Introduction

44 million annual patient visits to US emergency departments (EDs) are caused by pain (Pletcher 2008; Nawar 2007). Oligoanalgesia, or the inadequate treatment of pain, has been a vexing problem in emergency departments (Wilson 1989, Rupp 2004, Ritsema 2007, Stalnikowicz 2005). Only 50% of ED patients experience at least a 2-point reduction of pain on a 0 to 10 scale and 75% are discharged with moderate to severe pain (Todd, 2007). Elderly patients are at even greater risk for undertreatment of pain. They are less likely to receive pain medication and experience longer delays to treatment.

Intravenous opioids are used commonly to treat acute pain in US emergency departments. These medications are highly efficacious and safe when used in a monitored setting such as the ED. Use of opioids has fallen out of favor recently because of a spike in opioid-related overdose deaths throughout the US. While use of opioids in the ED is unlikely to contribute to outpatient opioid deaths, minimizing the use of opioids in the ED will contribute to an opioid free culture, in which opioids are used only when absolutely necessary. Thus, highly efficacious, non-opioid treatments are needed.

Acetaminophen has long been a mainstay for pain treatment. The intravenous (IV) form has been widely used in Europe for more than 20 years and received full FDA approval in the USA in 2010. As part of a continuing set of studies whose goal is to optimize treatment of pain among elderly ED patients, we will conduct a randomized study in which we compare efficacy and safety of IV acetaminophen to IV hydromorphone.

Primary null hypothesis: IV hydromorphone 0.5 mg IV will provide no more pain relief than 1000 mg IV acetaminophen among elderly patients with acute severe pain as determined by improvement in 0-10 pain scores between baseline and 60 minutes post administration of investigational medication.

Background data.

Efficacy of IV hydromorphone in the elderly.
In a randomized study conducted at this institution, 93 elderly ED patients (mean age 74) with acute pain received 0.0075mg/kg IV hydromorphone. (Chang 2009) 30 minutes after medication administration, 66% reported moderate to complete relief and 63% reported good to excellent satisfaction with the medication.

In a subsequent study, 175 elderly patients with acute severe pain were randomized to 0.5mg + 0.5mg of IV hydromorphone (those who requested another analgesic 15 minutes after the initial 0.5mg dose of hydromorphone were administered a second 0.5mg dose). 58% of patients reported adequate analgesia after the initial dose of medication.

Safety of IV hydromorphone in the elderly. In the study of 0.0075 mg/kg IV hydromorphone mentioned above, no patient required naloxone (to reverse the effects of hydromorphone) because of hemodynamic instability or respiratory compromise. Nausea and pruritis were each reported in $\leq$5% of the cohort. One episode of transient hypoxia was successfully treated with oxygen delivered by nasal cannula. Three patients developed transient systolic BP <90mmHg, which were successfully treated with IV saline boluses.

In the study of 0.5mg + 0.5mg IV hydromorphone, no patients required naloxone. 11% of patients reported nausea and 2 reported pruritis. No patient developed respiratory compromise or hemodynamic instability. 5% of patients experienced transient oxygen desaturations responsive to oxygen administration by nasal cannula. 3% of patients experienced mild hpotension responsive to IV saline boluses.

Efficacy of IV acetaminophen in the elderly. 107 elderly patients (mean age 73) who underwent major orthopedic surgery were randomized to IV acetaminophen or placebo in a series of three RCTs. Patients randomized to IV acetaminophen generally reported lower pain intensity and more satisfaction with the analgesic medication. Because of relatively small samples sizes, these differences did not always achieve statistical significance. (Jahr 2012)

Safety of IV acetaminophen in the elderly. Among 107 elderly adults status post major orthopedic surgery who received IV acetaminophen 1000mg, adverse events did not differ from placebo (Jahr 2012).

Is it unrealistic to think that acetaminophen might be as effective as hydromorphone?
In the non-elderly population, IV acetaminophen has often proven to be nearly as effective as IV morphine, another potent opioid (Appendix). Therefore, we believe there is equipoise in this study design.

Overview. This will be a randomized, double blind, double-dummy comparative effectiveness study conducted in two Montefiore EDs. Ethical oversight will be provided by the Montefiore Medical Center IRB. This trial will be registered online at http://www.clinicaltrials.gov.

Research setting. This study will be conducted in the Moses and Einstein EDs. Salaried, full-time, bilingual (English and Spanish) research associates (RAs) staff the EDs 24 hours per day in 8-hour shifts. All RAs have completed the University of Miami's Collaborative IRB Training Initiative Program for protection of human subjects and have extensive experience collecting data for clinical trials. The RAs will identify patients who are potentially eligible for the study in several ways. They will review the presenting complaint or triage description and consider all patients with complaint or mention of pain as potential participants. They will also ask attending physicians if they feel a patient's pain warrants use of parenteral opioids. The RAs will collect all data for the study

Population of interest: The target population is women and men aged 65 years and older presenting to the emergency department with acute severe pain. We will define acute pain as pain that has been present for no more than seven days. We will only include patients if the ED attending physician believes that patient's pain warrants IV opioids and would treat the patient with parenteral opioids. Patients will be excluded if they have used opioids or tramadol within the previous seven days, if they have had a prior adverse reaction to hydromorphone or acetaminophen, if they have a chronic pain syndrome, defined as use of analgesics on ≥10 days during the preceding months, if they have an oxygen saturation of <95% on room air, a respiratory rate < 12 breaths per minute, a systolic blood pressure < 90mmHg, or a diastolic blood pressure <60mmHg. Patients with cirrhosis (Childs-Pugh A or worse) will be excluded. Patients can only enroll once.

To participate, patients must have capacity to provide informed consent. This will be assessed in two ways: First, we will ask the attending physician to determine whether the patient has capacity to consent. Second, we will perform a rapid assessment of impaired cognition using a six-item screener (Appendix). (Pubmed ID 12218768)

Intervention: Patients will be randomized in a 1:1 ratio to:

Arm A: !000mg of IV acetaminophen in 100ml of normal saline, administered as an intravenous drip over 10 minutes, + 2ml of normal saline, administered as a slow intravenous push
Arm B: 100ml of normal saline, administered as an intravenous drip over 10 minutes, + 0.5mg of IV hydromorphone in 2ml of normal saline, administered as a slow intravenous push

The nurse will remove the study packet from the secured ED medication cabinet (Pyxis). The study packet will contain two items: a 100 ml vial containing either IV acetaminophen 1 gm (or 100 ml normal saline placebo) and a 2 ml vial containing either hydromorphone 0.5mg (or normal saline placebo). IV acetaminophen and IV hydromorphone are both clear solutions that appear identical to normal saline.

Assignment. Will be concealed. The research pharmacist will determine assignment based on a random number sequence.
Randomization. Randomization will occur in blocks of four based on a random number generator.
Blinding. Research subjects, clinicians, and research personnel will be blinded. To assess the success of blinding, which may be threatened by the occurrence of certain medication side-effects unique to particular arms of the trial, research subjects and research personnel will be asked, at the time of ED discharge, to guess which medications were administered.
Stratification. Subjects will be stratified by study site (Moses or Einstein)

Measures
1) Pain intensity will be measured using a verbal numerical scale of which 0 represents no pain and 10 represents the worst pain imaginable. This will be assessed 5, 15, 30, 45, 60, 90, 105,120, 180, and 240 minutes after medication administration
2) Medication preference. Preference for a specific medication is a highly patient centered outcome, in which an individual determines for herself the benefit of a particular drug versus the adverse effects experienced. We will include in this study a measure that has been used in multiple ED-based trials—"The next time you come to the ER for treatment of abdominal pain, do you want to receive the same medication again?" Patients will be asked to choose among the following responses: "Yes," "No," or "Not sure"
3) Use of additional analgesic medication. The following medications will be considered parenteral analgesic medications: any IV or IM opioid, any IV or IM non-steroidal anti-inflammatory drug, or IV acetaminophen if administered within 6 hours of investigational medication administration in the ED.
4) Use of additional medication to treat symptoms of nausea or pruritis if administered within 6 hours of investigational medication administration in the ED.
5) ED throughput time. Time of investigational medication administration to disposition time (discharged from ED or decision to admit)
6) Side effects. We will use the following question: "Did you have any new symptoms that began only after you got the study medication?" An affirmative response will be followed by an open-ended question eliciting details. This will be assessed 30 and 60 minutes after medication administration.
7) Nausea. Patients will be asked to rate the severity of their nausea using the descriptors "none", "a little" or "a lot". This will be assessed 30 and 60 minutes after medication administration.
8) Pruritis. Patients will be asked to rate the severity of their pruritis using the descriptors "none", "a little" or "a lot". This will be assessed 30 and 60 minutes after medication administration.
9) Oxygen saturation. This will be measured at baseline and 5, 15, 30, 60, 90, and 120 minutes after medication administration.
10) Blood pressure. This will be measured at baseline and 5, 15, 30, 60, 90, and 120 minutes after medication administration.

Outcomes:
Primary outcome**.** The primary outcome is the between group difference in change in 0-10 pain score between baseline and 60 minutes post administration of study medications. If required, patients will be eligible for rescue medication after the 60 minute assessment.

Secondary efficacy outcomes.
1) Zero to 10 pain scores at each of the time points described above.
2) We will determine whether or not subjects require any additional parenteral medication for pain or other symptoms for four hours after medication administration
3) We will determine ED throughput time
4) At the time of discharge from the ED, we will determine patient satisfaction with the medication

Safety outcomes.
1) Frequency of development of any new symptom after administration of the investigational medication
2) Frequency of requirement of naloxone
3) Frequency of a change in the disposition of the patient attributable to investigational medication
4) Rate of nausea, pruritis, oxygen desaturation and hypotension

Descriptive Variables
Background characteristics: Age, sex, race/ethnicity,

Cause, location of pain, and diagnosis: The location of pain will be described as: abdomen/pelvis, extremities, spinal (back or neck), head, chest, multiple locations, and other. The diagnosis will also be recorded.

Safety monitoring
Data Safety Monitoring committee: this committee will be headed by Dr. Polly Bijur, PhD, an epidemiologist, and include Dr. David Esses, MD, the director of the Moses ED. The committee will meet every month with the PIs to 1) monitor adverse events and develop strategies to minimize these; and 2) monitor recruitment and enrollment.

Data Management and Analysis:
Sample size calculation: A sample size of 148 (74 per group) was calculated based on the following parameters: alpha = 0.05, power = 0.8, between group delta 1.3 NRS units (commonly used in research as the minimum clinically significance difference or MCSD), and standard deviation of 2.8 NRS units (based on prior studies). We wish to enroll an additional 14 subjects (approximately 10%) in order to account for potential protocol violations and missing data. Thus, our final proposed sample size is 162 subjects.

Data Processing: Data will be entered directly into REDCap.

Analysis: Descriptive data will be calculated for all variables. The characteristics of patients in the two groups will be compared in order to confirm adequacy of randomization. If there is unequal distribution of background variables with p values of 0.15 or less, we will include them in a multivariable analysis of the outcomes. We will calculate the difference in NRS scores between baseline (time zero) and 60 minutes for the 2 groups. The difference between the two

groups will be reported with 95%CI. If the 95%CI of the between-group difference does not cross 0, the results will be considered statistically significantly different. For patients who do not provide a 60 minute 0-10 pain score, we will use the most proximate pain score available (we will use a mean score if there are two available scores equidistant from the missing 60 minute assessment). For patients who receive rescue analgesia prior to the 60 minute assessment, we will use the most recent pain score prior to rescue medication administration.

Secondary outcomes will be reported as mean or percentage with 95%CI. We will use 95% confidence intervals to compare means, proportions, and differences in both whenever possible. Multivariable analyses will use a significance criterion of $p<0.05$.

Computer data security, subject confidentiality, data storage, and maintenance: All data collection instruments will be secured within REDCap. Research records will be kept under lock and key in the Department of Emergency. Electronic database will require a username and password. The PI and co-investigators will be the only ones with access to the full database linking study IDs to patient identifying information. The limited electronic database used for analysis will be in the possession of the PI and be password protected. After the data analysis has been completed, data will be de-identified and stored on a secure, password protected computer.

Consent. Informed consent will be obtained after the patient has been evaluated in the ED, while they are having acute pain. Unfortunately, there is no other feasible way to obtain consent because severe acute abdominal pain is not predictable. As part of this consent process, we will be sure that patients understand they do not have to participate in the study to obtain analgesics. Also, we will offer to help patients call a family member or friend to discuss the study with them if they wish. Finally, we will have the patient's attending physician confirm that the patient has the capacity to consent to participate in the study at the time they are asked to provide consent. Both research associates and health care providers will participate in the consent process. Both will document their participation with a note in Epic and by signing the consent document.

Pyxis procedures. The healthcare provider will place an order in Epic for the study medication. The order will trigger a specific pocket in Pyxis to open. The research associate and the clinical nurse will then complete the RA/RN checklist (Appendix).

Description of orientation and education that providers receive about this study and about research procedures. This study in particular and research procedures in general are introduced during faculty meetings and reinforced with emails and Powerpoints. The PI then meets with providers in brief one-on-one sessions to describe these. Finally, the investigators and research associates discuss these during the in-shift briefs.

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Appendix. Literature review

IV APAP versus IV morphine for renal colic

Author, year	N	APAP	morphine	0-10 (or 0-100) pain scale	Rescue meds
Masoumi 2014	110	1gm over 5-10 min	0.1mg/kg	At 30 min: APAP improved 4.7, morphine improved 2.9	morphine 55% APAP 31%
Serinken 2012	73	1gm over 2-4 min	0.1mg/kg	At 30 min: APAP improved 6.4, morphine improved 5.7	morphine 20% APAP 16%
Bektas 2009	100	1gm	0.1mg/kg	At 30 min: APAP improved 43, morphine improved 40	APAP 46% morphine 49%
Morteza-Bagi 2015	100	1gm	5mg	At 35 min: APAP: 1.9 Morphine: 2.0	Morphine 40% APAP 36%
Azizkhani 2013	124	15mg/kg over 15 min	0.1mg/kg	At 30 min: APAP: 2.4 Morphine: 0.75	Not reported
Pathan 2016	110	1gm	0.1mg/kg	At 30 min: APAP 3.3 Morphine 3.8	APAP 20% Morphine 23%

IV APAP versus IV morphine for other indications

Author, year	Indication	N	APAP	Morphine	NRS	Rescue meds
Craig 2011	Isolated limb trauma with pain ≥7/10	55	1gm over15 min	10mg	At 60 min: APAP improved: 2.4 Morphine improved: 2.6	29% in both groups
Vahdati 2014	Post-traumatic headache	60	1gm over 10 minutes	0.1mg/kg	At 30 min: APAP improved 5.3 Morphine improved4.0	Not reported
Ankumah 2017	Labor	38	1gm	2mg	At 120 minutes: APAP	APAP 53% Morphine

					worsened 1.8 Morphine worsened 0.5	18%
Serinken 2016	Sciatica	200	1gm	0.1mg/kg	At 30 minutes: APAP improved: 2.9 Morphine improved 5.4	APAP 18% Morphine 6%

Six-Item Screener to Identify Cognitive Impairment Among Potential Subjects for Clinical Research.
Callahan, Christopher; Unverzagt, Frederick; Hui, Siu; Perkins, Anthony; Hendrie, Hugh; MB, ChB
Medical Care. 40(9):771-781, September 2002.

APPENDIX A. TABLE 1. Six-Item Screener

1. I would like to ask you some questions that ask you to use your memory. I am going to name three objects. Please wait until I say all three words, then repeat them. Remember what they are because I am going to ask you to name them again in a few minutes. Please repeat these words for me: APPLE—TABLE—PENNY. (Interviewer may repeat names 3 times if necessary but repetition not scored.)

Did patient correctly repeat all three words?	*Yes*	*No*
	Incorrect	Correct
1. What year is this?	0	1
2. What month is this?	0	1
3. What is the day of the week?	0	1
What were the three objects I asked you to remember?		
4. *Apple* =	0	1
5. *Table* =	0	1
6. *Penny* =	0	1