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Official Title: Benzodiazepines for the Reduction of Distress and Pain During and After Emergency Department Care

ClinicalTrials.gov ID: NCT03756038

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IRB Approval: This study had IRB approval through 11/13/2019 but was terminated on 10/08/2019.

Provide a detailed description of all research activities (e.g., all drugs or devices; psychosocial interventions or measures) that will be performed for the purpose of this research study.

Post-Consent: Study drug: After consent, a study drug order will be placed by a physician which will alert the hospital pharmacy of an enrolled participant. The pharmacy will then randomize the patient to either oral lorazepam (1mg) vs. oral placebo group.

A member of the research team will pick up the study drug at the pharmacy, and bring it to a member of the treating team to administer. The IDS and inpatient pharmacists will remain un-blinded; The RA and emergency care providers will be blinded. After drug administration, the treating team is free to administer open-label drugs at their discretion, but strongly discouraged from administering additional doses of the study agent.

Study Assessments: All study assessments will occur in the patients' private treatment room in the ED. If the patient does not have a private treatment room (e.g., hallway), they will not be eligible to participate.

Subjects will not be required to stay but may be asked if they are willing, if period of time is brief compared to 2-hour limit. Otherwise, assessments will be skipped.

Should participants choose to leave the ED prior to 2 hours, there are no major safety concerns from this low dose of lorazepam.

1) Assessments obtained after consent and before study drug.

- Cover sheet (contact information): with their contact information including their cell phone number and (2) another contact sheet of 1 or 2 friends or family members who will be contacted in the event that the research staff is unable to reach the patient. Obtaining family or friend contact information is recommended for maximizing follow-up retention rates in longitudinal trauma studies
- Pain location: 20-items from a modified Regional Pain Scale
- Expected analgesic response: "How much pain relief do you expect to get from the dose of pain medicine you get here? 0 = none; 10 = complete relief."
- Pain-related items (repeated serially):
    - Pain intensity (using the Numeric Rating Scale (NRS) 1-10; 3 questions for pain right now, worst pain in the past 24 hours, and average pain in the past 24 hours)
    - 1 pain tolerability item
    - Negative affect symptoms (Positive and Negative Affect Scale; PANAS); Instructions for the PANAS indicate to endorse "to what extent you feel this way right now, that is, at the present moment."
    - Quantitative Sensory Testing (QST; repeated serially as well): QST involves reported sensation of two fixed pressures (25 N/cm2 and 50 N/cm2) per time point.

2) Assessments obtained after study drug before discharge.

- At 1- and 2-hour post-drug administration, we will assess the effectiveness of the study drug by asking the patient if they want any further treatment for their pain and questions regarding their satisfaction with treatment

- Baseline measures: Prior to discharge, participants will complete secure web-based self-report surveys on a tablet (Research Electronic Data Capture, REDCap). Their email address will be associated with this data for follow-up assessments.
    - Demographic questions include: education, income, occupation, marital status, housing stability, insurance status, and history of mental health.
    - The surveys will include:
        - Distress Intolerance Index
        - Discomfort Intolerance Scale
        - Anxiety Sensitivity Index
        - Pain Catastrophizing Scale
        - Patient Health Questionnaire -8 (PHQ8)
        - Generalized Anxiety Disorder-7 (GAD-7)
        - Prior history of traumatic events via the Posttraumatic Diagnostic Scale Trauma Screen
        - 8-item PTSD Checklist- Short Version for past traumatic events
        - Medical history checklist
        - Multidimensional Scale of Perceived Social Support
        - perceived injustice from the injury("I am suffering because of someone else's negligence")
        - Pre-injury pain interference will also be assessed with the PROMIS pain interference items.

These assessments require approximately 10-15 minutes to complete; however, participants will be given additional time if necessary as delays may be incurred due to their injuries and/or treatments in the ED.

3) Assessments obtained serially, both before and after study drug

- At baseline, and 1-and 2-hours post-study drug, we will repeat:
- The NRS for pain-related items
- Negative affect symptoms from the Positive and Negative Affect Scale (PANAS)
- QST

4) Post- ED Discharge: Upon discharge, we will measure outcomes with daily text messaging, and a follow-up survey administered at 2-weeks post-injury (similar to the baseline self-report survey).

Text messaging protocol: In regards to the text messaging, the investigator or trained member of the research team will explain the texting protocol. Participants will receive 6 message questions per day for a total of 14 days), with the first message being sent at 6pm on the day following enrollment. Participants will receive one message at a time and will receive the next message after providing a response to the previous message. It will be made clear that participation may include up to receipt of 84 text messages over a 14 day period, and that these messages will require brief SMS responses. Participants will be told that they are able to respond with "STOP" at any point if they no longer wish to receive the text-messages. All participants will be advised to set up password protection on their cell phones and to erase messages after responding to minimize the chance of loss of private information. Content of all text messages has been uploaded in the attachment section.

• All text messages will be sent automatically from a secure UPMC server housed in the WPIC Office of Academic Computing. The messages are structured on an automatic contingency schedule wherein message 2 is contingent upon a response to message 1; message 3 is contingent upon response to message 2, and so on. The first text message will be sent at 6pm on the 1st day following ED discharge

(Day 1), and will continue at 6pm until Day 14. The response period for each day will be open from 6pm-12am.

• All message responses will be stored within a secure database to which only investigators will have access. The SMS system is designed to accept responses within an expected numeric range.

Medical Record Review. We will review patients' medical records to determine: mechanism of injury (e.g., fall, motor vehicle accident, assault, general accident, etc.), pain type and location (musculoskeletal; visceral, body regions, etc.); medications administered throughout the ED stay; cause of pain; prior medical and mental health history. We will also record treatments administered before and after the study drug.

Note: The contact sheet and demographics sheet will be linked to the data provided by participants with a unique research code number. The PI will retain the link between the assigned research code number and the participant's identity, and store this link separately from the signed consent form, and separately from the coded research data. We will also need to collect the participants' social security number in order to issue them their study reimbursement through the University of Pittsburgh Vincent payment system.

Follow-up surveys: In addition to the 14 days of text messages (6 messages per day), Participants will complete 1 follow-up survey at 15 days post-ED discharge. We will text and/or email participants a link to completed each survey through the secured University of Pittsburgh RedCap survey form. Participants will receive a single text message stating, "It's time to complete your follow-up survey. Log in to www.RedCapStudySurvey.pitt.edu". This must be completed within 1 day of this message to receive payment." Wherein 'www.RedCapStudySurvey.pitt.edu' will be a link to the RedCap Survey. We will also email participants a link to complete each survey through the secured University of Pittsburgh RedCap survey form. Participants will receive an email and or/ text message stating that it's time to complete their follow-up survey. Log in to www.RedCapStudySurvey.pitt.edu for details. Participants will provide their unique study ID to begin the survey.

The 2-week follow-up survey will contain the following information: participants will complete the PHQ8 and the GAD 7 for depression and anxiety, respectively, the 20-item Posttraumatic Checklist (for PTSD symptoms), the PROMIS pain intensity and interference scale, and information about pain location. Participants will also complete assessments regarding psychological factors associated with pain (e.g., catastrophizing, and perceptions of interpersonal functioning and social support from friends, family, and a significant other with the 12-item Multidimensional Scale of Perceived Social Support, and The 12-item Injustice Experiences Questionnaire will assess perceived injustice from the injury.

Statistical Analysis Plan:

All data analysis will be performed using SPSS v.23 or STATA. We will test for possible univariate associations of baseline characteristics with group assignment using chi square analyses for categorical variables, and one-way ANOVAs for continuous variables. If significant differences between groups are noted, these variables will be used as covariates. Chi-square analyses will also analyze whether differential dropout occurred between the groups across time.

Note: All data collection will include measures of and the statistical analysis will account for crossover in the study follow-up period (e.g., per protocol analysis and intent to treat analysis).

Aim 1. To determine if lorazepam reduces the primary outcomes of pain severity and negative affect (linear; change being normally distributed) in the ED to a greater extent than placebo, we will perform linear regressions with treatment group as the predictor. The primary endpoint is 1-hour post-study drug administration. We will explore patient-level predictors of response to Ativan, including demographic (e.g., age, gender), baseline factors (e.g., depressive symptoms, pain type and location) and vulnerability factors (e.g., anxiety sensitivity; history of mental health disorders). Specifically, an interaction will be created and tested between the predictor and modifier within the regression framework. Significant interaction effects will be examined by plotting simple regression slopes at the mean, and 1 standard deviation above and below the mean of the moderator variable.

Aim 2. To evaluate whether lorazepam reduces distress, anxiety, pain severity and opioid use after ED-discharge, we will fit a repeated-measures multilevel mixed-effects regression model with the following predictors: fixed-effects for observation time and person level variables, and their interactions, a random main effect for subject, a random two-way interaction between subject and observation time, and covariate effects. Time predictors will include a linear effect to test for time-related changes in the likelihood of distress, pain and opioid use outcomes. If substantial drop-out occurs, the conservative intent-to-treat method of last observation carried forward will be applied.

We will report the frequency of side effects from the lorazepam vs. placebo in the ED.