Haloperidol and/or Chlorpromazine for Refractory Agitated Delirium in the Palliative Care Unit

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This study was submitted to NIH, and received an impact score of 16 pending council review for funding of this protocol. We would like to request for expedited review of this protocol to facilitate study activation.

A. Study Objectives

Primary objective: Assess the within-arm effect of haloperidol dose escalation, rotation to chlorpromazine, and combination therapy on agitation intensity (Richmond Agitation Sedation Scale [RASS]) over 24 hours in patients admitted to an acute palliative care unit (APCU) who did not experience a response to low-dose haloperidol.
Our working hypothesis is that haloperidol dose escalation, rotation to chlorpromazine, and combination therapy will reduce agitation in patients.

Secondary objectives:

1. Obtain preliminary estimates of the effects of haloperidol dose escalation, rotation to chlorpromazine, and combination therapy on (1) the proportion of patients with target RASS -2 to 0, (2) delirium-related distress in nurses and caregivers (delirium experience questionnaire), (3) symptom expression (Edmonton Symptom Assessment Scale), (4) delirium severity (Memorial Delirium Assessment Scale), (5) the need for neuroleptics, (6) delirium recall (Delirium Recall Questionnaire), (7) adverse effects and (8) quality of end-of-life (Quality of Death and Dying questionnaire) over time. *Our working hypothesis is that haloperidol dose escalation, rotation to chlorpromazine, and combination therapy are associated with improvements in delirium-related outcomes.*

2. Obtain preliminary estimates of the between-arm effect size among haloperidol dose escalation, rotation to chlorpromazine, and combination therapy in the first 24 hours. *Our working hypothesis is that rotation to chlorpromazine and combination therapy are associated with a greater reduction in RASS than is haloperidol dose escalation. The effect size will inform future trial designs that are powered to directly compare delirium-related outcomes among treatment arms.*

3. To assess caregiver and nurse preferences regarding proxy sedation goals.

4. To examine the feasibility of novel measures for the assessment of agitation with continuous video monitoring.

B. Background and Significance

B.1. Delirium is the most common neuro-psychiatric complication in patients with advanced cancer (1-3), affecting over 50% of patients admitted to acute palliative care units (APCUs) (4) and up to 93% of cancer patients before death (5, 6). The cardinal features include acute confusion, altered levels of consciousness, restlessness, decreased attention and cognition, and perception abnormalities that fluctuate over the course of the day (7).

Approximately 50%-70% of patients with delirium have hyperactive or mixed subtypes that are characterized by agitation and are often associated with hallucinations, delusions, and hyper- vigilance (4). Agitation, which ranges from restlessness to aggressive violent behavior, can pose a safety risk for patients, caregivers, and healthcare professionals and can be highly distressing to all involved, particularly the 50% of patients with refractory delirium that does not respond to standard treatment with low-dose haloperidol (8). In a survey of 195 bereaved caregivers, 145 (74%) and 121 (62%) cancer patients were reported to have had restlessness and mood lability before death, respectively, which represented the main source of distress for caregivers (9). In a separate study examining agitation in delirium, the mean delirium-related distress level was 3.2 of 4 for patients (with 4 being the most severe), 3.75 of 4 for caregivers, and 3.1 of 4 for nurses (10, 11). In patients with delirium, agitation and

associated symptoms may impede their communication with their families and hinder their participation in treatment decisions, counseling and symptom assessment (12). Ultimately, delirium is associated with increased morbidity and mortality (13).

B.2. The current management of delirium involves (1) identifying and removing any reversible causes and (2) providing pharmacologic and non-pharmacologic interventions for palliation. Non-pharmacological measures, such as environmental control and orientation aids, are recommended. Pharmacologic measures include neuroleptics (e.g., haloperidol and chlorpromazine) and benzodiazepines (14). As shown in Table 1, few studies have evaluated delirium in cancer patients, and only one has been conducted in the palliative care setting (15). This landmark randomized controlled trial compared haloperidol (N=11), chlorpromazine (N=13), and lorazepam (N=6) for the first-line management of delirium in human immunodeficiency virus (HIV) patients (16). The primary outcome, as assessed by the Delirium Rating Scale, improved with haloperidol ($P<0.001$) and chlorpromazine ($P<0.001$), and no significant differences were detected ($P=0.44$). The lorazepam arm was stopped prematurely because of excessive drowsiness. To date, this study remains the only delirium trial to examine chlorpromazine.

Haloperidol is established as the first-line option in clinical guidelines (17, 18). However, there is currently no standardized approach for the management of agitated refractory delirium because of the paucity of research. Clinicians caring for patients with refractory agitated delirium are faced with the dilemma of deciding among (1) dose escalation, (2) neuroleptic rotation, or (3) combination therapy (i.e., the addition of a second neuroleptic or other agent). Although multiple typical and atypical neuroleptics are available, chlorpromazine represents one of the few feasible options for patients with refractory delirium because (1) unlike olanzapine, risperidone, and quetiapine, it can be given intravenously, facilitating rapid administration and control of agitation (onset 15 minutes); (2) its α1 adrenergic blockage effect may be particularly useful for treating agitation. Dexmedetomidine, which can *only* be used in the critical care setting to manage delirium, exerts its effect through both its α2 adrenergic agonist and α1 adrenergic antagonist activities); and (3) a recent retrospective study by our group reported that rotation to chlorpromazine may improve delirium in the second-line setting (19). Similar to the principles of opioid co-analgesia and multi-agent chemotherapy, combination neuroleptic therapy has potential merits (Table 2), although it has not been well studied.

B.3. Rationale. In patients who do not experience a response to low-dose haloperidol, increasing the dose of haloperidol, rotation to chlorpromazine, or both all represent feasible options, with potential advantages and disadvantages, as shown in Table 1. Given the absence of evidence to guide second-line treatment options for agitated delirium, a randomized controlled trial is urgently needed to determine the relative efficacy of these 3 options on agitation and other delirium-related outcomes. The effective management of agitated delirium may ultimately help decrease delirium-related distress in patients, caregivers, and healthcare professionals.

Table 1. Theoretical Advantages and Disadvantages of Dose Escalation, Neuroleptic Rotation, and Combination Therapy

Approach	Advantages	Disadvantages
Haloperidol dose escalation	• Maximize dose response curve	• Some patients may be refractory to haloperidol, regardless of dose • High doses of haloperidol may result in more severe side effects
Neuroleptic rotation to chlorpromazine	• Different spectrum of coverage (both D2 and α1 blockade) • Clearance of metabolites from haloperidol • Rapid onset (within 15 min)	• Chlorpromazine may result in over-sedation, hypotension
Combination therapy	• Wider spectrum of activity	• Logistics of having to administer 2 agents

with haloperidol and chlorpromazine	• Each agent can be used at lower doses and thus potentially fewer side effects

C. Experimental Approach

C.1. Overall Study design. This is a parallel, 3-arm, double-blind, double-dummy, randomized, placebo-controlled trial of dose escalation, neuroleptic rotation, and combination therapy for cancer patients with refractory delirium who are admitted to our APCU. We plan to enroll 90 patients (15 per arm x 3 arms x 2 =90). The eligibility criteria are shown in Table 3. After consent is given by the surrogate decision maker, we will conduct baseline assessments and the patient will be started on a standard dose of haloperidol: 2 mg IV q6h regularly and q1h as needed. RASS will be monitored every 2 hours until it reaches ≥+1; at that time, the patient will be start- ed on 1 of the 3 assigned study interventions and monitored frequently until discharge, death, or withdrawal from study. On the basis of our experience, this study is feasible and will not add an undue burden on patients or caregivers.

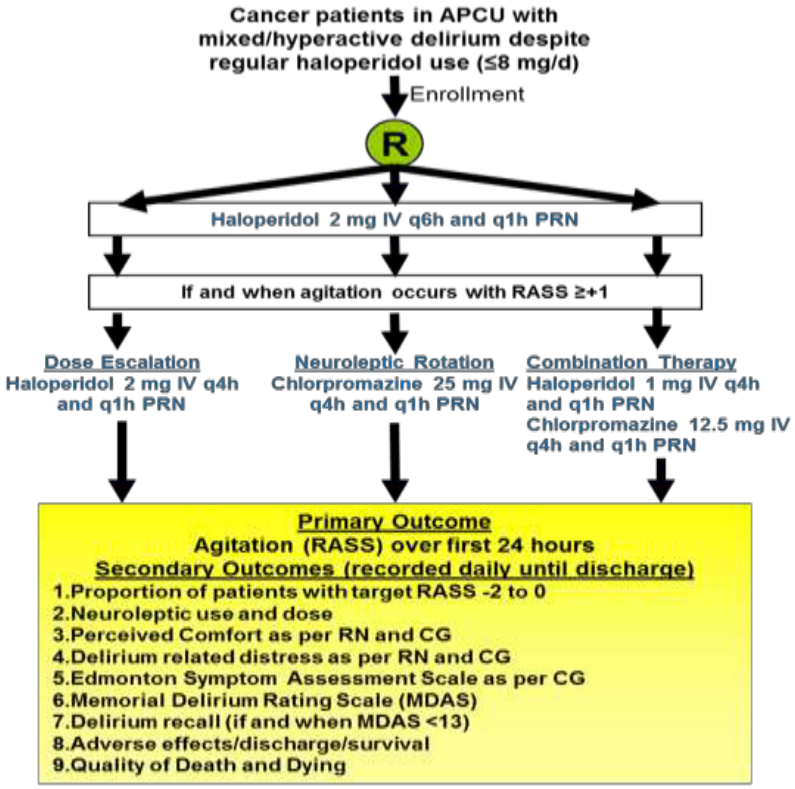

Figure 2. Study Flow Chart. See Table 3 for dosing/titration
Abbreviations: RN, registered nurse; CG, caregiver

C.1.1. Refractory agitated delirium was chosen as the study setting because haloperidol is already established as a first-line option; however, there have been no published trials to inform the management of refractory delirium, which can be particularly distressing.

C.1.2. Choice of study arms. We included both haloperidol dose escalation and chlorpromazine rotation on the basis of preliminary data suggesting that these 2 options are effective in the treatment of delirium. We also included the combination therapy arm, which has the theoretical advantage of minimizing side effects while maximizing the spectrum of receptor blockage.

C.1.3. A double-dummy design is necessary because in clinical practice, haloperidol and chlorpromazine are given separately instead of mixed together in the same bag (no compatibility data). We will administer haloperidol via IV syringe and chlorpromazine via IV bag. Thus, all participants will receive one syringe (haloperidol/placebo) and one bag (chlorpromazine/placebo) for each study drug administration (Table 3) to ensure proper blinding. The use of a placebo *alone* (i.e., no drug) is not justified because patients are already agitated despite receiving low doses of haloperidol.

C.1.4. Justification for neuroleptic dosing. The neuroleptic rotation ratio will be based on the concept of the defined daily dose, in which 8 mg of parenteral haloperidol is equivalent to 100-300 mg of parenteral chlorpromazine (20, 21). We will conservatively apply the lower end of this range as the starting dose for chlorpromazine in this study to minimize overdosing. Thus, the haloperidol to chlorpromazine ratio of 1:12.5 will allow us to convert between haloperidol and chlorpromazine in research studies (4, 22). This ratio is also consistent with clinical practice, in which the median daily dose of chlorpromazine for agitated delirium is 150 mg (19). Thus, all 3 experimental arms will start at the same scheduled haloperidol equivalent daily dose to facilitate a direct comparison: dose escalation (2 x 6 = 12 mg), chlorpromazine rotation (25/12.5 x 6 = 12 mg), and combination therapy (1 x 6 + 12.5/12.5 x 6 = 12 mg). Importantly, the ability to rapidly titrate the dose in each arm in the proposed study will allow us to identify the lowest effective dose while being responsive to the needs of each patient.

C.1.5. Rescue medications will be the same drugs and doses as the scheduled medications in each arm (Table 4) to keep the study arms clean and to make it logistically more feasible for pharmacists and nurses.

C.1.6. The duration of the primary endpoint will be 24 hours because the only randomized trial of chlorpromazine for delirium demonstrated that the peak benefit was achieved within 24 hours (16).

C.1.7. Dose titration of neuroleptics will be used in this study instead of a fixed dose to ensure that we are able to customize the doses according to the agitation level and be responsive to patients' needs. This approach has also been used in other delirium trials (23) and will help us identify the optimal doses for control for agitation in the second-line setting.

C.1.8. Baseline haloperidol requirement. Haloperidol is the most commonly used neuro- leptic for delirium, with an acceptable risk-benefit profile. Patients enrolled in this study will need to have agitated delirium despite low-dose scheduled haloperidol (i.e., <8 mg/day). This dose cut-off was selected because the defined daily dose for haloperidol is 8 mg per day (20). Upon enrollment, haloperidol treatment will be standardized with a scheduled dose of haloperidol (8 mg per day), and only patients who continue to experience agitation will be randomly assigned to the study medications.

C.2. Eligibility criteria. The eligibility criteria are shown in Table 2.

Table 2. Study Eligibility Criteria

Inclusion Criteria
1. [Patients] Diagnosis of advanced cancer (defined as locally advanced, metastatic recurrent, or incurable disease)
2. [Patients] Admitted to the acute palliative care unit
3. [Patients] Delirium as per DSM-V criteria
4. [Patients] Hyperactive or mixed delirium with RASS ≥1* in the past 24 h
5. [Patients] On scheduled haloperidol for delirium (≤8 mg in the past 24 h) or rescue haloperidol of ≥4 mg for restlessness/agitation in the past 24 h
6. [Patients] Age 18 years or older
7. [Family Caregivers] Patient's spouse, adult child, sibling, parent, other relative, or significant other (defined by the patient as a partner)
8. [Family Caregivers] Age 18 years or older

Exclusion Criteria
1. [Patients] History of myasthenia gravis or acute narrow angle glaucoma
2. [Patients] History of neuroleptic malignant syndrome or active seizure disorder (with seizure episode within the past week)
3. [Patients] History of Parkinson's disease or Alzheimer's dementia
4. [Patients] History of prolonged QTc interval (>500 ms) if documented by ECG within the past month
5. [Patients] History of hypersensitivity to haloperidol or chlorpromazine
6. [Patients] On scheduled chlorpromazine within the past 48 h

Abbreviations: DSM-V, *The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*
* RASS≥+1 indicates any degree of restlessness. In the electronic medical record nursing note, this behavior would be indicated by any documentation of "restless", "agitated", "hyperactive", "pulling on devices/IV" or similar wording, or indicated by an administered PRN dose of haloperidol, chlorpromazine, or lorazepam with the indication of restlessness/agitation/delirium.

C.3. Recruitment. The research staff will approach the APCU attending physician and charge nurse daily to identify potential candidates and approach the designated surrogate decision maker for permission to conduct further screening for eligibility. This 12-bed inpatient unit has over 500 admissions per year, with >50% of patients having a diagnosis of delirium on admission. Approximately 70% of patients are discharged alive.

Patients identified to be delirious on the APCU will be approached. Informed consent from the surrogate caregiver, either in person or by telephone if necessary, will be obtained by the study staff to proceed with screening of patients for eligibility and potential enrollment. The number of patients screened, approached, eligible and enrolled will be documented. Reasons for refusal will also be captured. For inpatients, we shall notify the inpatient attending physician of their participation in this study after the surrogate decision makers have signed the informed consent.

C.4. Randomization and stratification. After patient enrollment, randomization will be conducted using permutated blocks on the Clinical Trial Conduct website (https://biostatistics.mdanderson.org/ClinicalTrialConduct), which is maintained by the Department of Biostatistics at MD Anderson. To minimize the possibility that the baseline agitation level affects the outcome, we will stratify patients by RASS score at enrollment (≤1 vs. 2 or 3-4). Only pharmacists preparing the study medications will have access to the identity of treatment assignment. We will maintain allocation concealment.

C.5. Study interventions (Table 3). A commercial supply of haloperidol, chlorpromazine, and normal saline will be purchased. The appropriate dose of chlorpromazine will be prepared in a 1 mg/mL dilution in 0.9% normal saline in a plastic bag for intravenous infusion over 5 minutes per
12.5 mL of solution using a pump. The appropriate dose of haloperidol will be prepared in a 1 mg/mL (maximum) dilution in 5% dextrose in water solution for intravenous push over 1 minute per 5 mL of

solution using a syringe. Thus, each patient will receive 1 bag (chlorpromazine/placebo) and 1 syringe (haloperidol/placebo) for each scheduled or as-needed dose. Each drug administration will be followed by an IV flush. The study medications will be prepared by our investigational pharmacy ahead of time, placed in the APCU to facilitate rapid administration, and replaced on a daily basis before they expire. For each dosing level, the investigational pharmacy will also prepare one dose of study medications at the next higher level in the event that a dosage increase is needed (RASS ≥ 2) while the investigational pharmacy is not available. This approach has proven successful in our other delirium trials (23, 24). We expect that most patients will receive 400 mL to 600 mL of intravenous fluid per day, which should not cause fluid overload. We engineered a dose titration schedule (Table 3) to tailor medication doses according to patients' needs. The APCU physician may be contacted at any time for further treatment options if a patient remains significantly agitated or sedated despite study medications.

Table 3. Dosing Schedule and Titration Scheme

Dose	Haloperidol dose escalation	Neuroleptic rotation to chlorpromazine	Combination therapy with haloperidol and chlorpromazine
Starting dose	**Scheduled** Syringe: Haloperidol 2 mg (2 mL) IV q4h Bag: Placebo (25mL) IV q4h **As needed** Syringe: Haloperidol 2 mg (2 mL) IV q1h PRN Bag: Placebo IV (25 mL) q1h PRN	**Scheduled** Syringe: Placebo (2 mL) IV q4h Bag: Chlorpromazine 25 mg (25 mL) IV q4h **As needed** Syringe: Placebo (2 mL) IV q1h Bag: Chlorpromazine 25 mg (25 mL) IV q1h PRN	**Scheduled** Syringe: Haloperidol 1 mg (2 mL) IV q4h Bag: Chlorpromazine 12.5 (25 mL) mg IV q4h **As needed** Syringe: Haloperidol 1 mg (2 mL)IV q1h Bag: Chlorpromazine 12.5 mg (25 mL) IV q1h PRN
If persistent/ significant agitation†	**Increase** by 2 mg increment (up to 8 mg) of haloperidol and 25 mL of placebo per dose*	**Increase** by 25 mg increment (up to 100 mg) of chlorpromazine and 2 mL of placebo per dose*	**Increase** by 1 mg increment of haloperidol (up to 4 mg) and 12.5 mg increment of chlorpromazine (up to 50 mg) per dose *
If persistent/ significant sedation‡	**Decrease** by 1 dosage level (to 1 mg per dose if at starting level)*	**Decrease** by 1 dosage level (to 12.5 mg per dose if at starting level)*	**Decrease** by 1 dosage level (to 0.5 mg of haloperidol and 6.25 mg increment of chlorpromazine per dose if at starting level)*

† Persistent/significant agitation is defined as RASS ≥2 at any time or if the patient required ≥3 doses of a neuroleptic, as needed, for agitation within 4 h.

‡ Persistent/significant sedation is defined as RASS -5 at any time or if the patient required withholding of ≥2 doses of the scheduled neuroleptic due to sedation.

* The concentration of medication in each arm is fixed; only the volume will be changed. Dose titration is designed such that the change in volume of the study medication is identical regardless of the study arm to ensure *proper blinding*. For persistent or significant agitation, the patient will receive an incremental increase of 2 mL of syringe and 25 mL of bag medication for scheduled and as-needed administration. For persistent or significant sedation, the patient will decrease the dosage level in both the bag and syringe. The APCU physician may be contacted at any time for further treatment options if a patient remains significantly agitated/sedated despite study medications.

C.6. Blinding. Patients, caregivers, nurses, and the research staff conducting the assessment will be blinded to the treatment assignment with the double-dummy design. We will also assess blinding among caregivers, nursing staff, and research staff at the end of the study.

Based on our experience enrolling similar patients with severe agitated delirium, they often die in the APCU and have short survival (i.e. hours to days). In the rare event that a patient is doing well enough to be discharged, we would like to have the possibility of unblinding the treatment assignment to the APCU clinical team if requested because this would allow them to facilitate the discharge process and send patients home on a medication regimen that is optimal for control of delirium. We believe this should not jeopardize the scientific validity of this this study given that the need to unblind is expected to occur rarely, and this will only be done at the end of the APCU stay.

C.7. Study assessments (Table 4).

C.7.1. The RASS, as recorded by bedside nurses, will be the primary outcome measure because it is well validated, easy to use, and simple to assess. Specifically, RASS has high inter-rater reliability, ranging between 0.80 and 0.90 in multiple studies involving nurses as assessors (25, 26), and was strongly correlated with the Glasgow Coma Scale (r=0.85) and Ramsay Scale (r=-0.98) in a study involving patients with advanced cancer (27). An orientation will be conducted with bedside nurses and research staff involved in this study to introduce them to the study design and standardize the administration of questionnaires.

C.7.2. The MDAS (28-30) and DEQ/DRQ (10, 11) have been validated and used extensively in previous studies by our group and others.

The RASS and MDAS will be completed by the bedside nurse and scores will be recorded on Appendix D (RASS, MDAS, and Study Medication Form).

C.7.3. Video Monitoring (Optional Procedure): Although RASS is a well-established and validated outcome, there are some potential limitations. First, its assessment is intermittent and momentary in nature, based on the clinician's impression during the <3-minute observation period. Second, human error may result in missed assessments or documentation. Third, the timing of assessment is scheduled (e.g., q2-4 hours), which may not correspond with the timing of medication administration, making it more difficult to decipher the effects of treatment. Monitoring of RASS continuously via video may overcome some of these challenges. Specifically, continuous video monitoring may offer significant benefits, including (1) higher resolution data (continuous vs. periodic), (2) minimizing over-stimulation of patients, (3) use of a rater who is not only blinded but also removed from clinical care to increase objectivity, and (4) better assessment of the effect of each medication dose. These benefits need to be balanced against patient and caregiver privacy needs and the limited ability to fully assess the depth of sedation (i.e., differentiate among RASS -1 and below).

To attain the goal of assessing patients' level of agitation/sedation more continuously, we will include patient video monitoring as an optional procedure after informed consent has been obtained. Video monitoring (Sony AX33 4K Handycam with Exmor R CMOS sensor, Sony Corporation of America, San Diego, CA) will only occur during the first 24 hours of receiving the blinded study medication. When a patient begins the blinded study medication, the study staff will power on the video monitoring device and will begin recording the patient. The device will be positioned at the foot of the patient's bed to ensure that the patient is being recorded and minimize any other recorded activity (clinical care team, caregivers, etc.). Monitoring will be continuous, with the exception of instances when privacy is needed (e.g., bathing) or request from family members. Once the patient has completed the first 24 hours on the blinded study medication, the study staff will disconnect and remove the monitoring device from the patient's room. The study coordinator will immediately save the video from the device's SD card onto MD Anderson's secured server and will then delete the video from the SD card. Video records will be destroyed 7 years after study data collection is complete.

The video monitoring device consists of a small surveillance camera that is mounted to an IV pole, making

the device easily moveable and adjustable to best fit the needs of the patient's room. This device has infrared capability for night monitoring. This will also allow the bedside nurse to move the device for bathing, etc. The surveillance camera supports local, non-network, recording and will not be connected to the internet while monitoring patients. No audio will be recorded.

For analysis, two investigators who will be blinded to treatment assignment will assess the video footage and document the momentary-video RASS during each RN-RASS (i.e. RASS score documented by RNs). They will also scan the footage for the maximal level of agitation during the preceding 2-hour period (i.e., max-video RASS). We expect that the value of max-video RASS will be greater than RN-RASS and momentary-video RASS, underscoring the benefit of continuous monitoring to detect agitation and facilitate timely management if coupled with real-time observations.

Video monitoring has been successfully used in other MD Anderson clinical settings, (e.g., post-surgical telemetry) as well as in hospice settings. Further, the research team has consulted with MD Anderson's Institutional Compliance Office to ensure compliance with institutional policy.

C.8. Co-interventions. Other than the study medications, management of delirium will proceed as per the standard of care, including the treatment of any potentially reversible causes (e.g. medications) and environmental measures that are routinely provided in our APCU (e.g., orientation cues, hearing aid, visual aid, caregiver presence, ambulation as tolerated, hydration, sitter as needed) (1, 31, 32). In the unlikely event that patients develop severe agitation despite study medication titration (see Table 4), bedside nurses may contact the attending APCU physician, who can either over-ride the study protocol completely, allowing the patient to come off study, or give extra doses of medications, as needed, allowing the patient to remain on study. We will document the use of all neuroleptics and benzodiazepines (regular and as needed) given at enrollment and during admission.

C.9. Stopping rules. Patients who developed severe reaction to the study agents (e.g. seizures) will be taken off study, and treated with other medications as per standard of care. Patients, caregivers and clinicians may also decide to withdraw from the clinical trial after reasons for dropout have been recorded.

C.10. Patient Safety, Monitoring, and Confidentiality. During the study, trained research staff will be performing study assessments and monitoring the patient carefully throughout the study period. A study physician will also be available by pager to address any concerns, distress or questions, and will attend to the patient as needed. Because this study is conducted in the terminally ill population with survival in terms of days or weeks, a high mortality of enrolled patients is expected. Given the high level of agitation in these patients, the study medications are expected to have a favorable risk: benefit ratio. Regulatory monitoring will be provided by the principal investigator, the Institutional Review Board, and the Data Safety and Monitoring Board. Patient confidentiality will be ensured by use of patient initials, secure storage of clinical data, and anonymous reporting.

The MD Anderson IRB reviews and approves the data and safety monitoring plan for all clinical trials. In addition to ongoing monitoring by the PI and research staff, data and safety monitoring for this project will be conducted by two independent MD Anderson entities set up specifically to address these issues: the IRB and DSMB. Plans and procedures for maintaining data integrity, defining and reporting AEs or experiences, and IRB and DSMB oversight and monitoring of this project are described below. These procedures include monitoring of participant eligibility and accrual, AEs, and interim data analyses.

During the protocol review and approval process, the IRB determines the level of safety monitoring required for that protocol. The minimum monitoring requirements include investigator monitoring of participant safety, AE reporting in compliance with IRB, NIH, and FDA guidelines, and participation in the continuing review process with the IRB. The DSMB also monitors clinical trials. The outcomes of

IRB and DSMB reviews are conveyed to the PI via the administrative support staff in the Office of Protocol Research (OPR).

Open Session: During the open session of DSMB, members of the DSMB, voting and non- voting and Executive secretary, clinical trial team, and may be present, at the request of the DSMB Chair. The focus of the open session is on the general conduct and progress of the study. Specifically, the focus of the open session is: adverse events and toxicity issues, subject accrual, protocol compliance, demographic characteristics of enrollees, disease status of enrollees (if relevant), site performance, quality control, and timeliness and completeness of follow- up. During this time, no confidential data will be discussed and the blind, if present, will be maintained.

The PI and other appropriate study leadership and the protocol specific biostatistician should be in attendance in order to present results and respond to questions.

One National Institute of Nursing Research (NINR) program staff may participate in the open session at the discretion of the Chair. The Chair may decide not to invite NINR program staff if their presence may inhibit free and open discussion, or compromise or appear to compromise the board's independence. If NINR program staff are invited to participate, they should be in-formed of upcoming board meetings by the study team at least 1-2 weeks in advance, and receive the appropriate meeting materials at the same time as the board members. DSMB members must be informed prior to the meeting that NINR program staff are invited to the open session and, to contact the Chair if there is concern regarding NINR program staff attendance at the meeting.

NINR program staff, if invited to attend the open session, will act in the role of objective observer and will not provide additional information that may influence the recommendations of the DSMB.

Closed Session: The second part of the meeting is a closed session involving the voting members, invited ex officio members at the discretion of the DSMB Chair. External involvement in the closed session is against MD Anderson DSMB bylaws. During this part of the meeting, grouped safety data and, if appropriate, efficacy data to include unmasking of blinded data are presented by the protocol specific statistician(s).

Executive Session: The third part of the meeting involves only voting DSMB members, and the Executive Secretary, to allow the members the opportunity to discuss the general conduct of the trial, all outcome results, including toxicities and adverse events, and implications of data. External involvement in the executive session is against MD Anderson DSMB bylaws. The Chair, if applicable, may break the blind, if such action is required to make an informed decision. Recommendations will be made to continue the study as planned, to make adjustments to the study plan, suspend or to terminate the study.

At the end of the meeting, voting members discuss and vote on these recommendations. Votes may be done by voice/show of hands or by ballot. Every effort will be made to obtain a consensus. If consensus cannot be obtained, a majority vote is required to carry any recommendation. The Chair will participate in discussions. The PI will provide NINR with a DSMB summary (related to this study) within 20 days of each DSMB meeting upon request.

Table 4. Study Assessments

Assessment (person completing)	Base-line*	Day 1 (first 24 h from time of study medication administration)	Day 2 to discharge (daily)
Demographics (RS/MD)[1]	✓		
Use of neuroleptics/benzodiazepines (RS)[2]	✓	✓	✓
Edmonton Symptom Assessment Scale (Pt or CG)[3]	✓	✓	✓
Richmond Agitation Sedation Scale, primary endpoint (RN)[4]	✓	30m, 1h, Q2h	Q4h
Delirium Rating Scale, Revised-98 (RS)[5]	✓		
Memorial Delirium Assessment Scale (RN or RS)[6]	✓	Q8h	✓
Delirium Experience Questionnaire (RN and CG)[7]	✓	✓	✓
Adverse effects (RS)[8]	✓	✓	✓
Perceived Comfort and agitation (RN and CG)[9]	✓	✓	✓
Proxy Sedation Goals (RN and CG)[10]	✓	✓	
After Death Questionnaire (CG)[11]			After death

Abbreviation: CG, caregiver; MD, physician; Pt, patient; RS, research staff

* With the exception of demographics, DRS-R98, adverse effects and proxy sedation goals which will be collected once only, all baseline measures should be collected daily until study medication administration.

[1] Patients' medical record number, date of birth, sex, race, marital status, cancer diagnosis, co-morbidities, Karnofsky performance status, days in the palliative care unit, potential causes of delirium, and caregiver information.

[2] Medications used to treat delirium, including scheduled and as-needed neuroleptics and benzodiazepines, will be recorded. We will also document the need for palliative sedation.

[3] A 10-item symptom battery validated for assessing symptom burden over the previous 24 hours [1]. Specifically, it assesses pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and well-being using a numeric rating scale from 0 (best) to 10 (worst).

[4] A validated 10-point numeric rating scale that ranges from –5 (unarousable) to +4 (very agitated), where 0 denotes a calm and alert patient [2,3]. As a secondary measure, we will ask for permission from the surrogate to record the patient during the first 24 h of study medication administration. This will allow us to assess the utility of RASS on the basis of video recordings (blinded to study assignment) and its inter-rater reliability with the traditional nursing assessment.

[5] A 16-item scale that has been validated for assessing delirium over the previous 24 hours [4]. Each item is assigned a score between 0 (normal) and 3 (worst) that contributes to a severity score (13 items, total 39 points) and total score (maximum, 46 points). A total score of 18 or more suggests delirium.

[6] A 10-item clinician-rated assessment scale that is validated for assessing delirium in cancer patients [5,6]. It evaluates levels of consciousness, disorientation, memory, recall, attention, disorganized thinking, perceptual disturbance, delusions, psychomotor activity, and sleep, assigning a score from 0 to 3 (total score, 0-30). A score >13 suggests delirium.

[7] Our research staff will interview family caregivers and nurses separately to record the recalled frequency of delirium symptoms and associated distress, similar to the procedure used in a previous study [7]. These include disorientation to time and place, visual/tactile/auditory hallucinations, delusional thoughts, and psychomotor agitation, with symptom frequency and distress each rated on a scale from 0 to 4, where 0=no distress and 4=extremely distressed.

[8] Adverse effects related to the use of neuroleptics will be documented using NCI CTCAE v4.03; this will be supplemented by the UKU assessment, which is a validated questionnaire for documenting the adverse effects of neuroleptics. Vital signs will be assessed q8h during the first day of study medications and q12h thereafter. Discharge outcomes and survival will be assessed at the end of the study.

[9] To examine whether study medications impact as perceived by blinded caregivers and bedside nurses, we will be asking them to rate the patient's perceived patient comfort level on a 0-10 point numeric rating scale, where 0=not at all and 10=very much, on a daily basis. We will also assess the overall impression of change by asking the caregiver "In my opinion, the patient was more comfortable after the study medication." For the first 3 days after study medication administration. The response ranges from "strongly agree", "agree", "neutral", "disagree", and "strongly disagree". In this study, "strongly agree" and "agree" will be combined for analysis. Similarly, we will assess the average level of agitation over the past 24 hours on a 0-10 point numeric rating scale, where 0=not at all and 10=very much, on a daily basis. We will also assess the overall impression of change by asking the caregiver "In my opinion, the patient was less restless/agitated after the study medication." For the first 3 days after study medication administration. The response ranges from "strongly agree", "agree", "neutral", "disagree", and "strongly disagree". In this study, "strongly agree" and "agree" will be combined for analysis.

[10] We will assess proxy sedation goals from the perspective of the bedside nurses and caregivers. It begins with three brief vignettes, describing 3 different hypothetical patients (agitation delirium, mixed delirium, hypoactive delirium) and asking about the sedation goal. Bedside nurses and caregivers will then answer five items that assess sedation level goals specific to the enrolled patient. The research staff will also complete the 5-question Communication Capacity Scale (9).

[11] This is an instrument to examine the quality of death [8,9]. The questionnaire consists of 5 items to bereaved caregivers once over the telephone between 30-180 days after death in APCU. It contains one question based on the CanCORS study published by Wright et al. JAMA 2016 ("Overall, how would you rate the care received at the palliative care unit? Would you say it was excellent, very good, good, fair or poor?" We will define high quality end-of-life care as that which family member rated as excellent.)

C.11. Data Collection. Study data will be collected and managed using REDCap (Research Electronic Data Capture) tools hosted at MD Anderson or hardcopy surveys. Participants will have the option to complete surveys electronically or hardcopy. Data entry of any hardcopy survey will be completed using REDCap software. REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. In the case of multi-center studies REDCap uses Data Access Groups (DAGs) to ensure that personnel at each institution are blinded to the data from other institutions. REDCap (https://redcap.mdanderson.org) is hosted on a secure server by MD Anderson Cancer Center's Department of Research Information Systems & Technology Services.

REDCap has undergone a Governance Risk & Compliance Assessment (05/14/14) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and UTMDACC Institutional Policy #ADM0335. Those having access to the data file include the study PI and research team personnel. Users are authenticated against MDACC's Active Directory system. All protected health information (PHI) will be removed from the data when it is exported from REDCap for analysis. Following publication study data will be archived in RED- Cap.

D. Statistical Analysis

D.1. Sample size calculation. We will assess the within-arm effects of dose escalation, chlorpromazine rotation, and the combination over time by examining the change in RASS in each study arm separately. For a 1-way, repeated-measures ANOVA with 15 patients per arm (45 patients total) and 13 measurements over time (0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hours), we will have 90% power (with alpha = 0.025) to detect an effect size of 0.20 if the correlation between repeated measures is 0.7 (based on prior data) (computed using G*Power 3.1.6). Assuming 50% of patients enrolled will not proceed to receive the blinded interventions, we plan to enroll a total of 90 patients (45 x 2).

D.2. Data analysis.

D.2.1. Primary objective. We will perform a 1-way, repeated-measures ANOVA for each treatment arm by fitting a linear mixed-effects model to the RASS scores over time, separately for each treatment group. We will verify model assumptions by graphing the raw data and model residuals.

D.2.2. Secondary objective #1. Analyses for secondary endpoints will be performed separately within treatment arms. For the secondary aims, we will (1) estimate the proportions of patients within the target RASS range at 24 and 48 hours; (2 and 3) compare the responses at 24 hours and 48 hours to the baseline using the Wilcoxon signed rank test; (4) fit linear mixed models for longitudinal data; (5) estimate the proportion of patients taking neuroleptics at 24 and 48 hours; (6) summarize the distribution of responses; (7) tabulate the frequency of adverse events by type and time; and (8) summarize the distribution of responses. We will conduct analyses with and without adjustment for potential confounding factors, such as age.

D.2.3. Secondary objective #2. We will estimate the effect size between treatment arms by adding treatment as a between-subject factor in a linear mixed effects model. We plan to conduct per protocol analysis for this between-arm comparison.

D.2.4. Secondary objective #3. We will describe the data with summary statistics. As an exploratory analysis, we will compare the differences in proxy sedation goals between nurses and caregivers with Wilcoxon rank sum test.

D.2.5. Secondary objective #4. Feasibility will be defined as >50% of family caregivers accepting this optional video monitoring procedure. In addition to feasibility, we will assess the inter-rater reliability of momentary video RASS, max-video RASS and RN-RASS by asking 2 physicians to review the video and provide their ratings, with an intra-class correlation coefficient.

E. Data Confidentiality Procedures

Health information will be protected and we will maintain the confidentiality of the data obtained from the patient's chart.

Collection of identifiers: We will collect and securely store patients' identifiers (including name and medical record number). Each patient will be assigned a study number that will be the only identifier to figure in the analytical file and personal data will not be disclosed in any form. The key linking these numbers will be retained in a securely locked file by the investigator.

Data Storage: Electronic and paper records will be protected to the best of our ability. All electronic records will be stored on password-protected institution computers behind the institution firewall. Any paper records will be classified and stored in locked files inside a locked office.

Training of personnel: Only MDACC personnel trained in maintaining confidentiality, the principle investigators and co-investigators, will have access to study records.

Data sharing: Study data will not be shared with any individuals or entities without an IRB-approved protocol.

Final disposition of study records: PHI may be maintained indefinitely, aggregated in the future, and used for future IRB-approved research studies.

Video Recordings: Video records will be destroyed 7 years after study data collection is complete.

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