Document Date: 2/21/2017

NCT02735343

The CHECK Trial: A Comparison of Headache Treatment in the Emergency Department: Compazine Versus Ketamine (Check)

PROTOCOL FOR CLINICAL INVESTIGATION – NON-EXEMPT HUMAN
(Wilford Hall Ambulatory Surgical Center – WHASC)
PROTOCOL SUMMARY

1. Title:

The CHECK Trial: A Comparison of Headache Treatment in the Emergency Department: Compazine versus Ketamine. A Randomized, Double-Blind, Clinical Control Trial.
FWH20160057H

2.0. Principal Investigator (PI): **WHASC PI:**

Name	Christopher Pitotti, MD
Rank/Corps or Civilian Rating	Maj, USAF, MC
Date of IRB Approved CITI Training & Date of Good Clinical Practice Training	01/19/2016
Branch of Service	USAF
AD Mil/DoD Civilian/Ctr/Non-DoD Civ	AD Mil
Department & Base	Department of Emergency Medicine, Nellis AFB
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3.0. Research Plan:

3.1. Purpose:
This will be a prospective, double-blinded, randomized controlled trial on a convenience sample of patients presenting to the Emergency Department (ED) with a chief complaint of headache.

3.2. Hypotheses, Research Questions or Objectives:
We will determine the difference in pain scores between the compazine and Ketamine groups, as measured by a 25-mm difference between the groups mean on the visual analogue scale (VAS) at 60 min.

4. Brief Summary of the study:
We are comparing Ketamine to compazine for benign headaches in the ED. Subjects will be randomized into 1 of 2 groups. Group 1 will receive standard treatment of compazine 10 mg IV along with diphenhydramine (Benadryl) 25 mg IV. Group 2 (research arm) will receive Ketamine 0.3 mg/kg along with ondansetron (Zofran) 4 mg IV. Subjects will be seen at 15, 30, 45, and 60 minutes post-intervention to obtain Heart Rate, Blood Pressure, Headache severity, Nausea severity, Vomiting severity, Anxiety severity, and Restlessness severity. At 24-48 hours post intervention we will contact subjects and assess their pain and assess their satisfaction with their migraine pain management as part of this study. Subjects' participation will last up to 48 hours post headache. Diphenhydramine (Benadryl) and Ondansetron (Zofran) are being given in this study to manage the side effects from the comparison medications (Compazine –akathisia, ketamine –nausea). Diphenhydramine (Benadryl) itself doesn't add any benefit for migraines. [21] Ondansetron (Zofran) significantly reduces ketamine associated emesis [22]. Since nausea is common in migraines (73%) [23], and ketamine does not itself correct this it's logical and ethical to add this as an adjunct for ketamine. If we didn't add it to the regiment our satisfaction data would likely be clouded by persistent nausea. We are indeed comparing the two combinations but ondansetron (Zofran) and diphenhydramine (Benadryl) are simply adjuncts.

5. Subjects:
Male and female DoD beneficiaries aged 18-65 years who present to the Emergency Department (ED) with complaint of a headache will be recruited at the Mike O'Callaghan Federal Medical Center (MOFMC). No special populations (e.g., pregnant women, children, prisoners, detainees) will be recruited.

6. Inclusion/exclusion criteria:
Inclusion Criteria
- Age 18 to 65 years who present to the ED with complaint of a headache
- Temperature < 100.4° F
- Diastolic blood pressure < 104 mm Hg
- Normal neurologic exam and normal mental status

Exclusion Criteria
- Pregnant or breastfeeding
- Meningeal signs are present

- Acute angle closure glaucoma is suspected
- Head trauma within the previous two weeks
- Lumbar puncture within the previous two weeks
- Thunderclap (rapid) onset of the headache
- Weight more than 150 kg or less than 40 kg
- Known allergy to diphenhydramine (Benadryl)
- Known allergy to ondansetron. (Zofran)
- Known allergy to compazine
- Known allergy to Ketamine
- History of schizophrenia or bipolar disorder
- History of intracranial hypertension
- Is a prisoner
- Patient declined informed consent
- Non-English speaking patient
- Attending provider excludes patient
- Elderly patients with dementia
- Patients with severe headaches that diminish their decision making capability will not be able to participate.

7. Number of Subjects:
TOTAL NUMBER OF SUBJECTS (nation-wide/study-wide): 70

8. Use of an Investigational New Drug:
Ketamine and compazine are both drugs approved by the Food and Drug Administration. Ketamine is used as an analgesic during diagnostic and surgical procedures and compazine for the relief of nausea. In this protocol, they are both being used for a non-FDA approved indication (headache). Ketamine is frequently used for analgesia in the low doses described in this protocol. We are not intending to change marketing, FDA approved indications, or change dosing requirements. Compazine has been studied in multiple cases for migraine though is not specifically labeled for analgesia or migraine treatment, but is for nausea (an often experienced component of migraine).

9. Use of an Investigational Device: N/A

10. Use of a Placebo: N/A

PROTOCOL FOR CLINICAL INVESTIGATION – NON-EXEMPT HUMAN
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1. Title:

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2.0. Principal Investigator (PI): **WHASC PI:**

Name	Christopher Pitotti, MD
Rank/Corps or Civilian Rating	Maj, USAF, MC
Date of IRB Approved CITI Training & Date of Good Clinical Practice Training	01/19/2016
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Phone & Pager #	(702) 653-3298
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2.1. Associate Investigators (AI):

Name	AD/DoD Civ/Ctr/ Non-DoD Civ	Rank/Corps or Civilian Rating/Title	Date of CITI Training	Phone & Pager #
Joseph Sontgerath, MD	AD	Capt, USAF, MC	01/11/2016	(702) 653-3298
Lisa Mannina, MD	AD	Capt, USAF, MC	11/09/2016	(702) 653-3298

2.2. Research Assistants (RA) & Coordinators (RC):

Name	AD/DoD Civ/Ctr/ Non-DoD Civ	Rank/Corps or Civilian Rating/Title	Date of CITI Training	Phone & Pager #
Jill Clark, MBA/HCM	Ctr	Senior Research Associate/Clinical Research Manager	03/19/2014	(702) 653-3298
Tracy Bogdanovich, CCRC	Ctr	Clinical Research Coordinator	03/31/2014	(702) 653-2088
Lisa Stammers, RN, BSN	DoD Civ	DME Nurse	06/17/2014	(702) 653-3239
Daniel Shaffer, BSBA	Ctr	Clinical Research Coordinator	06/29/2015	(702) 653-2067
Heather Rider, B.S.	Ctr	Clinical Research Coordinator	07/15/2015	(702) 653-2521
Jennie Moss, RN, M.S.	CTR	Senior Research Associate	09/01/2015	(702) 653-3644
Amanda Crawford, B.A.	CTR	Clinical Research Coordinator	09/27/2016	(702) 653-2113

2.3. The research relevance of this protocol focuses on: [x] Treatment

2.4. Location(s):

a. Collaborating Facilities: N/A

b. Air Force Sites seeking Regional IRB: Mike O'Callaghan Federal Medical Center, Jill Clark, (702) 653-3298

c. List study sponsors: N/A

3. Research Plan:

3.1. Purpose:

This will be a prospective, double-blinded, randomized controlled trial on a convenience sample of patients presenting to the Emergency Department (ED) with a chief complaint of headache.

3.2. Hypotheses, Research Questions or Objectives:

We will determine the difference in pain scores between the compazine and Ketamine groups, as measured by a 25-mm difference between the groups mean on the visual analogue scale (VAS) at 60 min.

3.3. Significance:
Approximately 2.8% of ED visits are related to headache with a large percentage due to migraines making this diagnosis and its management a daily challenge for EM physicians [1]. The range of medications used to treat migraines has expanded without a clear first line therapy and each class has its own limitations not limited to medication interactions, cardiac effects, and short administration windows. Finding a safe and effective alternative to standard therapy could potentially save costs, reduce repeat visits, and more importantly alleviate this common and painful condition.

3.4. Military Relevance:
Military Treatment Facilities often treat this condition. Low Dose Ketamine (LDK) has been extensively studied for battlefield analgesia and thus is often available to the downrange provider whereas phenothiazines such as compazine or alternative migraine treatments may not be. There is the potential for returning patients to function earlier, improving readiness and reducing the reliance on quarters for this condition's management.

3.5. Background and Review of Literature:
In the emergency department (ED), one of the most common chief complaints is headache [1]. A number of prior studies have demonstrated the efficacy of a variety of medications for migraines and other benign headaches [2]. Some of the options for treating these types of headaches include dopamine antagonists, opioids, non-steroid anti-inflammatory drugs (NSAIDs), triptans, anti-epileptics, and ergot derivatives [2]. Amongst the available options, dopamine antagonists appear to be the most effective, with multiple studies demonstrating their superiority over opioids [3], NSAIDs [4], triptans [5], and anti-epileptics [6]. The dopamine antagonist that we use most frequently, and the one that has the most evidence to support its use for benign headaches, is compazine [5,6,7,8,9,10]. Although some data suggest that droperidol may be even more effective than compazine [11], the current national shortage limits its use.

Despite the general effectiveness of dopamine antagonists and the variety of options for benign headache treatment, many patients who present to the ED still have headaches 24 hours after treatment. In one study by Friedman, 31% of patients still had moderate to severe headaches 24 hours after discharge [12]. Often we resort to opiates in refractory headaches despite evidence to suggest that opiates increase both length of stay and bounce backs [13].

Ketamine is an N-Methyl-D-aspartate (NMDA) receptor antagonist that has both analgesic and dissociative properties [14]. Previous studies have demonstrated the effectiveness of Ketamine for post-operative pain [15,16], pain in burn patients [17], and chronic pain [18]. New studies have also shown Ketamine to be useful for acute pain in the ED by both the intranasal [19] and intravenous routes [20]. To our knowledge, there are no prospective studies that evaluate the effectiveness of Ketamine for the treatment of benign headaches in the ED.

Diphenhydramine (Benadryl) and Ondansetron are being given in this study to manage the side effects from the comparison medications (Compazine –akathisia, ketamine –nausea). Diphenhydramine (Benadryl) itself doesn't add any benefit for migraines. [21] Ondansetron (Zofran) significantly reduces ketamine associated emesis [22]. Since nausea is common in migraines (73%) [23], and ketamine does not itself correct this it's logical and ethical to add this as an adjunct for ketamine. If we didn't add it to the regiment our satisfaction data would likely be clouded by persistent nausea. We are indeed comparing the two combinations but ondansetron (Zofran) and diphenhydramine (Benadryl) are simply adjuncts.

3.5.1. Bibliography:

1. Pitts SR, Niska RW, Xu J, Burt CW. National Hospital Ambulatory Medical Care Survey: 2006 emergency department summary. National health statistics reports; no 7. Hyattsville, MD: National Center for Health Statistics. 2008.

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emergency department: a randomized controlled trial. J Emerg Med. 2008 Oct: 35(3):247-53.
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3.6. Research Design and Methods:

Male and female DoD beneficiaries aged 18-65 years who present to the ED with complaint of a headache will be offered an opportunity to participate in the study at the Mike O'Callaghan Federal Medical Center (MOFMC). Research subjects will be recruited when both research staff and a trained Pharmacist attached to this study are available. The PI or AI will not recruit their own patients to prevent any misconception of coercion or undue influence.

Screening Visit:

- Obtain signed Informed Consent Document and HIPAA Authorization (research-driven).
- Record: Date of birth, age, phone number, gender, race, ethnicity, social security number, name of standard of care rescue medications (over-the-counter and prescription), current email address (to be used for scheduling only), height (in inches), weight (in pounds), history of traumatic brain injury, concussion, or any mild to severe head trauma, medication use. (research only)
- Review past medical history in Armed Forces Health Longitudinal Technology Application (AHLTA) or ESSENTRIS to verify the inclusion/exclusion criteria.
- Women of childbearing potential will have a serum pregnancy test (5-10 milliliters, approximately 1-2 teaspoons of blood) or urine pregnancy test (10 drops or less than 1 milliliter of urine) (research-driven).

Visit 1:

- Heart rate
- Blood pressure
- Headache severity via 100-mm VAS.
- Nausea severity via 100-mm VAS.
- Vomiting severity via 100-mm VAS.
- Anxiety severity via 100-mm VAS.
- Restlessness severity via 100-mm VAS.
- Record type and amount of rescue medications (over-the-counter and prescription) use in the past 7 days. (research only)
- Subjects will be randomized by the pharmacy. We will use a random-number generator and use blocking to ensure roughly equal sample sizes. Both subjects and investigators will be blinded to the study group assignments. Subjects will be randomized by the pharmacy into one of two groups (research-driven):
    - Group 1: Standard treatment arm (compazine 10 mg IV along with diphenhydramine(Benadryl) 25 mg IV)
    - Group 2: Research arm (Ketamine 0.3 mg/kg along with ondansetron (Zofran) 4 mg IV)

15 minutes post treatment:

- Heart rate
- Blood pressure
- Headache severity via 100-mm VAS.
- Nausea severity via 100-mm VAS.
- Vomiting severity via 100-mm VAS.
- Anxiety severity via 100-mm VAS.

- Restlessness severity via 100-mm VAS.

30 minutes post treatment:
- Heart rate
- Blood pressure
- Headache severity via 100-mm VAS.
- Nausea severity via 100-mm VAS.
- Vomiting severity via 100-mm VAS.
- Anxiety severity via 100-mm VAS.
- Restlessness severity via 100-mm VAS.

45 minutes post treatment:
- Heart rate
- Blood pressure
- Headache severity via 100-mm VAS.
- Nausea severity via 100-mm VAS.
- Vomiting severity via 100-mm VAS.
- Anxiety severity via 100-mm VAS.
- Restlessness severity via 100-mm VAS.

60 minutes post treatment:
- Heart rate
- Blood pressure
- Headache severity via 100-mm VAS.
- Nausea severity via 100-mm VAS.
- Vomiting severity via 100-mm VAS.
- Anxiety severity via 100-mm VAS.
- Restlessness severity via 100-mm VAS.

24-48 hours post treatment:
- Subjects will be contacted either in-person or via phone and the following information will be collected:
  - Subjects will be asked "On a scale of 0-10, with 10 being the worst pain, what is your current level of pain?"
  - Subjects will be asked "On a scale of 0 to 10, how satisfied were you with your migraine pain management as part of this research study? (dissatisfied 0 – 10 very satisfied)
- Subjects will be alerted to what group they were randomized into.

Dose Administration: The diphenhydramine (Benadryl) or ondansetron (Zofran) will be administered first, and immediately afterward the compazine or Ketamine will be administered. For prevention/treatment of akisthesia from Compazine, diphenhydramine (Benadryl) is standard of care. For treatment of nausea, ketamine or otherwise ondansetron (Zofran) is a standard of care drug, other medications are often used with equivalent effectiveness but overlap class with the study drug Compazine in their use for migraines so would interfere with interpreting results. Ondansetron (Zofran) is not commonly used as an abortive for migraines. The compazine or Ketamine will be diluted in saline so that the total volume is 3 mL, and will be administered over 2 minutes. The diphenhydramine (Benadryl) will be diluted in saline so that it is 2 mL (the same volume as the ondansetron (Zofran)). Both groups will also receive a 500 mL normal saline bolus after the study medications are administered. The hospital pharmacist will be responsible for preparing the medications, using a double-blind protocol, and record which arm the patient was randomized to. Only the pharmacist and the Research Coordinator will have access to the randomization records and will not reveal the randomization until the end of the study. Emergency providers will be instructed not to administer any rescue medications for at least 30 minutes. The electronic medical record order will read "randomized study medication" (for the

Ketamine or compazine) and "randomized add-on medication" (for the ondansetron (Zofran) or diphenhydramine (Benadryl)). It is common practice to use the combination of compazine and diphenhydramine (Benadryl) or ketamine and ondansetron (Zofran). If the patient receives a rescue medication, he or she will definitely NOT be withdrawn from the study. The need for rescue medication is a secondary outcome of the study. We will still analyze groups based upon their original randomization and the intention to treat principle. Rescue medications do not bias the study results, and they have been part of every headache treatment study I have ever read. The data from the first 30-minutes will be maintained as research data, and this is important data for the study.

Safety: After 30 minutes, the treating provider will be permitted to administer any medication they would like for further treatment. Only if there is an untoward event that requires the treating provider to know which medication was administered will the pharmacist unblind the randomization for that individual patient.

3.6.1. Interventions, Observations, or Data Sought:
The primary outcome measure will be the difference in pain scores between the compazine and Ketamine groups, measured as the absolute difference between the means at 60 min. Secondarily, we will measure the difference between the rates of decline in pain scores, rate of admission, nausea scores, rate of vomiting, rate of development of akathisia, heart rate and blood pressure changes, headache resolution with telephone follow up, and patient satisfaction.

3.6.2. Data Collection and Processing:
Data will be collected and recorded in a spreadsheet. At the conclusion of the study, all personally identifying information will be removed prior to analysis. De-identified data will be shared with research staff at University Medical Center of Southern Nevada at the conclusion of the study. A Cooperative Research and Development Agreement (CRADA) for the data sharing is pending.

3.6.3. Setting:
Male and female DoD beneficiaries aged 18-65 years will be recruited at the Mike O'Callaghan Federal Medical Center (MOFMC). No special populations (e.g., pregnant women, children, military basic trainees, prisoners, detainees) will be recruited.

3.6.4. Date(s):
April 2016-April 2019

3.6.5. Source of Research Material:

Source of Research Material per Participant (Procedures)	# Routine Care	# Research Driven	# Total Procedures
Medical Record Review	0	1	1
Serum or urine pregnancy test	0	1	1
Heart rate	0	5	5
Blood pressure	0	5	5
Headache severity via 100-mm VAS	0	5	5
Nausea severity via 100-mm VAS	0	5	5
Vomiting severity via 100-mm VAS	0	5	5
Anxiety severity via 100-mm VAS	0	5	5
Restlessness severity via 100-mm VAS	0	5	5

3.6.6. Subjects:
Male and female DoD beneficiaries aged 18-65 years who present to the ED with complaint of a headache will be recruited at the Mike O'Callaghan Federal Medical Center (MOFMC). No special populations (e.g., pregnant women, children, prisoners, detainees) will be recruited.

3.6.7. Inclusion/Exclusion Criteria:

Inclusion Criteria

- Age 18 to 65 years who present to the ED with complaint of a headache
- Temperature < 100.4° F
- Diastolic blood pressure < 104 mm Hg
- Normal neurologic exam and normal mental status

Exclusion Criteria

- Pregnant or breastfeeding
- Meningeal signs are present
- Acute angle closure glaucoma is suspected
- Head trauma within the previous two weeks
- Lumbar puncture within the previous two weeks
- Thunderclap (rapid) onset of the headache
- Weight more than 150 kg or less than 40 kg
- Known allergy to diphenhydramine (Benadryl)
- Known allergy to ondansetron. (Zofran)
- Known allergy to compazine
- Known allergy to Ketamine
- History of schizophrenia or bipolar disorder
- History of intracranial hypertension
- Is a prisoner
- Patient declined informed consent
- Non-English speaking patient
- Attending provider excludes patient
- Elderly patients with dementia
- Patients with severe headaches that diminish their decision making capability will not be able to participate.

3.6.8. Instrumentation: N/A

4.0. Human Subject Protection:

4.1. Recruitment:

All potentially eligible patients, presenting to the ED with a chief complaint of headache, will be offered an opportunity to participate. Some patients may be patients of the PI or AI, however, they will have the study staff recruit their patients to prevent any misconception of coercion or undue influence. When a potential subject is identified by the treating physician, the Research Staff will be contacted to speak with the patient directly. Research subjects will be recruited when both research staff and a trained Pharmacist attached to this study are available. Research subjects will be offered the opportunity to participate when they present to the Emergency Department either when they check-in, are waiting in the waiting area, or being triaged by Emergency Department personnel. Emergency Department staff will ask the patient if they are willing to speak with the research staff and, if they agree, then the research staff will be contacted to come discuss the study with the potential participant. An advertisement will be placed in the Emergency Department.

4.2. Consent Processes:

Informed Consent and HIPAA authorization will be sought in advance of any study-related procedures from each prospective subject and appropriately documented in accordance with 32 CFR 219.117. Potential candidates will be notified about the study either through posted advertisements or by their care provider and will be given the opportunity to consent by one of the referred study coordinators. The study coordinator will provide a written copy of the Informed Consent Document (ICD). The subject may decline to consent without prejudice. At the subjects' discretion, they may take the ICD home to discuss further prior to making a decision

and if they decide they are interested in participating, they can contact the research department the next time they present to the Emergency Department with a headache. If the subject consents, a copy of the ICD will be given to the subject. No vulnerable populations are included in this research study. Subjects who cannot provide Informed Consent will not be allowed to participate. No Legally Authorized Representatives (LAR) will be utilized. Patients who experience severe headaches that are unable to provide informed consent will not be able to participate.

4.3 Participation Compensation:
Subjects will not be paid for participation in this study.

4.4. Assent Process: N/A

4.5. Benefits:
There may be no direct benefits to the subjects for participating in this study. Personal benefits include intended reduction in headache symptoms and the satisfaction that the patient may be assisting investigators in determining a more effective headache treatment.

4.6. Risks: There is a risk of inadvertent breach of confidentiality. The potential risks to participate in this study are minimal and include:

DRUG NAME	**LIKELY *and not serious***	**LESS LIKELY *and not serious***	**RARE and serious**
COMPAZINE (PROCHLORPERAZINE)	Drowsiness	Blurred vision Xerostomia (dry mouth) Congestion Nausea Akasthisia (restlessness) Tardive dyskinesia (involuntary movements) Electrocardiogram (ECG) changes Tachycardia (rapid heartbeat) Constipation Urinary retention Allergic reaction	Neuroleptic Malignant Syndrome (NMS) Blood dyscrasia (disease) Hypotension (low blood pressure)
KETAMINE	Drowsiness	Sialorrhea (excessive drooling) Nausea/vomiting Elevation in blood pressure or heart rate Nystagmus/diplopia (uncontrolled eye movements) Fasciculations (muscle twitch) Hallucinations Bradycardia (slow heart rate) Hypotension (Low blood pressure) Arrythmias (abnormal heart rhythm) Respiratory depression Cystitis (bladder inflammation) Pain at injection site	None
ONDANSETRON (ZOFRAN)	None	Headache Constipation Diarrhea	Serotonin syndrome Torsade de pointes

		Dizziness Drowsiness Fatigue Weakness QT interval prolongation Abdominal pain Dry mouth Elevated liver enzymes	Stevens-Johnson Syndrome Toxic Epidermal Necrolysis Hypersensitivity ECG changes
DIPHENHYDRAMINE (BENADRYL)	Drowsiness Dry mouth	Dizziness Headache Blurred vision Tinnitus Hypotension Palpitations Anorexia Dry mouth Constipation Nausea Dysuria (Painful or difficult urination) Urinary retention or increase in frequency	None

4.7. Costs: N/A

4.8. Safeguards for Protecting Information:
The research consents will be stored in a locked cabinet in a locked room. Medical records will be annotated with ICD-10 code Z00.6 to reflect the subject's participation in a research study. All research data including patient demographics will be kept in an electronic database, which will be encrypted, double password protected and the access will be restricted. The research data will be coded and any links to identifiable data will be destroyed as soon as the Final Report Approval has been obtained from the IRB. Only the pharmacist and the Research Coordinator will have access to the randomization records and will not reveal the randomization until the end of the study or in the event of a research related adverse event. The anonymized research data will not be utilized for further research activity beyond the protocol stipulations without additional IRB approval. De-identified data will be shared with research staff at the University Medical Center of Southern Nevada at the conclusion of the study. A Cooperative Research and Development Agreement (CRADA) for the data sharing is pending.

4.9. Safeguards for Protecting Subjects:
The principal investigator will be responsible for the protocol safety monitoring. The PI will make study documents (*e.g.*, consent forms, data pulls) and pertinent hospital or clinical records readily available for inspection by the local IRB and oversight staff for confirmation of the study data.

4.9.1. Minimizing Risks:
Subjects will have access to study personnel should they have any issues. If there are any issues, they will be immediately reported to one of the Investigators and an applicable medical evaluation will be initiated.

4.9.2. Vulnerable Populations: N/A

4.9.3. Clinical Care:

All subjects will receive standard of care regardless of inclusion into this study. If at any time a subject experiences any injury or adverse effects, appropriate clinical care will be given or subject will be referred to appropriate provider.

4.9.4. Injury Compensation: N/A

4.9.5. Data Safety Monitoring:
The principal investigator will be responsible for the protocol safety monitoring. The PI will make study documents (*e.g.*, consent forms, data pulls) and pertinent hospital or clinical records readily available for inspection by the local IRB and over sight staff for confirmation of the study data.

5.0. Alternatives:
The alternative is to receive standard of care and not to participate in this study.

6.0. Data Analysis:
A couple prior studies have used a 25-mm difference in mean VAS score reduction between groups to show a clinical benefit [6,9]. We define adequate pain relief as an absolute decrease in the mean VAS score of 25 mm [24, 25, 26, 27].

6.1. Outcome Measures:
The primary outcome measure will be the difference in pain scores between the compazine and Ketamine groups, measured as the absolute difference between the means at 60 min. Secondarily, we will measure the difference between the rates of decline in pain scores, rate of admission, nausea scores, rate of vomiting, rate of development of akathisia, heart rate and blood pressure changes, headache resolution with telephone follow up, and patient satisfaction.

6.2. Sample size estimation/power analysis:
Thirty-two patients will be needed in each group to find a 25-mm difference between the group means on the VAS at 60 min, with a power of 0.80 and an alpha of 0.05. We will aim for 35 patients per group to account for about a 10% dropout rate

6.3. Statistical Analysis:
The groups will be compared using a **t** -test on gender, race, and age; and a χ^2 test with Yates correction on severity of presenting headache, to determine if they are similar. The individual VAS measurements will be compared using a repeated measures analysis of variance (ANOVA) test.

6.4 Number of Subjects:

Number of subjects planned for MOFMC	Enrolled in Study	70	to result in	64	completing the study.

TOTAL NUMBER OF SUBJECTS (nation-wide/study-wide): 70

7. Duration of Study: Approximate duration of the study: 3 year
8. Local and External Support Services: Pharmacy Letter of Support
9. Intramural (GME) and Extramural Funding Support: None
10. Conflict of Interest: None

11. Use of an Investigational New Drug, use of a Drug for a non-FDA approved purpose, use of an investigative device or use of a placebo:
This research uses an Investigational New Drug
[ ] YES **[x] NO**
This research uses a FDA approved drug for a non-FDA approved purpose
[x] YES **[ ] NO**

This research uses an Investigational Device

[ ] YES **[x] NO**

This research uses a placebo.

[ ] YES **[x] NO**

12. Medical Research Area for the Study: (Pick as many as appropriate)

[] Analytical Chemistry	[] Anatomy	[] Anesthesiology	[] Biochemistry
[] Cardiovascular Surgery	[] Cardiology	[] Cell Biology	[] Dentistry
[] Dermatology	[] Dietetics	[] Electrophysiology	[] Endocrinology
[x] Emergency medicine	[] Gastroenterology	[] General Surgery	[] Hematology
[] Histology	[] Immunology/Allergy	[] Infectious Disease	[] Microbiology
[] Molecular Biology	[] Neonatology	[x] Neurology	[] Neurosurgery
[] Nursing	[] OB/GYN	[] Occupational Medicine	[] Occupational Therapy
[] Oncology	[] Ophthalmology	[] Oral/Maxillofacial Surgery	[] Orthopedics
[] Pathology	[] Pediatrics	[] Pharmacology	[] Physical Therapy
[] Mental Health	[] Radiology/Imaging	[] Urology	[] Wellness
[] Other (state):			

13. Attachments:

1. Form A-Signature Sheet
2. Form A2-Study Personnel
3. Advertisement
4. Certificate of Compliance
5. Informed Consent Document
6. HIPAA Authorization Document
7. Form O: Use of a Drug in Research
8. Pharmacy Support Letter