

Study Title: A randomized double-blind multicenter double-dummy non-inferiority trial of inhaled loxapine and intramuscular haloperidol + lorazepam for the reduction of agitation

Principal Investigator: Michael Wilson
University of Arkansas for Medical Sciences
4301 W. Markham Street, Slot # 584
Little Rock, AR 72205
Telephone: 501-686-5515
Email: MPWilson@uams.edu

Sub-Investigator (s): Rawle Seupaul
Department of Emergency Medicine
University of Arkansas for Medical Sciences
4301 W. Markham Street, Slot # 584
Little Rock, AR 72205
Telephone: 501-686-5515
Email: RASeupaul@uams.edu

Carly Eastin
University of Arkansas for Medical Sciences
4301 W. Markham Street, Slot # 584
Little Rock, AR 72205
Telephone: 501-686-5515
Email: CDEastin@uams.edu

Study location: UAMS

Title: A randomized double-blind multicenter double-dummy non-inferiority trial of inhaled loxapine and intramuscular haloperidol + lorazepam for the reduction of agitation

PI: Wilson

Background and Rationale

Scientific rationale: Agitation is dangerous

Agitation, and its more serious form, physical violence, is a frequent problem in the emergency department. In a 2011 study by the Emergency Nurses' Association, more than half of all nurses reported physical or verbal assault in the previous 7 days. Agitation is life-threatening both for clinicians and for patients (Zeller et al 2014). The control of agitation is therefore of extreme importance in the emergency setting, and emergency clinicians often place great importance on medications which result in quick calming.

Despite an emerging national consensus over the use of oral or inhaled medications, emergency departments nationwide have been slow to adopt their use (Wilson et al 2014). This may be in part because there is limited data about the use of oral medications in the typical adult/pediatric emergency department. Additionally, the use of intramuscular haloperidol and droperidol are common in emergency departments nationwide (Campillo et al 2015). The safety of haloperidol has been confirmed with 40+ years of clinical practice and numerous publications. Thus, the continued use of IM haloperidol and IM droperidol in emergency departments occurs because educated clinicians, who are familiar with the extant literature in their specialty, believe that these medications are preferred. The fact that haloperidol is not a preferred medication long-term in the outpatient setting does not seem to impact its use acutely in the emergency department.

The study proposed below attempts to test intramuscular haloperidol/lorazepam against inhaled loxapine in the reduction of agitation associated with psychiatric illness. Adasuve® is an insufflation system designed to provide 10mg of loxapine to a patient. Although the use of this medication is not as widespread as haloperidol, loxapine is an FDA-approved medication which is thought to have two advantages: faster onset of action and no need for needlestick.

Hypothesis & Specific Aims

The hypothesis of this study is that inhaled loxapine is non-inferior to intramuscular haloperidol/lorazepam in the reduction of agitation at 120 minutes.

Study Design and Procedures

Please see Figure 1 for a schematic of study flow. Please note that this study utilizes a double-blind double-dummy design with haloperidol and lorazepam in separate syringes, and neither the subjects nor the study team will know which patient is assigned to which group. UAMS investigational pharmacy will be involved in both the randomization process and preparation of placebo.

Title: A randomized double-blind multicenter double-dummy non-inferiority trial of inhaled loxapine and intramuscular haloperidol + lorazepam for the reduction of agitation

PI: Wilson

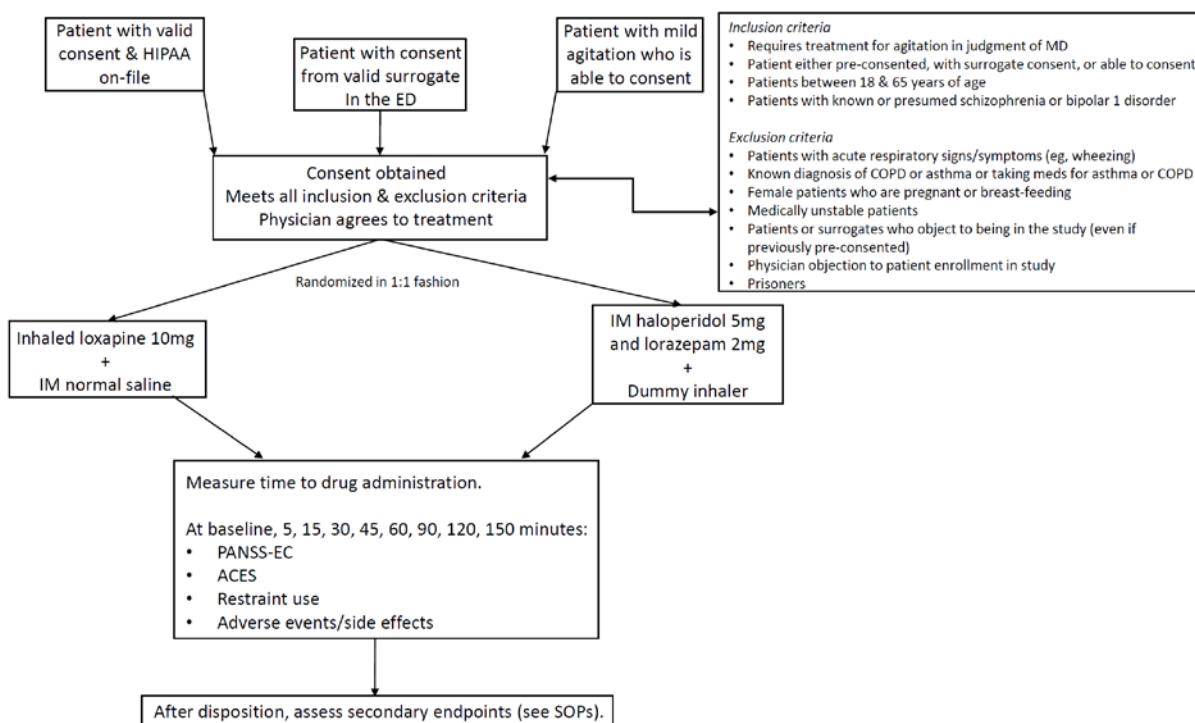


Figure 1. Study flow.

In brief, patients who are preconsented for the study (see below), who have a consent from a valid surrogate in the ED (see below), or who have mild agitation and are able to consent (see below), and who additionally meet all inclusion/exclusion criteria as assessed by a REDCap questionnaire containing questions about health and allergies, will be randomized into the study. In this study, patients will be administered either a placebo loxapine inhaler + an injection of intramuscular (IM) haloperidol 5mg/lorazepam 2mg or inhaled loxapine (loxapine) + intramuscular (IM) normal saline. Patient agitation will be rated using the Positive And Negative Syndrome Scale-Excited Component (PANSS-EC) and Agitation-Calmness Evaluation Scale (ACES) at 5, 10, 15, 20, 30, 45, 60, 90, 120, and 150 minutes. Physicians will be allowed to prescribe any other medications that they feel are in the best interest of their patient after 5 minutes. After disposition from the emergency department (ED), research staff will view the electronic medical record to calculate lengths of stay, admission rates, and additional calming medications ordered by physicians.

Study medications will be placed in the ED Pyxis for easy access, and will be labeled only as "study drug" in sequentially-numbered opaque sealed envelopes. This process will be performed by UAMS pharmacy (please see medications/test articles section below).

Primary outcome/hypothesis

- Inhaled loxapine is not inferior to IM haloperidol/lorazepam in the reduction of agitation at 120 minutes.

Secondary outcome/hypothesis

- Inhaled loxapine is associated with shorter lengths of stay, less associated restraint use, fewer admission rates, fewer adverse events/side effects, shorter time to administration of study medication, more patients calmed by 20 minutes, and less additional calming medication ordered by clinicians.

Title: A randomized double-blind multicenter double-dummy non-inferiority trial of inhaled loxapine and intramuscular haloperidol + lorazepam for the reduction of agitation

PI: Wilson

Medications/Test articles

This protocol proposes to test 3 medications: injected haloperidol, injected lorazepam, and inhaled loxapine.

Justification of comparator drugs (haloperidol/lorazepam):*The use of haloperidol and droperidol is standard in EDs*

In part because of the lack of evidence about other types of anti-agitation drugs in general (and inhaled loxapine in particular) in emergency settings, IM haloperidol + lorazepam is widely used in emergency departments nationwide (Campillo et al 2015; Wilson et al 2015). The safety of haloperidol has been confirmed with 40+ years of clinical practice and numerous publications (see for instance Clinton et al 1987; Raveendran et al 2007). In addition, both haloperidol and droperidol are thought by many EM physicians to be the safest medications in agitated emergency department patients. In part, this is because undifferentiated agitation in the ED often has a non-psychiatric or dual-diagnosis cause. If this is true, ED clinicians must often choose an appropriate agent carefully, since many types of antipsychotics may interact with certain ingested substances.

Thus, the continued use of IM haloperidol in emergency departments occurs because educated clinicians, who are familiar with the extant literature in their specialty, believe that 1) oral meds are inappropriate for severely agitated patients (which anecdotally is thought to represent the only type of agitated patient seen in the ED); and 2) haloperidol may be safer antipsychotics acutely given their lack of interaction with multiple receptor types. The fact that haloperidol is not a preferred medication long-term in the outpatient setting does not seem to impact its use acutely in the emergency department.

The study medications were chosen after careful thought for a number of reasons:

(1) IM haloperidol has been used in clinical practice for >40 years. There are numerous studies citing both safety and efficacy. Haloperidol mainly interacts with the D2 receptor, and has few actions at other receptor subtypes. This first-generation antipsychotic (or FGA) is the most common emergency department antipsychotic nationwide. Haloperidol is an FDA-approved medication, although it carries a black-box warning for use in elderly dementia-related psychosis and carries a warning about use intravenously.

(2) IM lorazepam has been used extensively in clinical practice in emergency medicine. It has a relatively short half-life (10-20 hours), highly protein bound, is glucuronidated by the liver to lorazepam glucuronide, an inactive metabolite, and has virtually no drug-drug interactions. When used in combination with haloperidol, it reduces the side effects of haloperidol use alone (Battaglia et al 1997). Lorazepam is FDA-approved for treating agitation.

(3) Inhaled loxapine is a recently FDA-approved medication for treating agitation associated with schizophrenia or bipolar disorder. Loxapine is a first-generation antipsychotic, is in the pharmaceutical class dibenzoxazepine, has affinity for D1/D2/D4 receptors, and has a plasma half-life of approximately 4 hours (Nordstrom & Allen 2013). There have been 5 studies to date on the effectiveness of inhaled loxapine (Adasuve®) which show efficacy in psychiatric patients (de Berardis et al 2017). However, there have been no studies of this medication in the emergency department. Theoretically, inhaled loxapine is thought to be more patient-friendly, as it does not require injection in an uncooperative patient.

Title: A randomized double-blind multicenter double-dummy non-inferiority trial of inhaled loxapine and intramuscular haloperidol + lorazepam for the reduction of agitation

PI: Wilson

Please note that all medications will be bought by pharmacy and shipped directly to this department. The randomization and randomization scheme will also be performed by investigational pharmacy. Placebo inhalers will be provided by Alexza Pharmaceuticals.

Study Population

Please see Figure 1 (study flow). Approximately 140 patients will need to be enrolled between two sites. We expect anywhere between 70-140 patients to be enrolled at UAMS. As this study utilizes preconsent in the outpatient setting (please see below), it is currently unknown how many patients will need to be consented before coming to the emergency department with agitation. Conservatively, we expect to consent approximately 6000-7000 patients since many of these patients will never subsequently require treatment in an emergency department.

With permission of UAMS psychiatry, patients will be approached in the UAMS outpatient mental health clinic or Psychiatric Research Institute. Study staff will only approach patients if the medical director gives permission, and patients do not object. Patients will be identified using the electronic medical record in a manner similar to the emergency department (see below). Furthermore, study staff will only approach patients in a private area of the emergency department or Psychiatric Research Institute in order to preserve patient confidentiality. In the UAMS emergency department, research assistants may approach patients for screening who have been placed in private rooms. Additionally, research assistants may scan the trackboard and triage screen to identify patients with chief complaints of a psychiatric nature. Patients will be asked to consent for this study should they ever find themselves agitated in the UAMS emergency department and in need of emergency medication. Patients who are critically ill or who are unable to be consented for any other reason will not be approached. Patients will only be approached after evaluation by the treating team, but in order to avoid overly burdening clinical staff who are typically dealing with many critically-ill patients, may be approached without treating providers first discussing the study. Adults who are visiting a patient may also be consented for the study if they have been a patient at UAMS before (as evidenced by a medical record number), meet all inclusion criteria, and express an interest in being screened without being asked while in the room with the patient.

Consents will be kept on file with the study, with an expiration date of 3 years from date of signing, and are revocable by the patient at any time before administration of medication. Given the expiration date on consents, it is possible that a patient who was not 65 at time of consent might have their 65th birthday before the consent expires (see inclusion/exclusion criteria below). Consequently, we will limit preconsents to patients 62 years or less. (Please note that earlier versions of the research plan asked for a one-year expiration date on consent forms. However, given that the study will last at least 2 years, this would mean that some patients would need to be reconsented during the course of the study in addition to being reconsented at time of enrollment. This is therefore not feasible for this study.)

If patients arrive in the emergency department without a valid consent, they may be approached for consent if the agitation is mild enough to allow for the complicated process of true informed consent and if they meet all other inclusion/exclusion criteria. If they are too agitated for this, they may be enrolled in the study if there is a valid surrogate present in the emergency department. In Arkansas, a valid surrogate consists of (in order): a legal power of attorney; a spouse unless legally separated; an adult child; a parent; or an adult sibling. Surrogate consent will not be obtained during the pre-consent process; surrogates will only provide consent for emergency department patients immediately prior to medication administration and observation.

Title: A randomized double-blind multicenter double-dummy non-inferiority trial of inhaled loxapine and intramuscular haloperidol + lorazepam for the reduction of agitation

PI: Wilson

Please note that if the patient objects to being in the study, a patient's surrogate objects to being in the study, or if the patient's physician objects to the patient being in the study, the patient will not be randomized and enrolled, even if previously consented. As the patient's treating physician is responsible for ordering all medications, including study drugs, physicians may elect at their discretion not to order one of the randomized drug kits as prepared by the investigational pharmacy. Should the patient's treating physician object after the medication has been ordered & administered, they will be responsible for making their objection known to the observing RA, who will cease all observation of the patient and withdraw him or her from the study.

Please note that physicians and nursing staff will be notified when the study is ongoing with posted flyers. These will be posted in physician & nursing workspaces. Please note that these do not constitute advertising for the study, but serve as provider notification in a busy environment in a way that is not otherwise feasible. The flyers will contain the PI name & notification number as requested by the IRB. However, they will not contain information that is not relevant to treating clinicians, ie, the numerous inclusion & exclusion criteria. These will be verbally communicated to clinicians by study staff if the need arises.

Inclusion Criteria

- Requires treatment for agitation in judgement of a physician (ie, will place an order for study medication in the medical record)
- Patient either pre-consented, with surrogate consent, or able to consent
- Patients between 18 & 64 years of age inclusive (or age 62 at time of consent)
- Patients with known or presumed schizophrenia or bipolar 1 disorder.

Exclusion Criteria

- Patients with acute respiratory signs/symptoms (eg wheezing)
- Known diagnosis of COPD or asthma, or taking meds for asthma or COPD
- Female patients that are obviously pregnant or breast-feeding
- Medically unstable patients
- Patients or surrogates who object to being in the study (even if previously pre-consented)
- Physician objection to patient enrollment in the study for any reason
- Prisoners
- Known diagnosis of Parkinson's disease
- Known diagnosis of acute narrow-angle glaucoma
- History of toxic central nervous system depression or comatose states
- Known hypersensitivities to loxapine, amoxapine, haloperidol, lorazepam, or any benzodiazepines
- History of seizures or conditions that lower the seizure threshold

Risks and Benefits

The main potential risk to study participants is in loss of confidentiality. Measures to protect the confidentiality of study participants will be implemented as described in the Data Handling and

Title: A randomized double-blind multicenter double-dummy non-inferiority trial of inhaled loxapine and intramuscular haloperidol + lorazepam for the reduction of agitation

PI: Wilson

Recordkeeping section below.

There are of course also potential adverse reactions to study medications, and these will be described in the consent form. In this regard, however, the risk to patients as a part of research is not greater than if these patients received the same medications as part of normal clinical care. All medications are FDA-approved, and it is currently unknown whether one medication combination offers advantages over the other.

Risks described in consent form for loxapine: allergic reaction, hypersensitivity, wheezing/bronchospasm in patients with COPD or asthma, increased chance of death or stroke over 65, low blood pressure, passing out, seizures, impairment of thinking/motor skills, urinary retention. Loxapine is not approved for use in pregnancy or in elderly patients with dementia-related psychosis. Please note that elderly dementia-related psychosis is not listed as an exclusion criterion because patients over the age of 64 are already excluded from the study. Major depressive disorder with psychotic features is not listed as an exclusion criterion because it is not contraindicated in the prescribing information for inhaled loxapine. In addition, patients with major depressive disorder are not being recruited for this study. The information contained in the black box warning below is also outlined in the consent form in less technical language.

**WARNING: BRONCHOSPASM and
INCREASED MORTALITY IN ELDERLY PATIENTS
WITH DEMENTIA-RELATED PSYCHOSIS**

Bronchospasm

ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Administer **ADASUVE** only in an enrolled healthcare facility that has immediate access on site to supplies and personnel trained to manage acute bronchospasm, and ready access to emergency response services [see *Warnings and Precautions* (5.1, 5.2)]. Facilities must have a short-acting bronchodilator (e.g., albuterol), including a nebulizer and inhalation solution, for the immediate treatment of bronchospasm. Prior to administering **ADASUVE**, screen patients regarding a current diagnosis, history, or symptoms of asthma, COPD and other lung diseases, and examine (including chest auscultation) patients for respiratory signs. Monitor for signs and symptoms of bronchospasm following treatment with **ADASUVE** [see *Dosage and Administration* (2.2, 2.4) and *Contraindications* (4)].

Because of the risk of bronchospasm, **ADASUVE** is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the **ADASUVE** REMS [see *Warnings and Precautions* (5.2)].

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. **ADASUVE** is not approved for the treatment of patients with dementia-related psychosis [see *Warnings and Precautions* (5.3)].

Risks described in consent form for haloperidol/lorazepam: allergic reaction, increased chance of death or stroke if over 65, QT prolongation, increased motor movements/abnormal contractions of muscles, increased chance of pneumonia, impairment of thinking/motor skills, possible disturbance of white blood cells, fast heart rate, or worsening of glaucoma (if the patient has this disease). These medications are not approved for use in pregnancy or in elderly patients with dementia-related psychosis. A black box warning for patients with the latter condition is shown below:

Title: A randomized double-blind multicenter double-dummy non-inferiority trial of inhaled loxapine and intramuscular haloperidol + lorazepam for the reduction of agitation

PI: Wilson

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. HALDOL Injection is not approved for the treatment of patients with dementia-related psychosis (see **WARNINGS**).

All study medications are not approved in patients that are pregnant. The potential risk to the fetus will be described in detail in the consent form. In the emergency department, ED clinicians typically use a combination of either self-report or urine pregnancy test to exclude pregnancy, depending on the urgency of treatment. This protocol will use a similar strategy, as ED physicians must agree to treatment by placing an order for study medication in the electronic medical record.

If patients require treatment for agitation, there may be a potential direct benefit to the study participants as both study medications are thought to prevent harm to both patients and staff. In addition, knowledge gained from the study could potentially benefit patients in the future.

Safety assessment section

Research staff will be trained to adhere to the “Steps for Safe Use of Adasuve” as developed for the Risk Evaluation and Mitigation Strategy (REMS Program). Please note that some of these steps will be performed at time of screening and consent, and some will be performed at time of enrollment:

Title: A randomized double-blind multicenter double-dummy non-inferiority trial of inhaled loxapine and intramuscular haloperidol + lorazepam for the reduction of agitation

PI: Wilson

Steps for Safe Use of ADASUVE	
 SCREEN	Ask if patient is taking medication to treat asthma or COPD and/or check medical records
	Ask if patient has a current diagnosis or history of asthma, COPD or other lung disease and/or check medical records
	Examine patients (including chest auscultation) for respiratory abnormalities (e.g., wheezing)
	Do not use in patients with acute respiratory signs or symptoms; with a current diagnosis or history of asthma, COPD or other lung disease associated with bronchospasm; or with current use of medications to treat airways disease, such as asthma or COPD
 COUNSEL	Counsel patient/caregiver on potential for bronchospasm that may occur after dosing and the need for them to report symptoms immediately
 MONITOR	Monitor patient every 15 minutes for at least 1 hour after treatment for signs and symptoms of bronchospasm including chest auscultation
	Ask patient every 15 minutes about any difficulty breathing
 MANAGE <small>If bronchospasm occurs</small>	Treat bronchospasm with an inhaled short-acting beta-agonist bronchodilator (e.g., albuterol)
	If medically necessary, provide additional therapy for bronchospasm per asthma guidelines

Research staff will report any unusual or adverse events to the treating physician and PI immediately. Patients may be terminated from the study either based on the judgment of the treating physician or the PI.

A serious adverse event is defined as one where the patient is seriously injured; the staff is seriously injured; there is airway compromise requiring intubation; or neuroleptic malignant syndrome. All serious adverse events will be reported to the IRB following applicable guidelines for doing so. Serious adverse events will be reported to the sponsor, and will be reported to the FDA as required.

Formal oversight of the study will rest with the PI and a data safety monitoring board. The DSMB will be convened through the UAMS Translational Research Institute (or TRI). Stopping rules and meeting frequency will be designed by the study statistician.

Data Handling and Recordkeeping

The Principal Investigator and a data safety monitoring board will carefully monitor study procedures to protect the safety of research subjects, the quality of the data, and the integrity of the study. All study subject material will be assigned a unique identifying code or number in REDCap. The key to the code will be kept in a locked file in the principal investigator's office. Only Dr Wilson, the DSMB, study statistician, and select study staff will have access to the code and information that identifies the subject in this study.

Records will be maintained for 7 years per IRB requirements. At the discretion of the PI, records may be

Title: A randomized double-blind multicenter double-dummy non-inferiority trial of inhaled loxapine and intramuscular haloperidol + lorazepam for the reduction of agitation

PI: Wilson

scanned and maintained in electronic format instead of paper format once the study is complete. If so, electronic records will be audited to ensure high fidelity with the originals. These electronic copies will also be maintained on secure password-protected UAMS servers. When eventually destroyed, copies will be shredded per UAMS disposal guidelines.

Data collection will be performed through Research Electronic Data Capture (REDCap), and is being set up in cooperation with the UAMS Translational Research Institute (TRI) in order to assure 21 CFR Part 11 and HIPAA compliance. The Hennepin site will be given access to the REDCap collection forms through TRI, and the Hennepin data will be accessed by UAMS researchers through this mechanism.

Data Analysis

The primary outcome for this study will be the non-inferiority of inhaled loxapine compared to IM haloperidol + lorazepam on the reduction of agitation at 2 hours using the PANSS-EC scale. The authors recognize the three main sources of statistical uncertainty outlined in the FDA guidelines on NI trials: the constancy assumption (effect size estimates from the current study are in line with past studies), maintaining a fixed type I error rate, and calculating an accurate estimate of the historical evidence of sensitivity to drug effect (HESDE). Constancy of the effect of haloperidol + lorazepam has been demonstrated in the Cochrane meta-analysis [22-23]. We will use a significance level of 0.05, and apply the appropriate adjustments at the interim analysis to ensure that the overall type I error rate is maintained. We will also use the interim analysis to confirm that the effect size estimates are in line with the HESDE.

We plan on a blinded early assessment of our assumption of equal variances in both study groups at approximately 25% accrual. No assessment of treatment differences will be made during this assessment, and a decrease in the total sample size will not be considered.

Using articles identified by an unpublished systematic review of all antipsychotics measuring reduction in agitation at timepoints <24 hours (currently in development), we selected two randomized controlled trials comparing haloperidol vs placebo. Utilizing estimates from these articles, Wright et. al. (2001) and Breier et. al. (2002), for the effect of haloperidol at 2 hours against placebo (4.00 with a sample size of $n = 126$ and 4.60 with a sample size of $n = 40$, respectively), we arrive at a pooled mean estimate for M1 (the assumed entire effect of the active control, haloperidol + lorazepam) of 4.14. We also combine the standard deviations of the differences between measurements at baseline and 2 hours from these two studies (5.00 and 5.90) to arrive at a pooled estimate of $\sigma = 5.23$, which we assume to be common to measurements of both of our treatment groups. If there is truly no difference between haloperidol + lorazepam and loxapine, then 140 total patients are required to be 90% sure that the upper limit of a one-sided 95.2% confidence interval for the difference in the change in PANSS-EC scores between baseline and 2 hours in haloperidol + lorazepam and loxapine will be below the non-inferiority limit (M2) equal to 2.61 (approximately 63% of the entire effect of the active control). We note that the margin M2 is chosen to maintain a clinically relevant non-inferiority margin.

We will also plan an interim analysis at 50% accrual to test the non-inferiority limits, using the O'Brien and Fleming alpha spending limits to maintain an overall type I error rate of $\alpha = 0.05$. This entails testing the non-inferiority limit with a 99.75% one-sided confidence interval at the first look, and a 95.2% one-sided confidence interval after complete accrual.

Title: A randomized double-blind multicenter double-dummy non-inferiority trial of inhaled loxapine and intramuscular haloperidol + lorazepam for the reduction of agitation

PI: Wilson

A priori stopping rules will be pre-specified with the project biostatistician in case that the interim analysis provides an estimate of futility.

As per FDA guidance, this trial will demonstrate non-inferiority in both an intention-to-treat analysis (ITT) and an as-treated analysis. Although superiority trials generally utilize ITT analyses, this may reward sloppy planning or execution of the trial. If this occurs, non-inferiority would be demonstrated in an ITT analysis but would not be demonstrated in an as-treated analysis, and so is an important additional statistical test.

Justification of a non-inferiority design

The use of a non-inferiority design is appropriate in this trial for two reasons. First, we expect similar efficacy but better tolerability (i.e., side effects) with loxapine than with haloperidol + lorazepam. However, side effects and adverse events are relatively rare in both groups, and powering a standard superiority study on this basis would be unfeasible. Although it is considered theoretically possible that inhaled loxapine may be more efficacious than haloperidol + lorazepam at early timepoints (such as 5 & 15 minutes), this has never been tested. Thus, powering a standard superiority trial is unfeasible. Second, utilizing a placebo as a sole comparison of the efficacy of loxapine is unethical in this trial. Thus, a study of loxapine is only ethical if it includes a standard of care active comparator (i.e, haloperidol + lorazepam).

Secondary outcomes

Measurement of efficacy at additional timepoints

It is unknown how inhaled loxapine compares to IM haloperidol + lorazepam at early timepoints. One randomized study showed effects of inhaled loxapine 10mg as early as 10 minutes after administration (the earliest timepoint studied). Thus, a measure of particular interest is the reduction in agitation at timepoints other than the main outcome of the study (2 hours), particularly early timepoints such as 5 & 15 minutes. After testing for normality, differences between drugs will be compared using an analysis of covariance (ANCOVA) with baseline score as the covariate.

Measurement of side effects/adverse events

The most important secondary outcome is the proportion of adverse events in each group. Serious adverse events such as death, a life-threatening condition, prolonged inpatient hospitalization, or disability will be reported to the sponsor and the FDA on the MedWatch 3500A form. These events are expected to be extremely rare. More common side effects such as dysgeusia or wheezing will be noted at each time point. In addition, the following will also be considered to be adverse events: pregnancy exposure, infant exposure during breast-feeding, overdose, abuse, misuse, medication errors, transmission of an infectious agent, or accidental pediatric exposure. The number of patients with adverse events will be compared between groups using chi-square.

Measurement of length of stay

Given the confounds inherent in disposition from the emergency department, lengths of stay will be measured instead with length of time to disposition order using a two-sample t-test. As lengths of stay are non-normally distributed, these will be log-transformed before analysis.

Measurement of restraint use

Although similar proportions of patients might be expected to be placed into restraints, rapid-acting calming medication such as loxapine would be expected to reduce the total patient time in restraints. The number of patients with any type of restraints (wrist, ankles, or other) will be compared using chi-square.

Title: A randomized double-blind multicenter double-dummy non-inferiority trial of inhaled loxapine and intramuscular haloperidol + lorazepam for the reduction of agitation

PI: Wilson

The total time in restraints is likely to be normally distributed, and will be compared between groups using two-sample t-tests if the assumption of normality holds.

Measurement of admissions vs discharge

If clinicians are able to effectively engage with their patients, this might be expected to reduce admission rates. The number of admitted vs discharged patients will be compared between groups using chi-square.

Time to administration of study medication

It is likely that the time of administration (calculated as administration time – physician order time) will be reduced in patients who are using inhaled medications since these medications do not have to be drawn from a vial and injected. The difference in these times are expected to be normally distributed, and will be analyzed with two-sample t-tests if the assumption of normality holds.

Measurement of additional medications

Clinicians are of course free to treat their patient in any manner they deem appropriate. This may include adjunctive medications, although we will ask clinicians not to do so for the first 10 minutes. The number of patients receiving any additional medications will be compared between groups using chi-square.

Ethical Considerations

All patients will be consented before randomization and drug administration. Please see below for description of informed consent process:

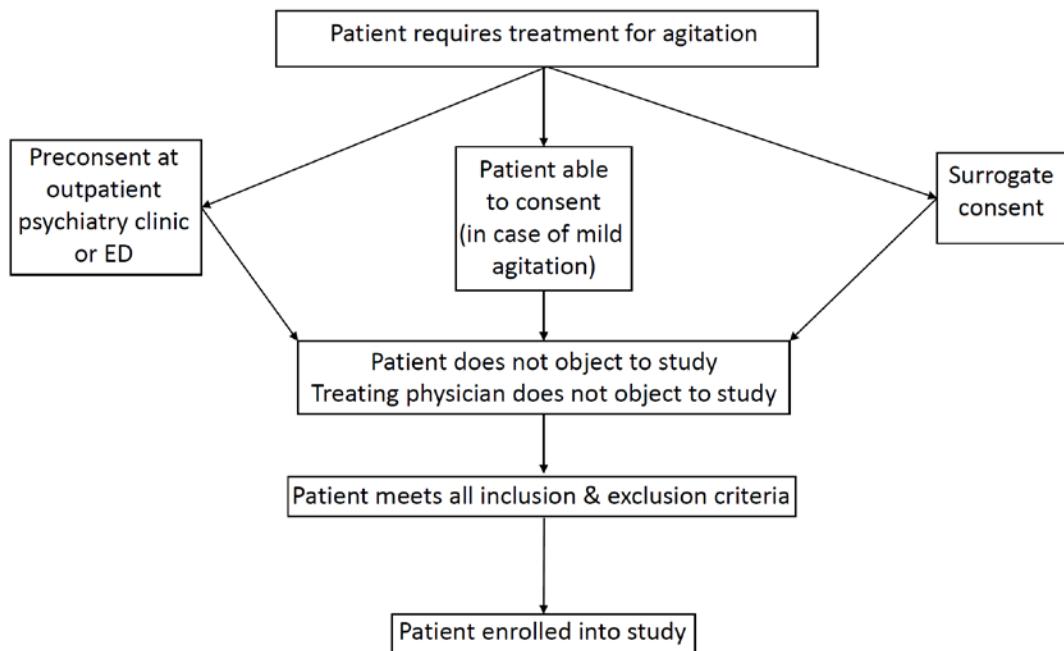


Figure 2: informed consent process

Title: A randomized double-blind multicenter double-dummy non-inferiority trial of inhaled loxapine and intramuscular haloperidol + lorazepam for the reduction of agitation

PI: Wilson

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB) to conduct the study.

The formal consent of each subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. All subjects for this study will be provided a consent form describing this study and providing sufficient information in language suitable for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study. The consent process will take place as described in the "Study Population" section above, and subjects may take as much time as needed to make a decision about their participation.

Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent form must be signed by the subject or legally authorized representative and the individual obtaining the consent. A copy of the signed consent will be given to the participant, and the informed consent process will be documented in each subject's research record.

Dissemination of Data

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a participant.

References

Campillo A, Castillo E, Vilke GM, Hopper A, Ryan V, Wilson MP. First generation antipsychotics are still preferred in the emergency department but are often not administered with adjunctive medications. *J Emerg Med.* 2015; 49(6):901-906.

Clinton JE, Sterner S, Stelmachers Z, Ruiz E. Haloperidol for the sedation of disruptive emergency patients. *Ann Emerg Med.* 1987; 16:319-322.

De Berardis D, Fornaro M, Orsolini L, et al. The role of inhaled loxapine in the treatment of acute agitation in patients with psychiatric disorders: A clinical review. *Int J Mol Sci.* 2017; 18(349):1-15.

Nordstrom K, Allen MH. Alternative delivery systems for agents to treat acute agitation: Progress to date. *Drugs.* 2013; 73:1783-1792.

Raveendran NS. Rapid tranquillisation in psychiatric emergency settings in India: Pragmatic randomised controlled trial of intramuscular olanzapine versus intramuscular haloperidol plus promethazine. *BMJ.* 2007; 335(7625):865.

Wilson MP, Minassian A, Bahramzi M, Campillo A, Vilke GM. Despite expert recommendations, second-generation antipsychotics are not often prescribed in the emergency department. *J Emerg Med.* 2014; 46(6):808-13.

Title: A randomized double-blind multicenter double-dummy non-inferiority trial of inhaled loxapine and intramuscular haloperidol + lorazepam for the reduction of agitation

PI: Wilson

Zeller SL, Holloman GH, Wilson MP. Management of agitation. Chapter in Section 10, "Emergency Psychiatry and Violence," in Tasman A, Lieberman JA, Kay J, First MB, Riba MB [editors]. Psychiatry, 4th edition. Oxford, UK: Wiley Publishing; 2014.

Additional references may be found in:

Zeller S, Nordstrom K, Wilson MP. The diagnosis and management of agitation. Cambridge Press. In press.

https://www.amazon.com/Diagnosis-Management-Agitation-Scott-Zeller/dp/110714812X/ref=sr_1_1?ie=UTF8&qid=1483904339&sr=8-1&keywords=zeller+wilson

Appendices

- REDCap forms for patient assessment
- Consent/HIPAA forms