headache	3, bothersome
Feeling of unreality	4, very bothersome
Changes in hearing	
Changes in vision	
Mood change	
Generalized discomfort	
Hallucination	

C. ECOG score

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair

5 Dead

D. <u>ESAS score -</u> Edmonton Symptom Assessment System

Please circle the number that best describes how you feel NOW:

No Pain **0 1 2 3 4 5 6 7 8 9 10** Worst Possible Pain

No Tiredness **0 1 2 3 4 5 6 7 8 9 10** Worst Possible Tiredness
(Tiredness = lack of energy)

No Drowsiness **0 1 2 3 4 5 6 7 8 9 10** Worst Possible Drowsiness
(Drowsiness = feeling sleepy)

No Nausea **0 1 2 3 4 5 6 7 8 9 10** Worst Possible Nausea

No Lack of Appetite **0 1 2 3 4 5 6 7 8 9 10** Worst Possible Lack of Appetite

No Shortness of Breath **0 1 2 3 4 5 6 7 8 9 10** Worst Possible Shortness of Breath

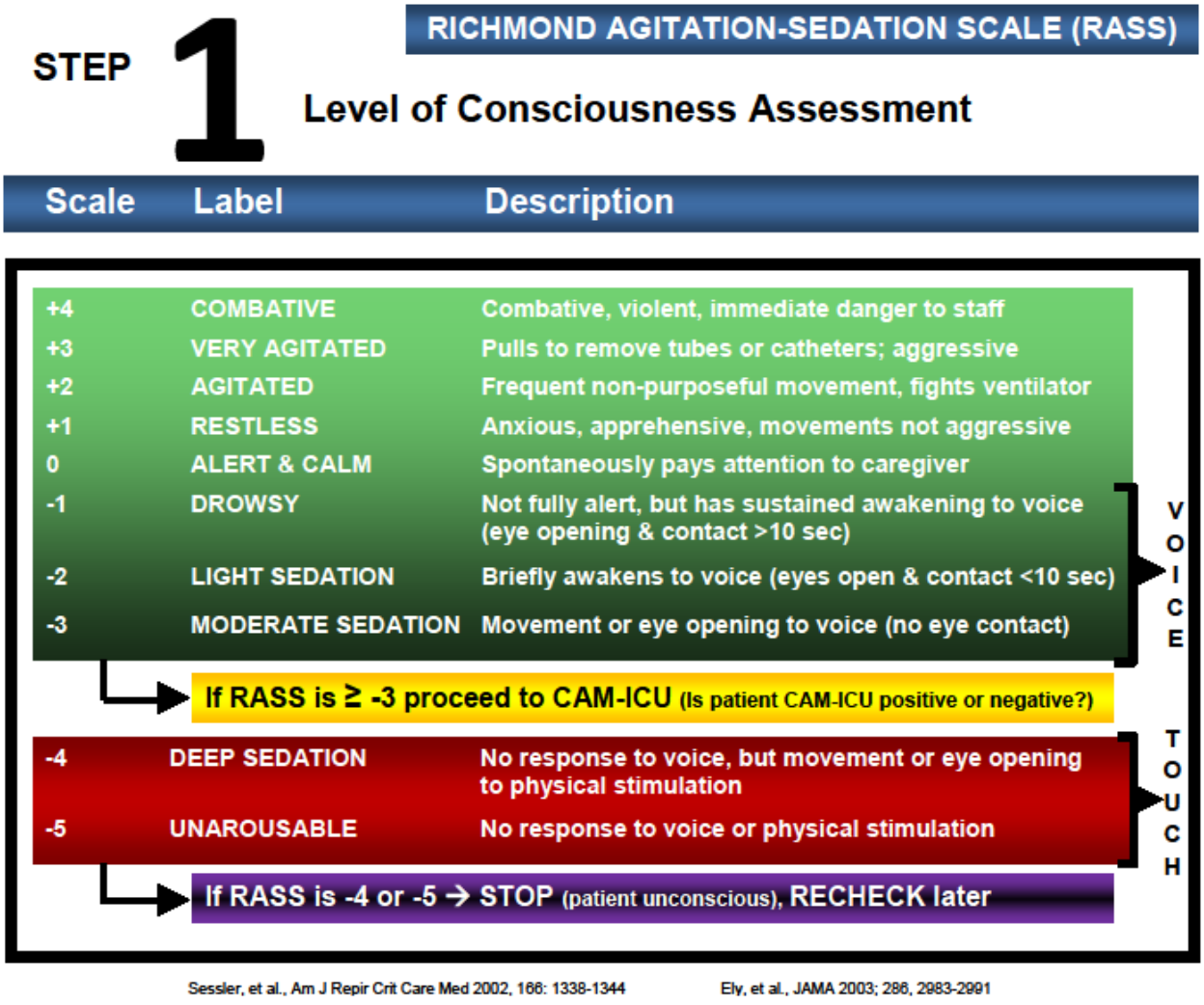
No Depression **0 1 2 3 4 5 6 7 8 9 10** Worst Possible Depression
(Depression = feeling sad)

No Anxiety **0 1 2 3 4 5 6 7 8 9 10** Worst Possible Anxiety
(Anxiety = feeling nervous)

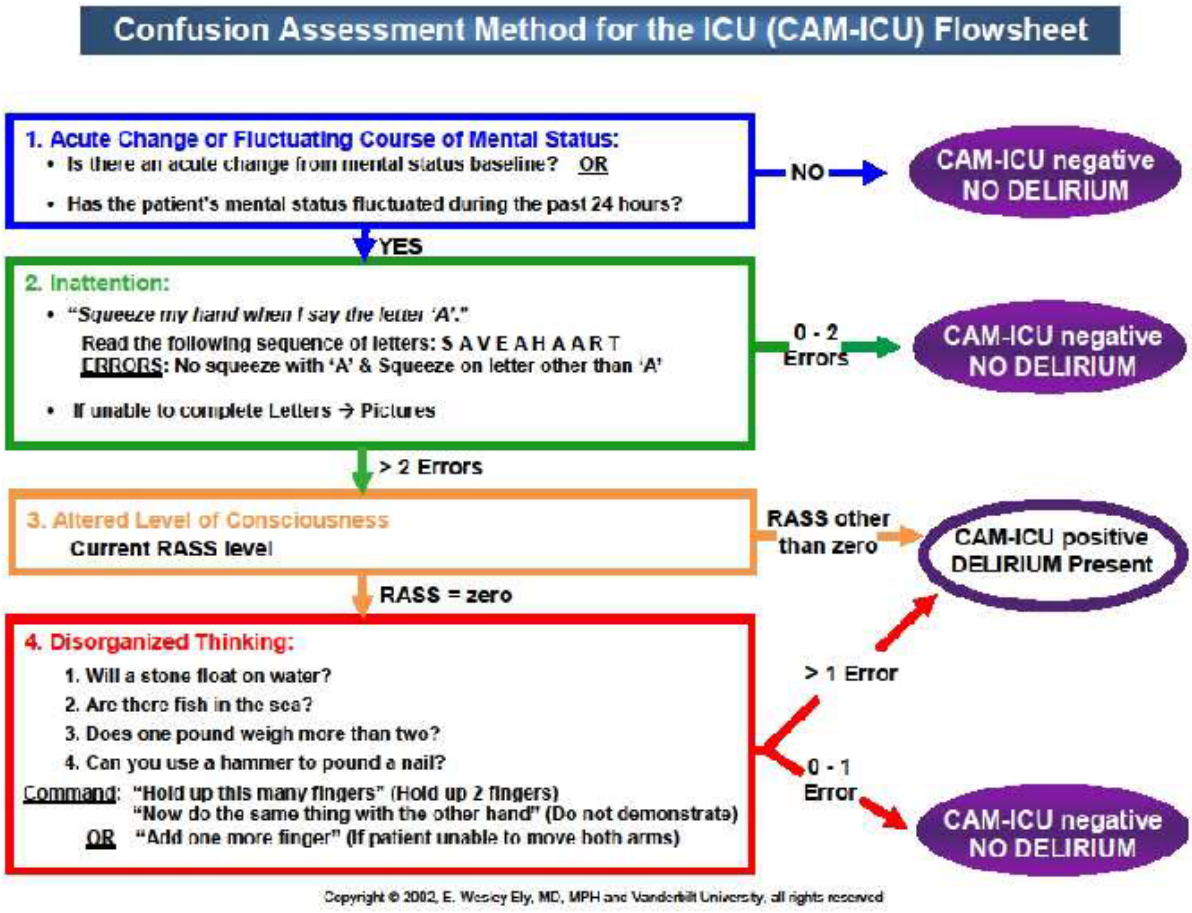
Best Wellbeing **0 1 2 3 4 5 6 7 8 9 10** Worst Possible Wellbeing
(Wellbeing = how you feel overall)

No _____ **0 1 2 3 4 5 6 7 8 9 10** Worst possible _____
Other Problem *(for example constipation)*

E. RASS Scale to Assess Sedation.-PDF file.



F. <u>CAM scale to assess for delirium if RASS score is between +4 to -3. –PDF file.</u>



G. PHQ-9 questionnaire.-PDF file.

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

H. MADRS questionnaire to be filled out based on clinical interview during the study.-PDF file

Name:_____ Date:_____

Montgomery-Asberg Depression Scale (MADRS)

Instructions: The ratings should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5). It is important to remember that it is only rare occasions that a depressed patient is encountered who cannot be rated on the items in the scale. If definite answers cannot be elicited from the patients, all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice. This scale may be used for any time interval between ratings, be it weekly or otherwise, but this must be recorded.

1. ***Apparent Sadness***
Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate on depth and inability to brighten up.
0 No sadness
1
2 Looks dispirited but does brighten up without difficulty.
3
4 Appears sad and unhappy most of the time.
5
6 Looks miserable all the time. Extremely despondent.

2. ***Reported Sadness***
Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or feeling of being beyond help without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.
0 Occasional sadness in keeping with the circumstances.
1
2 Sad or low but brightens up without difficulty.
3
4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5
6 Continuous or unvarying sadness, misery or despondency.

3. ***Inner Tension***
Representing feelings of ill-defined discomfort, edginess, inner turmoil mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.
0 Placid. Only reflecting inner tension.
1
2 Occasional feelings of edginess and ill-defined discomfort.
3
4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
5
6 Unrelenting dread or anguish. Overwhelming panic.

4. ***Reduced Sleep***
Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.
0 Sleeps as usual.
1
2 Slight difficulty dropping off to sleep or slightly reduced light or fitful sleep.
3
4 Sleep reduced or broken by at least two hours.
5
6 Less than two or three hours sleep.

5. ***Reduced Appetite***
Representing the feeling of loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.
0 Normal or increased appetite.
1
2 Slightly reduced appetite.
3
4 No appetite. Food is tasteless.
5
6 Needs persuasion to eat.

6. ***Concentration Difficulties***
Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.
0 No difficulties in concentrating.
1
2 Occasional difficulties in collecting one's thoughts.
3
4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5
6 Unable to read or converse without great initiative.

7. ***Lassitude***
Representing a difficulty getting started or slowness initiating and performing everyday activities.
0 Hardly no difficulty in getting started. No sluggishness.
1
2 Difficulties in starting activities.
3
4 Difficulties in starting simple routine activities which are carried out with effort.
5
6 Complete lassitude. Unable to do anything without help.

8. ***Inability to Feel***
Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.
0 Normal interest in the surroundings and in other people.
1
2 Reduced ability to enjoy usual interest.
3
4 Loss of interest in surroundings. Loss of feelings for friends and acquaintances.
5
6 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. ***Pessimistic Thoughts***
Representing thoughts of guilt. Inferiority, self-reproach, sinfulness, remorse and ruin.
0 No pessimistic thoughts.
1
2 Fluctuating ideas of failure, self-reproach or self-depreciation.
3
4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
5
6 Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.

10. ***Suicidal Thoughts***
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and the preparations for suicide. Suicidal attempts should not in themselves influence the rating.
0 Enjoys life or takes it as it comes.
1
2 Weary of life. Only fleeting suicidal thoughts.
3
4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5
6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Total Score:_____

I. PROMIS questionnaire.

PROMIS v.1.1 - Global

Global Health

Please respond to each item by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

 Page 1 of 2

J. **Weekly Pain Diary**

weekly pain diary

week & dates: *pain/distress as*
no pain/distress *bad as it could be*

0 1 2 3 4 5 6 7 8 9 10

Appendix II: Ketamine related information (click on files A, B, and C to open the files)

A. Test **summary sheets from** NMS **labs** where ketamine and its metabolites will be measured.

Lab testing ketamine.xps

B. Ketamine product insert. –PDF file

Ketamine Hydrochloride
Injection, USP

Ⓒ Ⅱ

Rx only

SPECIAL NOTE

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12 PERCENT OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT DREAM-LIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY IS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETAMINE.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY AND THE INCIDENCE IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

THE INCIDENCE OF PSYCHOLOGICAL MANIFESTATIONS DURING EMERGENCE, PARTICULARLY DREAM-LIKE OBSERVATIONS AND EMERGENCE DELIRIUM, MAY BE REDUCED BY USING LOWER RECOMMENDED DOSAGES OF KETAMINE IN CONJUNCTION WITH INTRAVENOUS DIAZEPAM DURING INDUCTION AND MAINTENANCE OF ANESTHESIA. (See DOSAGE AND ADMINISTRATION Section.) ALSO, THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS.

IN ORDER TO TERMINATE A SEVERE EMERGENCE REACTION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRA SHORT-ACTING BARBITURATE MAY BE REQUIRED.

WHEN KETAMINE IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

DESCRIPTION

Ketamine hydrochloride is a nonbarbiturate anesthetic chemically designated (±)-2-(*o*-Chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride. It is formulated as a slightly acid (pH 3.5 to 5.5) sterile solution for intravenous or intramuscular injection in concentrations containing the equivalent of either 50 or 100 mg ketamine base per milliliter and contains not more than 0.1 mg/mL benzethonium chloride added as a preservative. Ketamine hydrochloride has a molecular formula of $C_{13}H_{16}ClNO \cdot HCl$, a molecular weight of 274.19 and the following structural formula:

C. Ketamine 500mg/5ml multidose vial safety data sheet from manufacturer, Hospira.-PDF file.

Hospira

SAFETY DATA SHEET

Product Name: Ketamine Hydrochloride Injection

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Manufacturer Name And Address	Hospira, Inc. 275 North Field Drive Lake Forest, Illinois 60045 USA
Emergency Telephone	CHEMTREC: North America: 800-424-9300; International 1-703-527-3887; Australia - 61-290372994; UK - 44-870-8200418
Hospira, Inc., Non-Emergency	224 212-2000
Product Name	Ketamine Hydrochloride Injection
Synonyms	(±)-2-(*o*-Chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride

2. HAZARD(S) IDENTIFICATION

Emergency Overview

Ketamine Hydrochloride Injection is a solution containing ketamine hydrochloride, a rapid-acting non-barbiturate anesthetic indicated as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketamine is a general anesthetic that is a Schedule III controlled substance. In the workplace, this material should be considered potentially irritating to the eyes and respiratory tract. Based on clinical use, possible target organs include the respiratory system, cardiovascular system, and nervous system.

U.S. OSHA GHS Classification

Physical Hazards	**Hazard Class**	**Hazard Category**
	Not Classified	Not Classified

Health Hazards	**Hazard Class**	**Hazard Category**
	Eye Damage / Irritation	2A
	Skin Irritation	2
	STOT – RE	2

Label Element(s)

Pictogram

Signal Word

Warning

Hazard Statement(s)

Causes serious eye irritation
Causes skin irritation
May cause damage to organs through prolonged or repeated exposure

Precautionary Statement(s)

Prevention

Do not breathe vapor or spray
Wear eye protection/face protection
Wear protective gloves
Wash hands thoroughly after handling

Response

Get medical attention if you feel unwell.

IF ON SKIN: Wash with plenty of water. If skin irritation occurs: Get medical advice/attention. Take off contaminated clothing and wash it before reuse.

IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. If eye irritation persists, get medical attention.

D. -Cytochrome P450 3A4 and 3A5 Known Drug Interaction Chart

CYP3A4 and CYP3A5 Substrates		CYP3A4 and CYP3A5 Inhibitors
ANTIHISTAMINES	NEUROPSYCHIATRIC	STRONG INHIBITORS
astemizole	alprazolam	clarithromycin
chlorpheniramine	diazepam	indinavir
ANTIMETRIC	midazolam	itraconazole
aprepitant	triazolam	ketoconazole
ondansetron	haloperidol	nefazodone
ANESTHESIA/PAIN	aripiprazole	ritonavir
cafergot	buspirone	saquinavir
codeine-N-demethylation	carbamazepine	suboxone
fentanyl	pimozide	telithromycin
levolevomethadyl acetate (LAAM)	quetiapine	INTERMEDIATE STRENGTH INHIBITORS
lidocaine,	risperidone	aprepitant
methadone	trazodone	erythromycin
ANTIBIOTIC/ANTIVIRAL	zaleplon	fluconazole
alfentanil	ziprasidone	grapefruit juice
boceprevir	zolpidem	verapamil
clarithromycin	ONCOLOGY	diltiazem
efavirenz	docetaxel	WEAK INHIBITORS
erythromycin (not CYP3A5),	gleevec	cimetidine
indinavir	irinotecan	OTHER POSSIBLE INHIBITORS
nelfinavir	paclitaxel	amiodarone
nevirapine	romidepsin	boceprevir
quinine	sorafenib	chloramphenicol
ritonavir	sunitinib	ciprofloxacin
saquinavir	torisel	delaviridine
telaprevir	vemurafenib	diethyl-dithiocarbamate
telithromycin.	vincristine	fluvoxamine
CARDIOVASCULAR	PULMONARY	gestodene
amlodipine	salmeterol	imatinib
cilostazol	sildenafil	mibefradil
diltiazem	STEROID	mifepristone
eplerenone	dexamethasone	norfloxacin
lercanidipine	estradiol	norfluoxetine
nifedipine	hydrocortisone	starfruit
nisoldipine	progesterone	telaprevir
nitrendipine	testosterone	voriconazole
propranolol	OTHER	
quinidine (not CYP3A5)	cocaine	
verapamil	dapsone	
HMG COA REDUCTASE INHIBITORS	dextromethorphan	
atorvastatin	finasteride	
lovastatin	nateglinide	
simvastatin		
IMMUNE MODULATORS		
cyclosporine		
sirolimus		
tacrolimus		

CYP3A4 and CYP3A5 Inducers
barbiturates
carbamazepine
efavirenz
glucocorticoids
modafinil
nevirapine
oxcarbazepine
phenobarbital
phenytoin
pioglitazone
rifabutin
rifabutin
St. John's Wort
troglitazone