VCU Palliative Care ECHO*

September 26, 2019

Outpatient Palliative Care

*ECHO: Extension of Community Healthcare Outcomes

Continuing Medical Education

September 26, 2019| 12:00 PM | teleECHO Conference

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Continuing Nursing Education: 1.5 CE Contact Hours

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September 26, 2019| 12:00 PM | teleECHO Conference

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The following Planning Committee and Presenting Faculty Members report having no relevant financial relationships:

Egidio Del Fabbro, MD
Danielle Noreika, MD

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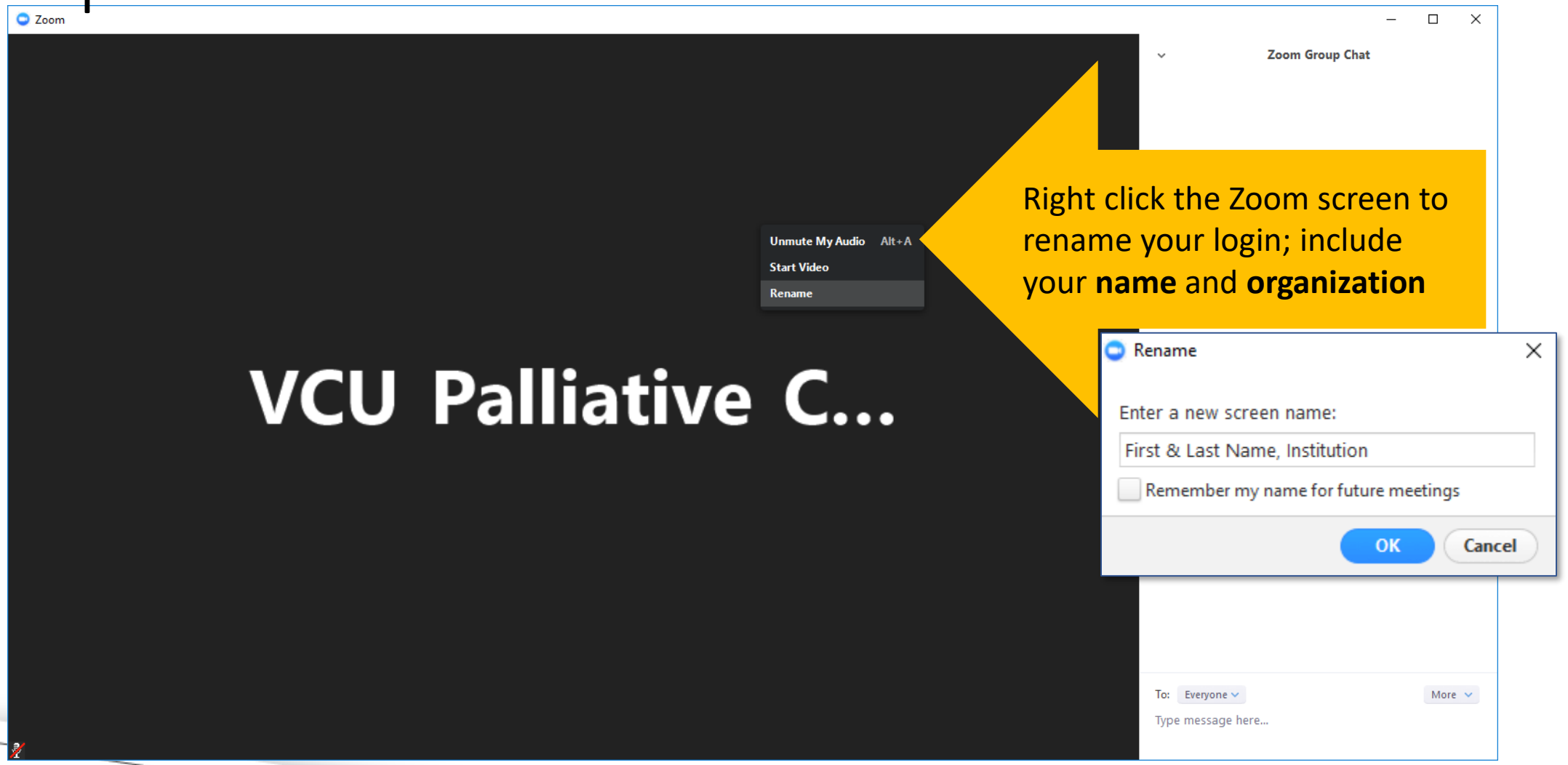
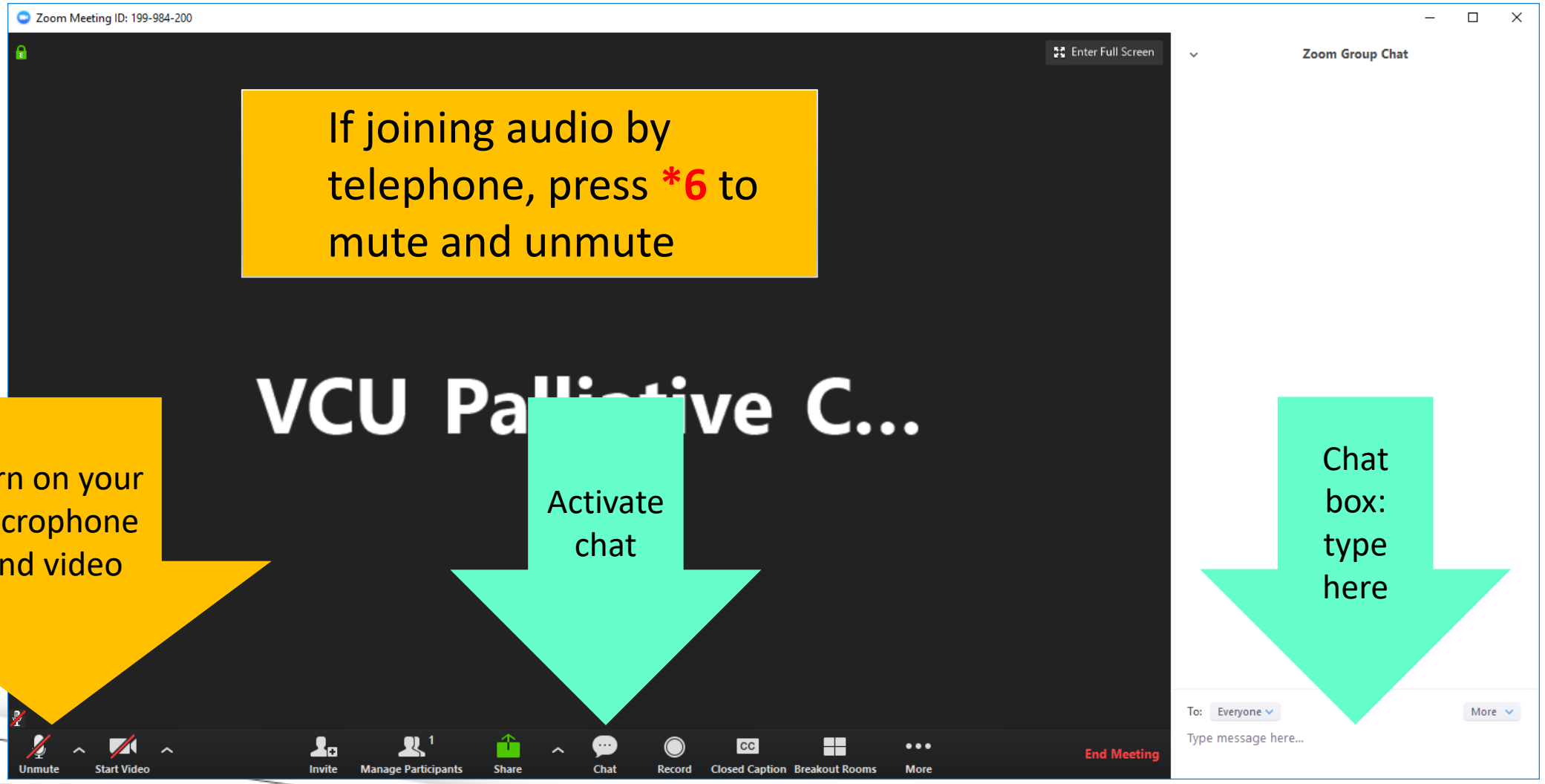
Helpful Reminders



Helpful Reminders



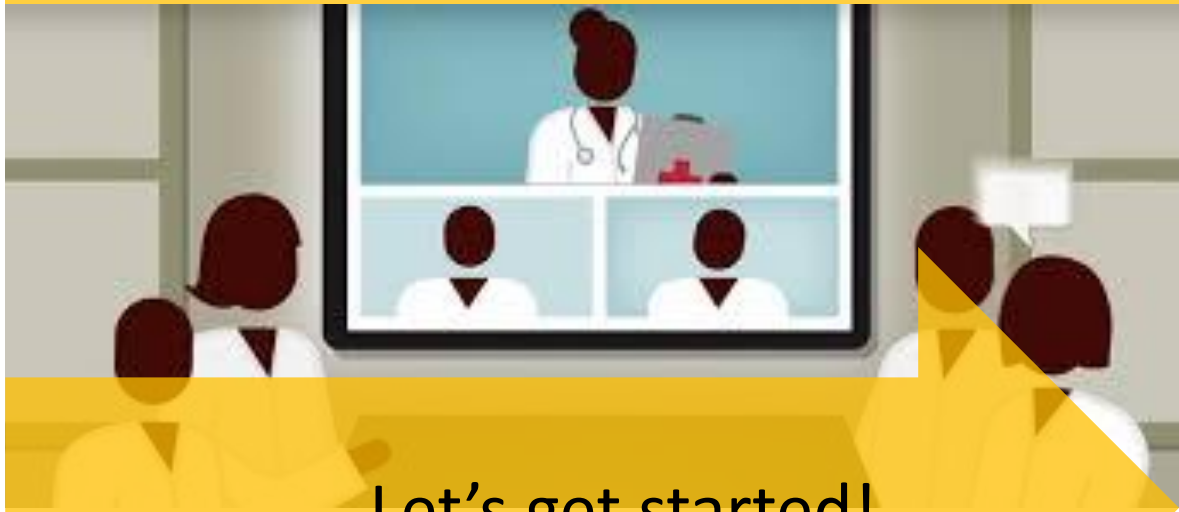
What to Expect

I. Didactic Presentation
   20 minutes + Q&A

II. Case Discussions
   - Case Presentation
     5 min.
   - Clarifying questions from spokes, then hub
     2 min. each
   - Recommendations from spokes, then hub
     2 min. each
   - Summary (hub)
     5 min.

III. Closing and Questions

- Bi-weekly tele-ECHO sessions (1.5 hours)
- Didactic presentations developed by inter-professional experts in palliative care
- Website: www.vcuhealth.org/pcecho
- Email: pcecho@vcuhealth.org



Let's get started!

Hub Introductions

VCU Team	
Clinical Directors	Egidio Del Fabbro, MD VCU Palliative Care Chair and Program Director Danielle Noreika, MD, FACP, FAAHPM Medical Director/Fellowship Director VCU Palliative Care
Clinical Experts	Candace Blades, JD, RN – Advance Care Planning Coordinator Brian Cassel, PhD – Palliative Care Outcomes Researcher Jason Callahan, MDiv – Palliative Care Specialty Certified Felicia Hope Coley, RN Diane Kane, LCSW – Palliative Care Specialty Certified Tamara Orr, PhD, LCP – Clinical Psychologist
Support Staff Program Manager Telemedicine Practice Administrator IT Support	 Teri Dulong-Rae & Bhakti Dave, MPH David Collins, MHA Frank Green

Spoke Participant Introductions

Name and Institution

Objectives

- Define delirium
- Overview tools of delirium screening
- Overview of management strategies for delirium

Delirium in palliative care

Egidio Del Fabbro, MD

Rotation, Escalation, Combination, Or Reduction to treat Delirium Study (RECORD)

A Randomized Controlled Trial

PI: Dr. Hui

Local PI: Dr. Del Fabbro

VCU Study Coordinator: Sarah Womack

MASSEY CANCER CENTER VCU

HOSPITAL DE CÂNCER DE BARRETOS Fundação Pio XII

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

NIH NATIONAL CANCER INSTITUTE

Perspective of the family

"How people die remains in the memories of those who live on"

- 55% were conscious during their last 3 days
- 40% severe pain most of the time
- 80% severe fatigue *(Lynn,Teno Ann Int Med 1997)*
- >25% were dysphoric

Delirium

- Core criteria from DSM-IV: Inattention
  Disorganized thinking
  Acute onset organic etiology

- Screening and diagnostic tools

Mechanisms

- Decreased acetylcholine or Increased dopamine. More complex
- Clinical presentation

  Hypoactive or hyperactive or Mixed
- Survival/outcomes for the subsets inconsistent
- Treatment may be slightly different for the purely hypoactive patient

Table 2 Neurotransmitter targets and pharmacological agents studied in delirium management

Table 2 | Neurotransmitter targets and pharmacological agents studied in delirium management

Neurotransmitter (receptor)	Drug class	Specific drug and study reference
Dopamine (dopamine [primarily D2] receptors)	Typical antipsychotics	Haloperidol (less sedating);[188,191] levomepromazine (more sedating)[192]
	Atypical antipsychotics	Olanzapine;[193] risperidone;[194] quetiapine[197]
5-hydroxytryptamine (5-HT serotonin receptors)	Atypical antipsychotics	Olanzapine;[193] risperidone;[194] quetiapine[197]
Acetylcholine (acetylcholine receptors)	Cholinesterase inhibitors*	Donepezil;[116,117] rivastigmine[204]
Norepinephrine (α_2-adrenergic receptors)	α_2-receptor agonists	Dexmedetomidine[134] (used specifically for sedation in ICU setting)‡
GABA (GABA receptors)	GABA agonists (benzodiazepines)	Lorazepam[198] (in alcohol withdrawal delirium) Midazolam[199] (sedation in palliative care)

*No evidence of efficacy from randomized controlled trials. ‡Mixed evidence of preventive efficacy in ICU settings only. Abbreviations: 5-HT, 5-hydroxytryptamine; GABA, γ-aminobutyric acid; ICU, intensive-care unit.

Lawlor, P. G. & Bush, S. H. (2014) Delirium in patients with cancer: assessment, impact, mechanisms and management
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2014.147

nature REVIEWS CLINICAL ONCOLOGY

Clinical features of delirium in patients with cancer.

Disturbance in level of consciousness (alertness or arousal)
Attentional disturbances
Rapidly fluctuating clinical course and abrupt onset of symptoms
Disorientation
Cognitive disturbances (ie, memory impairment, executive dysfunction, apraxia, agnosia, visuospatial dysfunction, and language disturbances)
Increased or decreased psychomotor activity
Disturbance of sleep-wake cycle
Mood symptoms (depression, dysphoria, mood lability, euphoria)
Perceptual disturbances (hallucinations or illusions) or delusions
Disorganized thought process
Incoherent speech
Neurologic findings (may include asterixis, myoclonus, tremor, frontal release signs, changes in muscle tone)

Breitbart W , and Alici Y JCO 2012;30:1206-1214

Prevalence

- In advanced cancer patients 25-50% experience delirium
- Prospective obs study in PCU 40% delirium hui 2015 pall med
- Days/hours before death 90% experience delirium
- Geriatric patients -25%

PCU, consults and missed Delirium

- Geriatrics >40% misdiagnosed as depression

Farrell 1995 Arch Int Med

- Delirium recall =delusions are distressing for hyper & hypo

Breitbart 2002 Psychosom

  - Misdiagnosis of hypoactive or mixed delirium– missed in 25% when no objective assessment

- 252 of 771 pall care consults=delirium and missed in 61% (153)
  Pain most common reason for consult
  Most common etiology of delirium=opioid related

De La Cruz Oncologist 2015
De la Cruz Supp care 2013

Reversibility of Delirium *Lawlor et al. Arch Intern Med, 2000*

De la cruz Supp care cancer 2105

- Prospective study, 104 admissions to PCU

42% delirium on admission

68% delirium at some stage

49% were reversible

Reversibility associated with psychoactive medication

Delirium =poorer survival

- 556 PCU patients =323 (58%) diagnosed with delirium

71% on admission and 29% developed delirium

26% were reversible

Delirium=poorer survival

Table 1 Delirium assessment tools and criteria

Table 1 | Delirium assessment tools and criteria

Tool or criteria	DSM-5 criteria covered (A–E)	Use to date in cancer and palliative care	Administration characteristics
Screening			
MMSE*[32]	A, C	Used in nonvalidation studies	Brief; verbal tasks and manual task; minimal training needed
SOMCT*[33]	A, C	Used in nonvalidation studies	Brief; verbal tasks only; minimal training needed
CAM*[37]	A (attention), B	Used in validation and nonvalidation studies	Brief; moderate level of training needed; verbal; co-administration of brief cognitive test required
MDAS*[40]	A, C	Limited use	Potentially burdensome; can prorate scores
NuDESC‡[34]	A (awareness)	Used in nonvalidation studies and in studies validated according to DSM-IV	Brief; criteria are easily rated; moderate training needed
DOSS‡[35]	A, C	Used in studies validated according to CAM criteria	Brief; criteria are easily rated; moderate training needed
SQiD‡[36]	B (onset or change)	Used in studies validated according to DSM-IV	Brief; single question to friend or relative; no specific training required
Diagnosis			
DSM-5§[14]	(A–E)	Not used	Limited data available as the criteria were published in 2013; high level of training required
ICD-10§‖[15]	A, B, C and E	Used in nonvalidation studies	Broadly similar to DSM-5 criteria except for criteria D; high level of training needed
Severity rating			
MDAS‖[40]	A, C	Used in nonvalidation and validation studies according to DSM-IV	Comprehensively captures distressing features; suitable mainly for research study
DRS-R-98‖[44]	A, B, C	Used in nonvalidation and validation studies according to DSM-IV	Comprehensively captures distressing features; suitable mainly for research study
DOM‡[29]	A, B (fluctuation), C	Not used	Brief; moderate training required; validated in geriatric population using DSM-IV criteria
NuDESC‡[34]	A (awareness)	Used in nonvalidation studies	Captures most distressing features
DOSS‡[35]	A, C	Used in nonvalidation studies	Captures most distressing features
Agitation/sedation			
RASS-PAL‡[47]	A (awareness)	Used in nonvalidation studies	Brief; easily administered by interprofessional team members; minimal training needed

*Cognitive, ‡observational, §operationalized, or ‖active tool format. Abbreviations: CAM, Confusion Assessment Method; DOM, Delirium-O-Meter; DOSS, Delirium Observation Screening Scale; DRS-R-98, Delirium Rating Scale-Revised; DSM-5, Diagnostic and Statistical Manual, 5th edition; DSM-IV, Diagnostic and Statistical Manual, 4th edition; ICD-10, International Classification of Diseases, 10th edition; MDAS, Memorial Delirium Assessment Scale; MMSE, Mini-Mental State Examination; NuDESC, Nursing Delirium Screening Scale; RASS-PAL, Richmond Agitation–Sedation Scale in Palliative Care; SOMCT, Short Orientation Memory Concentration Test; SQiD, Single Question in Delirium.

Lawlor, P. G. & Bush, S. H. (2014) Delirium in patients with cancer: assessment, impact, mechanisms and management
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2014.147

nature REVIEWS CLINICAL ONCOLOGY

Management

- Treat the cause
- Treat symptoms

Etiology

- ***I WATCH DEATH*** (Infections, Withdrawal, Acute metabolic causes, Trauma, CNS pathology, Hypoxia, Deficiencies, Endocrinopathies, Acute vascular, Toxins or drugs, Heavy metals);
- ***DELIRIUM*** (Drugs, Electrolyte disturbances, Lack of drugs withdrawals, Infection, Reduced sensory input, Intracranial infection, Urinary/fecal retention, Myocardial/pulmonary causes);
- ***THINK*** (Toxic Situations such as CHF, shock, dehydration, deliriogenic medications, organ failure, e.g., liver, kidney; Hypoxemia; Infection/sepsis (nosocomial), Immobilization; Non-pharmacological interventions such as hearing aids, glasses, reorient, sleep protocols, music, noise control, ambulation; K+ or electrolyte problems);
- ***DIMES*** (Drugs, Infections, Metabolic, Environmental, Structural)

Evidence-based management recommendations for patients with cancer with delirium.

I. Current evidence is supportive of short-term use of antipsychotics in the treatment of symptoms of delirium (ie, agitation, sleep-wake cycle disturbances, delusions, hallucinations) with close monitoring for possible adverse effects especially in elderly patients with multiple medical comorbidities.

The longest clinical and research experience and safety/efficacy data available is for haloperidol. Low-dose haloperidol is still considered the gold standard in treatment of delirium. There is growing evidence for the efficacy of atypical antipsychotics in the management of delirium as well. The choice of antipsychotic medication for the treatment of delirium should be based on the clinical presentation of the patient and the adverse effect profile of each antipsychotic drug, given that none of the antipsychotics were found to be superior to others in comparison trials.

II. It is strongly recommended to implement nonpharmacologic interventions in the routine care of patients who are at risk for delirium and of patients with established delirium, based on the evidence from nononcology settings. There are no known risks associated with the use of nonpharmacologic interventions.

III. There is no evidence to support the use of cholinesterase inhibitors in treatment or prevention of delirium in patients with cancer.

IV. The use of psychostimulants in the treatment of hypoactive subtype of delirium in terminally ill patients has been considered. In the absence of randomized controlled trials psychostimulants cannot currently be recommended in the treatment of patients with cancer with delirium.

V. Current evidence is not supportive of the use of antipsychotics for the prevention of delirium in patients with cancer.

VI. The evidence supporting the use of intravenous dexmedetomidine for the prevention of delirium has been mixed and is limited to patients in intensive care settings only; there is currently no evidence to support its use in patients with cancer as a treatment for delirium.

Breitbart W , and Alici Y JCO 2012;30:1206-1214

JOURNAL OF CLINICAL ONCOLOGY ASCO

Table 3 Behavioral and educational intervention as a part of the management of delirium (from [1••], adapted and modified)

Patient

- Environment: having the patient in a single room, reduction of the noises—nursing activity, beeps, alarms, ringing bells, respirators, etc.—keeping the room quiet and well lit, to improve confusion and decrease frightening illusions; availability of objects—photographs, pictures, personal objects—that are familiar to the patient; returning aids—eyeglasses, hearing aids—in order to ameliorate the quality of sensory input and in decreasing misinterpretation of the surroundings)
- Orientation: reorienting the patients to time and space by repeating the date and the time, in having a room with a calendar and a big clock; reorientation to space, context, and persons by repeating where the patient is, why he is there, and the identity of the people assisting him
- Information: regular explanation of the procedures the staffs are applying (e.g., blood exams, pharmacological treatment and route, restraints when needed) and reassurance about what is happening; after delirium is cleared, information about the symptoms and their meaning as a reassurance

Family

- Allow company: family members and close relatives or friends should be permitted to visit the patient and stay with him/her both to reassure the patient, to reduce his/her feelings of abandonment and strangeness determined by unknown persons, to help the staff in reorienting him/her to time and space, and to give the staff information about fluctuation of symptoms
- Information and support: explanation to the family of the causes and characteristics of delirium and its symptoms as a reassurance to what family members are witnessing to; explanation about procedures the staff are applying; elicit and respond to the family concerns, problems, and needs and identify and accept the family emotional reactions

Staff

- Schedule: when possible, avoid that the patient is attended by new, unknown, and unfamiliar health care professionals, by maintaining them in their rotation scheme
- Training: train the staff on communication skills (e.g., maintaining the communication channels open, active listening, give meaning to symptoms); training to the use of delirium assessment tools (e.g., CAM), implementation of application of protocols for delirium management

Table 2 Antipsychotics for the management of delirium (adapted, modified, and expanded from [36•])

Drug	Mechanism of action	Dosing per day/Route of administration	Clinical characteristics and pearls	Side effects and precautions
Typical APs				
Haloperidol	DA	0.5–10 PO, IV, IM, SC	1st choice in delirium (recommended by guidelines) RCTs available Antiemetic properties	Monitor QTc Extrapyramidal effects common
Chlorpromazine	DA	12.5–200 mg IV, IM, SC	Anxiolytic and sedative effects RCTs available	Monitor QTc Sedation, hypotension
Methotrimeprazine		PR 6.25–12.25 PO, IV, SC	Analgesic, antiemetic, and sedating effects	Anticholinergic side effects common (constipation, dry mouth, blurred vision, tachycardia): NB in patients in opioid treatment and poly-drug therapy
Atypical APs				
Olanzapine	MARTA	2.5–20 PO, IM, SC	Sedating effects Appetite stimulant and antiemetic properties RCT available (vs risperidone)	Monitor QTc Anticholinergic side effects (constipation, dry mouth)
Quetiapine	MARTA	25–300 PO	Sedative effects Hypotension RCT available (vs haloperidol; vs amisulpride)	Monitor QTc Sedation
Risperidone	SDA	0.25–6 mg PO	Less side effects vs typical APs if in low doses (otherwise as haloperidol) RCT available (vs olanzapine)	Monitor QTc Possible extrapyramidal effects
Ziprasidone	SDA	40–160 PO, IM	Sedating profile No RCT	Monitor QTc and EKG Few research in delirium
Other atypical APs				
Aripiprazole	DPA	5–20 PO, IM	Less side effects of typical APs Data on efficacy in hypoactive delirium	Monitor QTc Agitation, possible extrapyramidal symptoms
Perospirone	SDA	5–15 PO	Effective in 86.8 % of cases Effect within several days No RCT	Reported low incidence of side effects (fatigue, sleepiness, akathisia, hypotension) Few data in delirium and drug available only in Japan
Amisulpride	DA (D2 and D3); GA	150 PO	Effective in delirium RCT available (vs quetiapine)	Few side effects

DA dopamine antagonist, *SDA* serotonin-dopamine antagonist, *MARTA* multi-acting receptor-targeted antipsychotics, *DPA* dopamine partial agonist, *GA* γ-hydroxybutyrate agonist

a. Recommendations in oncology and palliative care settings [34•]

1. Neurological symptoms (e.g., extrapyramidal symptoms, including dystonias, akathisia, and Parkinsonian symptoms; reduction of seizure threshold): monitor at baseline and daily; 2. Cardiological symptoms: blood pressure and pulse at baseline and at least daily (closer or continuous monitoring for at risk or medically unstable patients); EKG at baseline and with every AP dose increase or daily if high doses of AP are used (closer attention to patients with underlying unstable cardiac disease, electrolyte disturbances, on other QTc prolonging medications for the increased risk of *torsades des pointes*)

From: **Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative CareA Randomized Clinical Trial**

JAMA Intern Med. 2017;177(1):34-42. doi:10.1001/jamainternmed.2016.7491

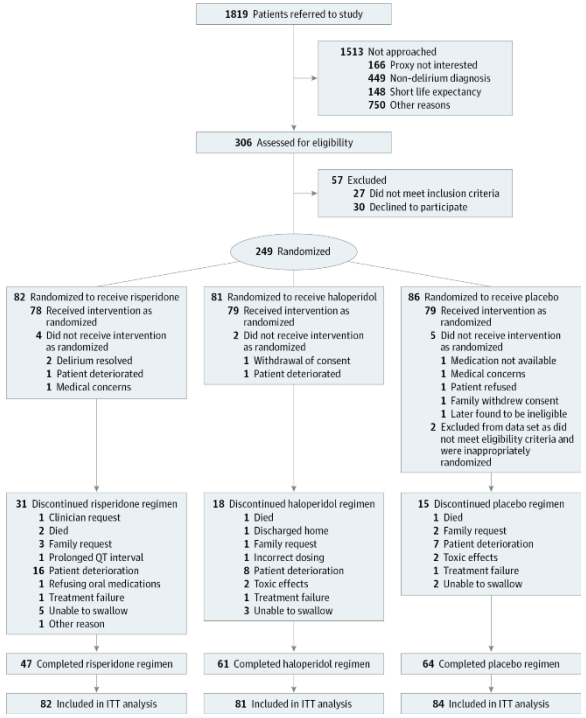


Figure Legend:

Numbers of Participants Assessed and Enrolled in the TrialITT indicates intention-to-treat.

From: **Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative CareA Randomized Clinical Trial**

JAMA Intern Med. 2017;177(1):34-42. doi:10.1001/jamainternmed.2016.7491

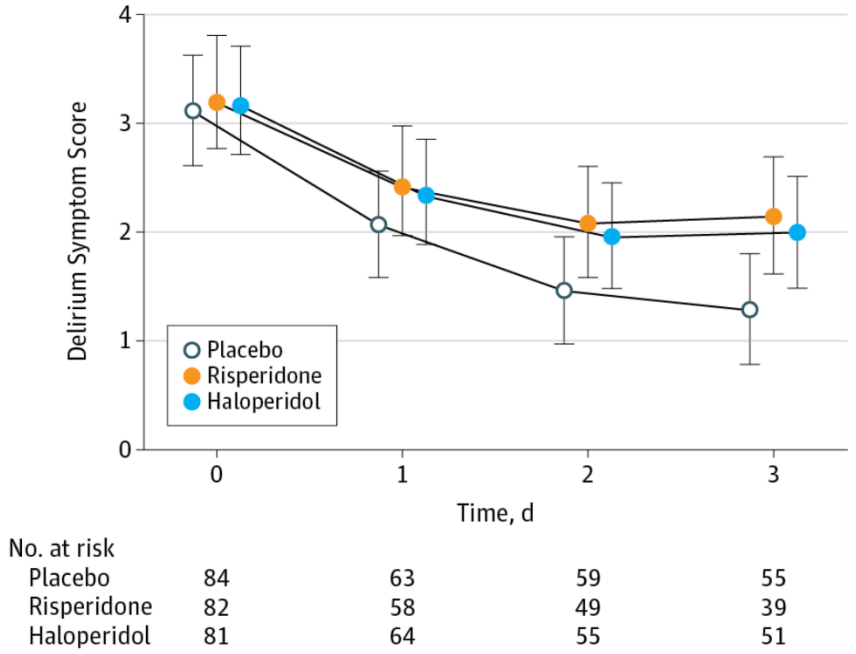


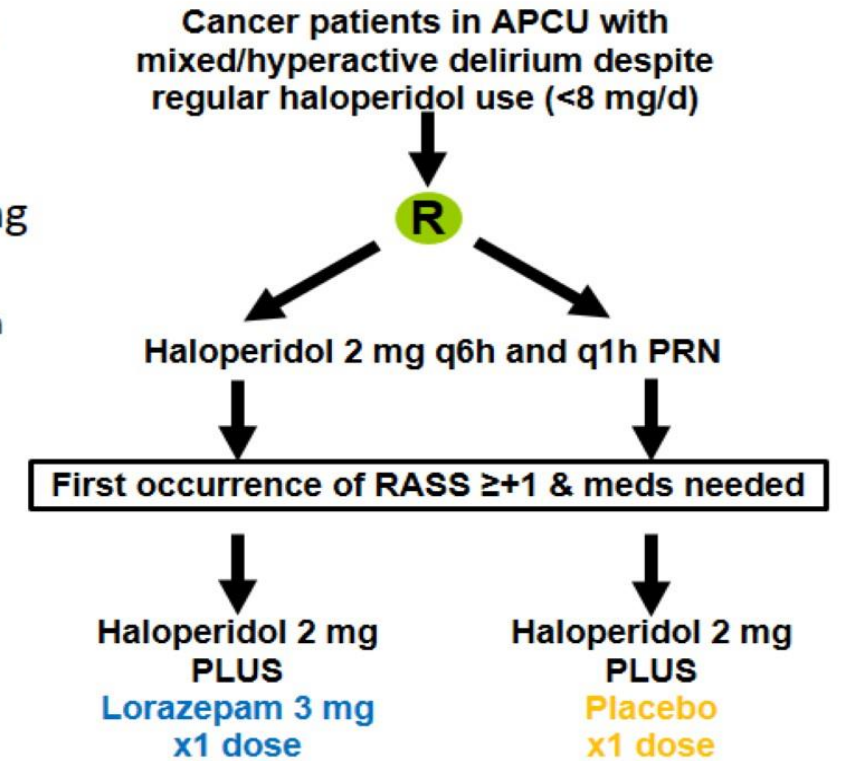
Figure Legend:

Secondary Multivariable Mixed-Model Analysis of DeliriumThe dependent variable was delirium score at each day. The independent variables comprise the covariates in Table 2, group, time, and 2 interaction terms, time × risperidone and time × haloperidol. The relative difference in improvement between groups at 72 hours was determined using the lincom function in Stata. Placebo vs risperidone: P < .001; placebo vs haloperidol: P = .002. Error bars indicate 95% CIs.

Haloperidol ± Lorazepam

Palliative Care, Persistent Agitation

- Double-blind, randomized controlled trial
- Single dose instead of repeated dosing
  - Short survival (i.e. hours to days)
  - Uncertain risks associated with lorazepam in a frail population
- Study outcomes:
  - Richmond Agitation Sedation Scale (1°)
  - Use any additional psychotropic agents
  - Perceived patient comfort
  - MDAS, ESAS, DEQ
  - Communication capacity
  - Adverse effects
  - Discharge outcomes, survival



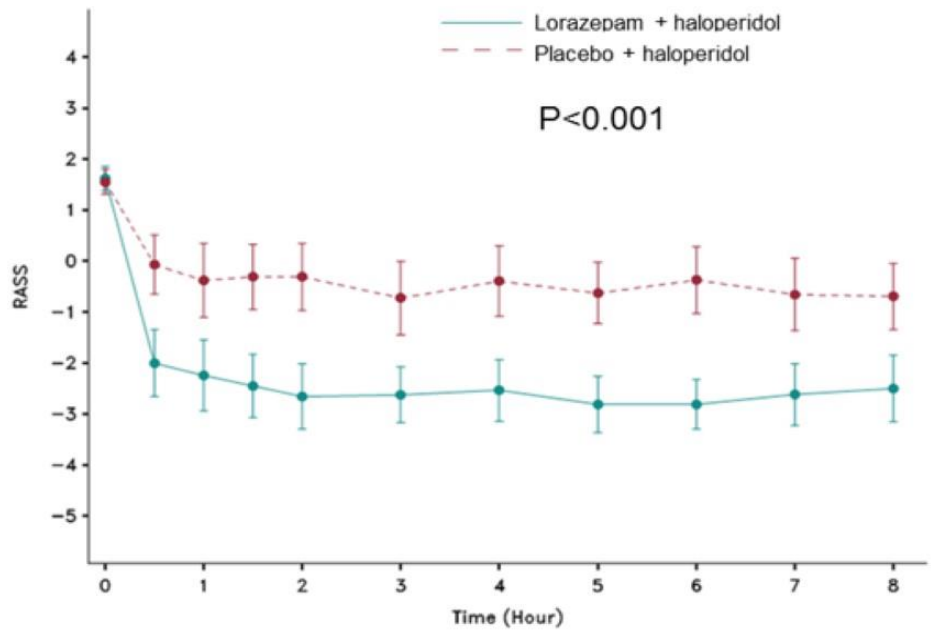
Hui et al. *JAMA* 2017

Credit to: Dr. David Hui, PI, MD Anderson

Haloperidol ± Lorazepam

Palliative Care, Persistent Agitation

- Lorazepam/haloperidol was associated with a significantly greater reduction of RASS compared to placebo
  - 0-30 min: mean Δ -2.0, 95% CI -2.9, -1.1, P<0.001
  - 0-8 h: mean Δ -1.9, 95% CI -2.8, -0.9, P<0.001



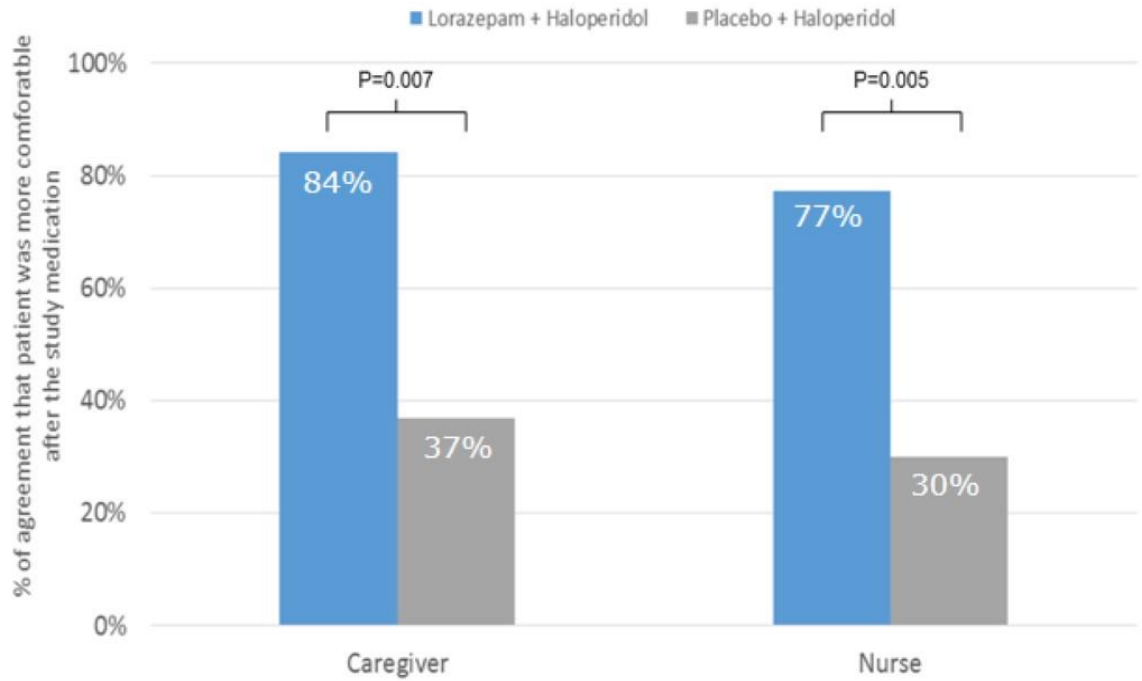
Hui et al. *JAMA* 2017

Credit to: Dr. David Hui, PI, MD Anderson

Haloperidol ± Lorazepam

Palliative Care, Persistent Agitation

Patients on lorazepam/haloperidol arm were perceived to be more comfortable after the study medication by *blinded* caregivers and nurses



Hui et al. *JAMA* 2017

Credit to: Dr. David Hui, PI, MD Anderson

Haloperidol ± Lorazepam

Palliative Care, Persistent Agitation

- Lorazepam and haloperidol, given to the *right* individuals for the *right* reason at the *right* time, may reduce agitation and improve comfort.

- Limitations:
  - Single center study
  - Small study not powered to examine secondary outcomes
  - Only examined a single dose of lorazepam (3 mg)

More Research is Needed

- Further research is needed to examine the role of benzodiazepines and neuroleptics in delirium management.

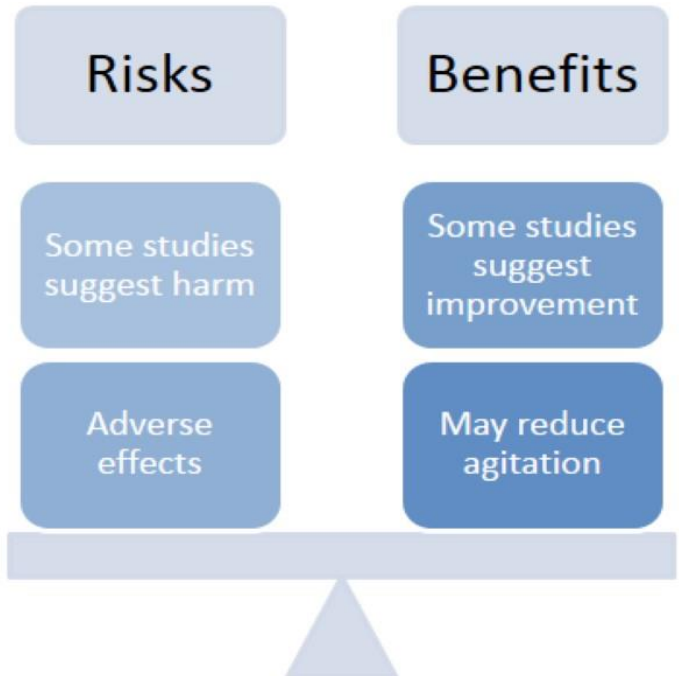
Hui et al. *JAMA* 2017

Credit to: Dr. David Hui, PI, MD Anderson

Pharmacologic Therapies

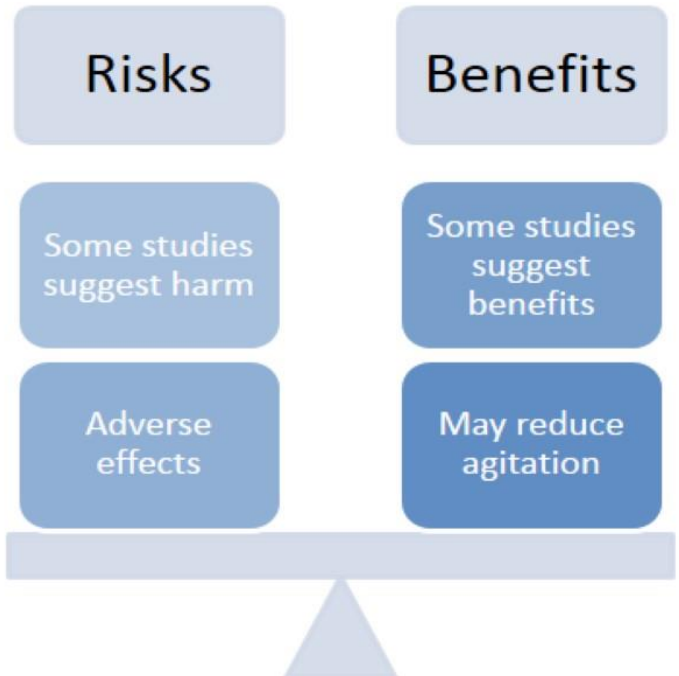
Take Home Message

Neuroleptics



Prevention: Mixed evidence
Treatment: Limited evidence; however, *may be* considered for selected patients given limited options

Benzodiazepines

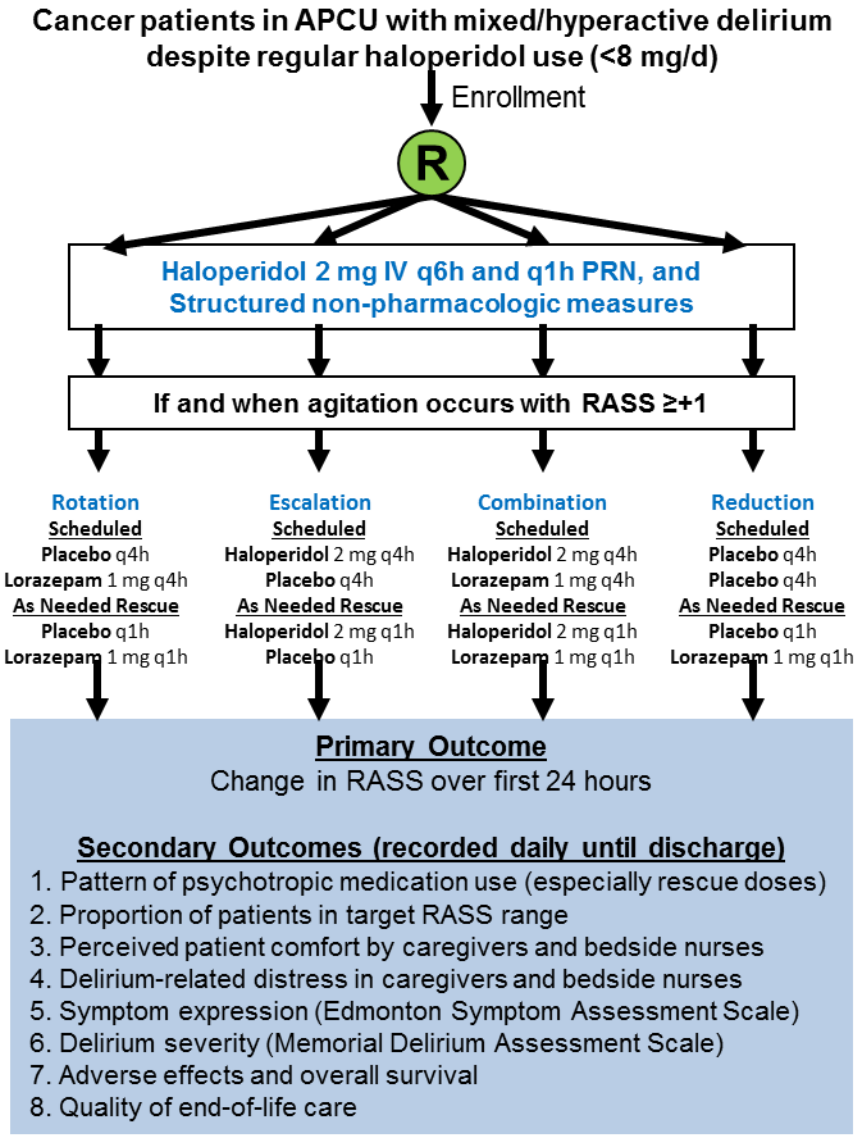


Prevention: No evidence
Treatment: Some evidence for agitation control; use with great caution

Credit to: Dr. David Hui, PI, MD Anderson

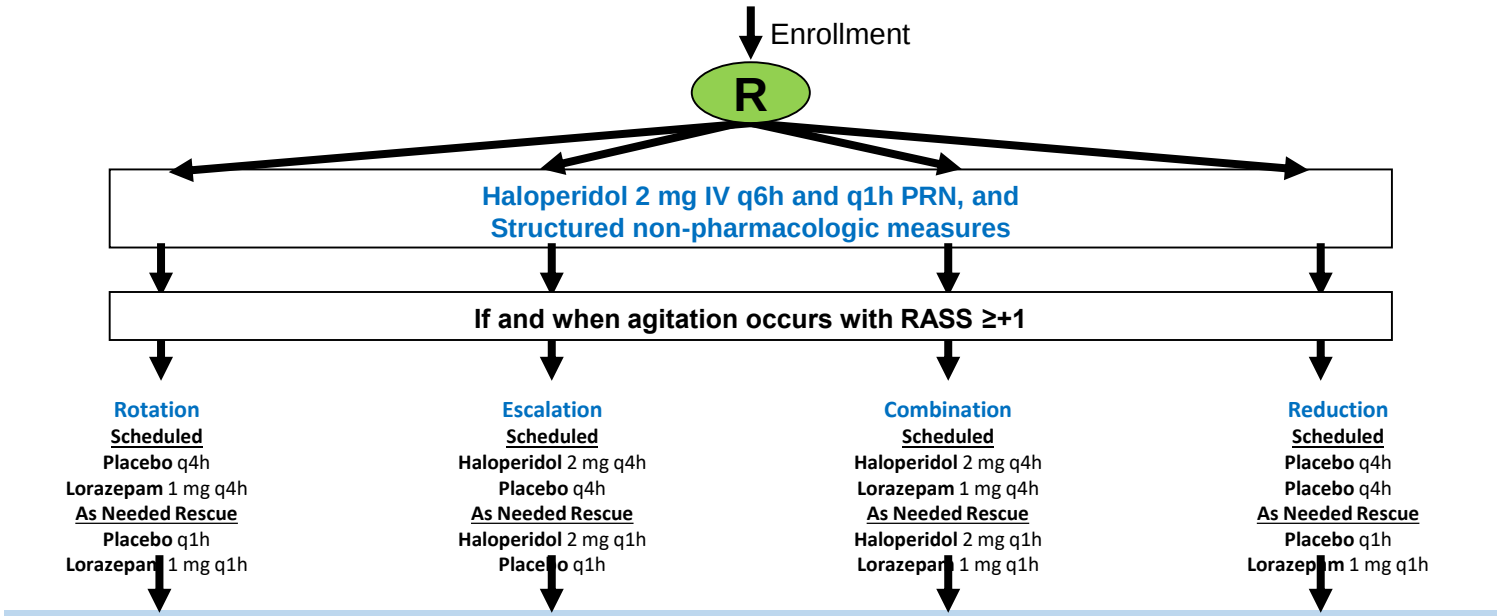
Goal of the RECORD Study

- Not all patients respond to current standard treatment (Haldol, non-pharmacological interventions)
- What are other options and are the effective?



Credit to: Dr. David Hui, PI, MD Anderson

Cancer patients in APCU with mixed/hyperactive delirium despite regular haloperidol use (<8 mg/d)



Primary Outcome

Change in RASS over first 24 hours

Secondary Outcomes (recorded daily until discharge)

1. Pattern of psychotropic medication use (especially rescue doses)
2. Proportion of patients in target RASS range
3. Perceived patient comfort by caregivers and bedside nurses
4. Delirium-related distress in caregivers and bedside nurses
5. Symptom expression (Edmonton Symptom Assessment Scale)
6. Delirium severity (Memorial Delirium Assessment Scale)
7. Adverse effects and overall survival
8. Quality of end-of-life care

Credit to: Dr. David Hui, PI, MD Anderson

Secondary Outcomes

Patient Initials/MRN: _____
Subject study ID: _____

Protocol 2018-0706
Rev. March 6, 2019
Page **24** of **39**

Appendix L. Proxy Comfort Goal

To be completed by caregiver and bedside nurse at baseline

Questionnaire completed by:
☐ Caregiver
☐ Bedside nurse

Assessment completed on:
Date (MM/DD/YY): _____ (Study day [#]:_____)
Time (HH:MM): _____

The following questionnaire consists of several scenarios to help study staff better understand the ideal level of sedation for patients with agitation/restlessness and confusion. At the end, we will also ask what is the desirable level of sedation for your specific family member or patient.

For the purpose of this questionnaire, please imagine that you are the main caregiver/bedside nurse for a patient with advanced cancer who is staying at a palliative care unit. She has been confused for the last few days. She is no longer on active cancer treatment. You have been spending the last few days with her in the hospital.

Scenario #1

She is awake most of the day, and sometimes quite agitated. She keeps moaning and sometimes pulls

Credit to: Dr. David Hui, PI, MD Anderson

Discussion and Questions

Case Presentation

Case presentation

How to better manage end-of-life delirium

- 51-year-old female
- History of metastatic rectal cancer, hypertension
- Presented to the hospital with acute limb ischemia
- Found to have complete occlusion of the left iliac artery, underwent open thrombectomy and fasciotomy, and the clot was found to be tumorigenic;
- Also found to have an AV Vegetation also likely tumorigenic in nature.
- Hospital course was complicated by acute liver injury and acute kidney injury and acute delirium
- After a goals of care discussion with the patient's mother (mPOA) they decided to make her comfort measures only and she was transferred to the palliative care unit for end-of-life care

Social/Spiritual History

Lives with her young son. No history of smoking, alcohol use or illicit drug use

Symptom Assessment

Pain, Dyspnea, Agitation

Pertinent Findings: Physical Exam

General exam: Sedated, does not respond to verbal stimuli; does not appear to be in overt distress

HEENT: Moist mucous membranes

Lungs: Clear to auscultation bilaterally

CVS: regular rate & rhythm, systolic murmur, tachycardic

Abdomen: BS+, soft

Extremities: LLE wrapped in dressing: cool LLE extremity; no dorsal pedis pulses appreciated on LLE; RLE warm, dorsalis pedis pulse present on the RLE; b/l lower extremity edema +2 till mid-thigh

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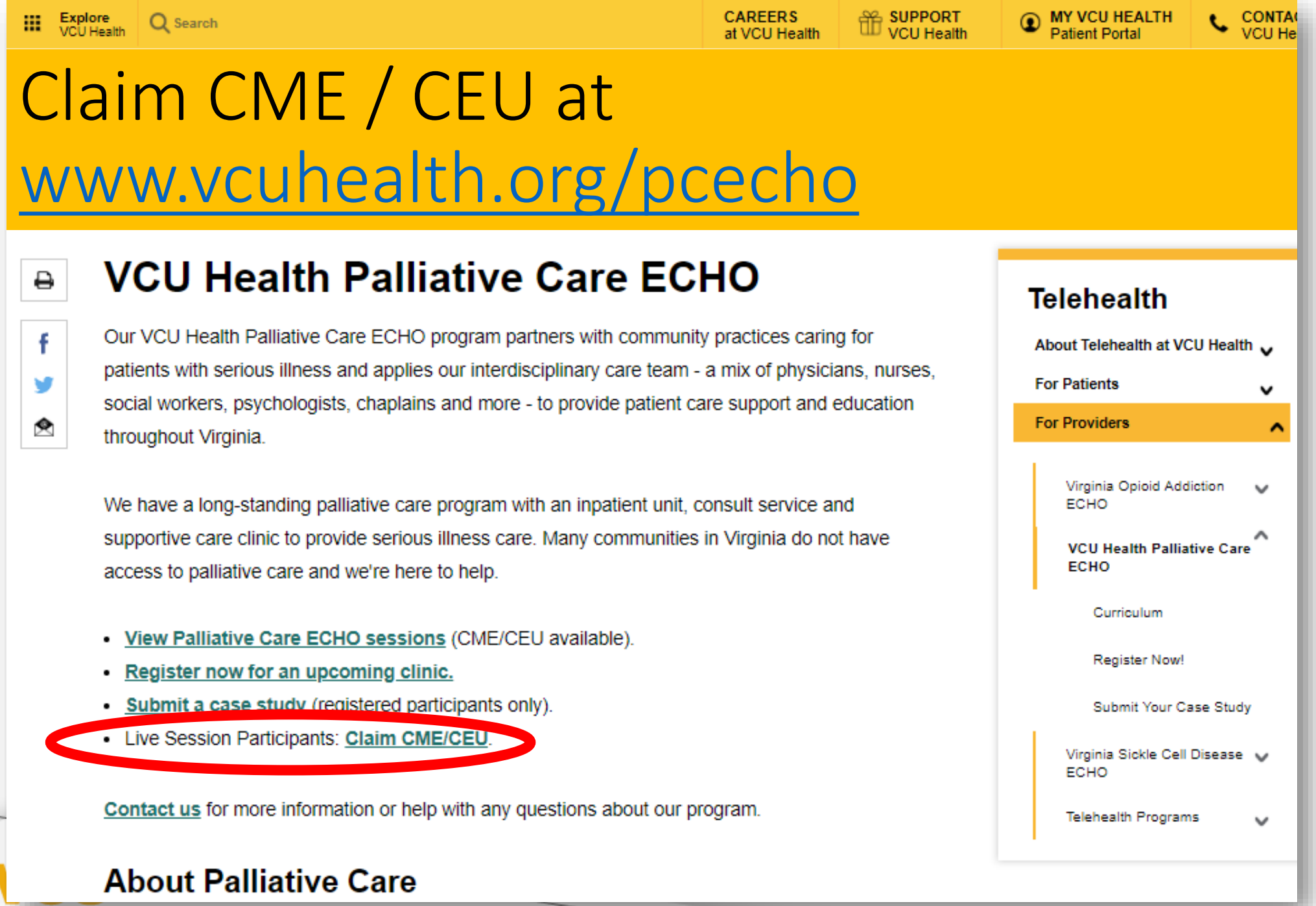

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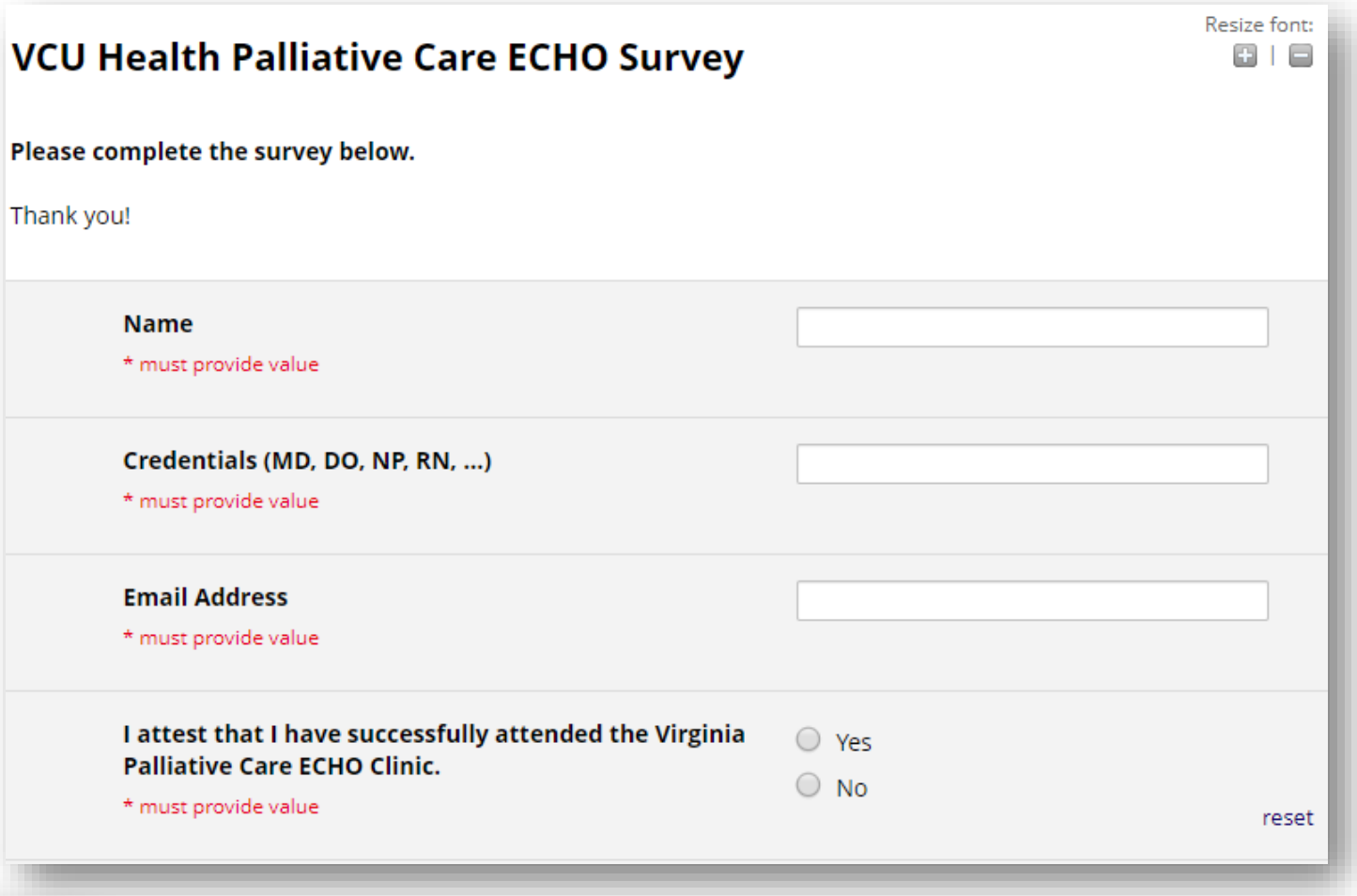

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Credentials (MD, DO, NP, RN, ...)

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Email Address

* must provide value

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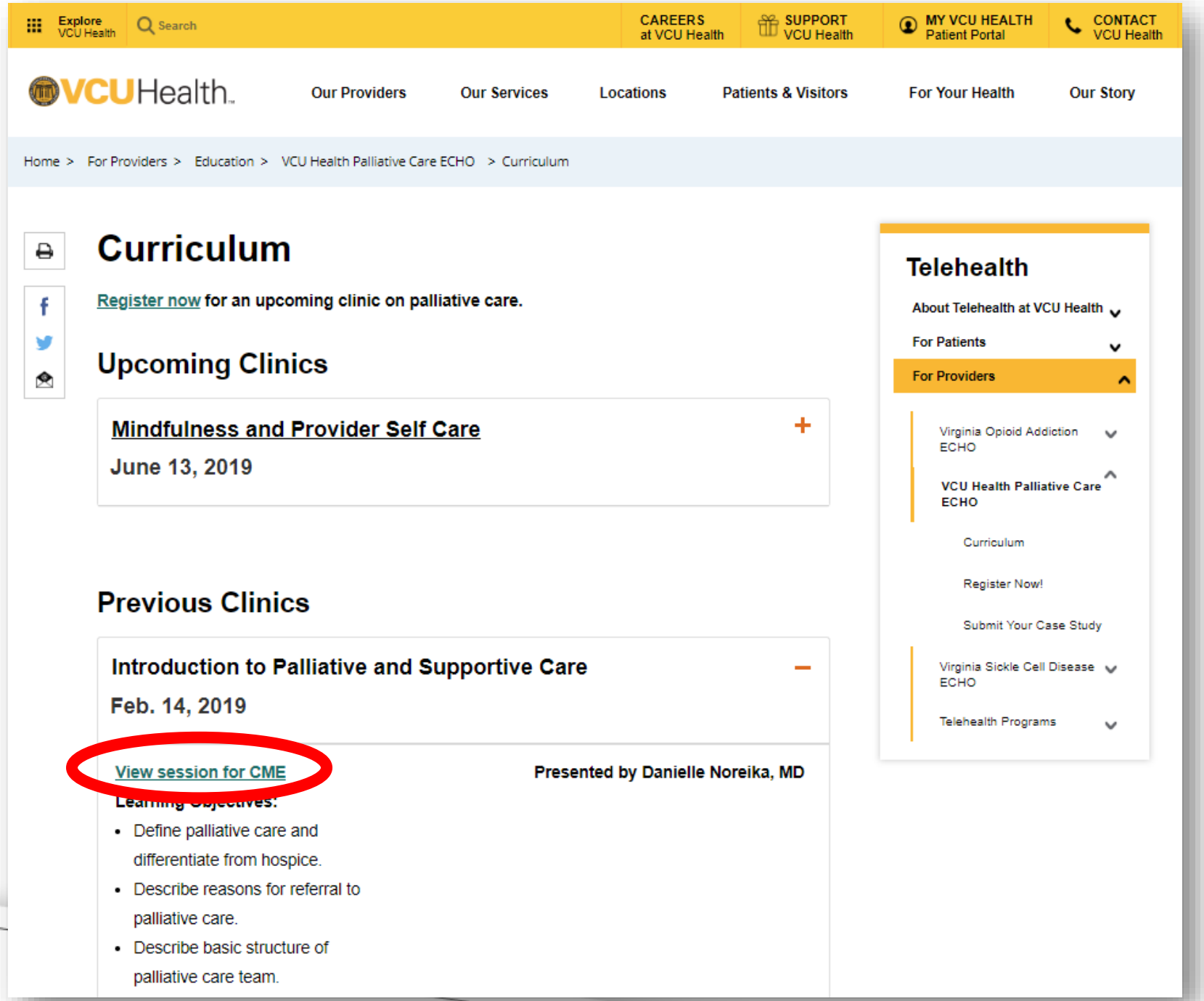

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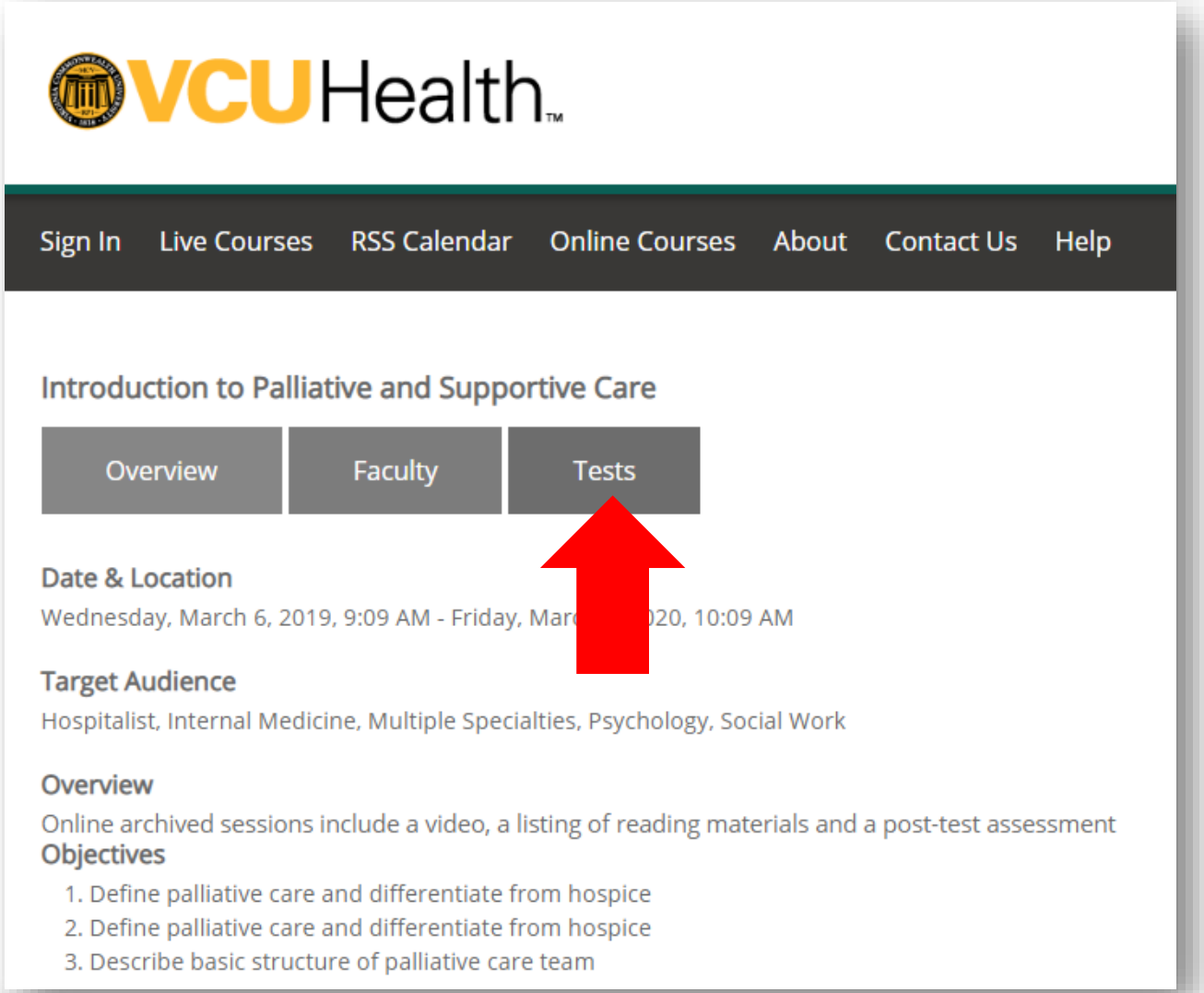

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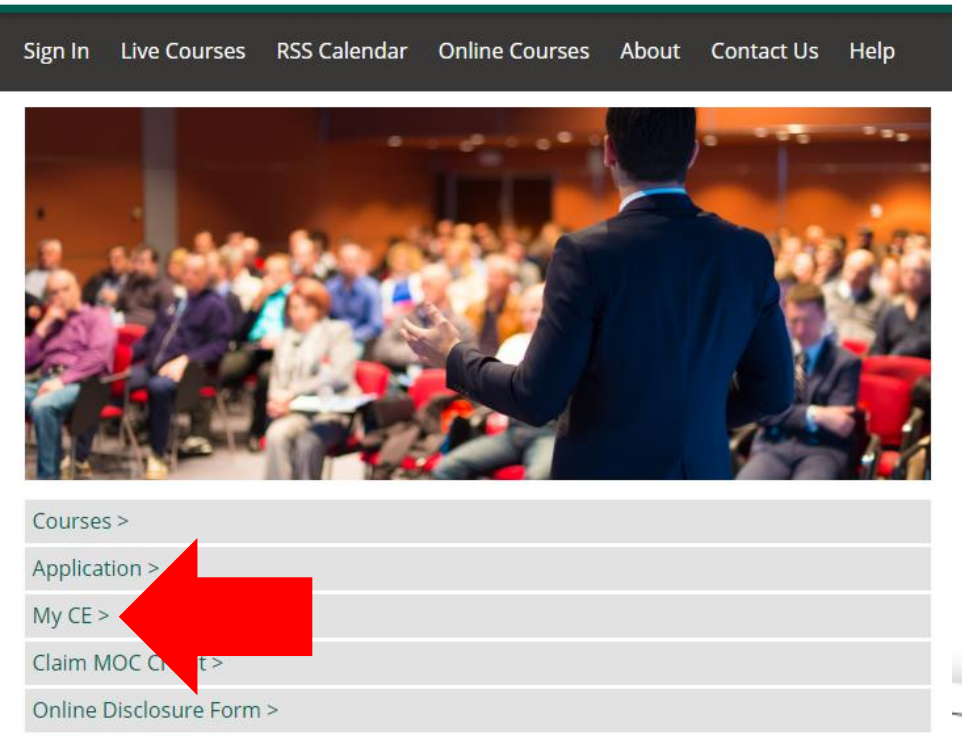

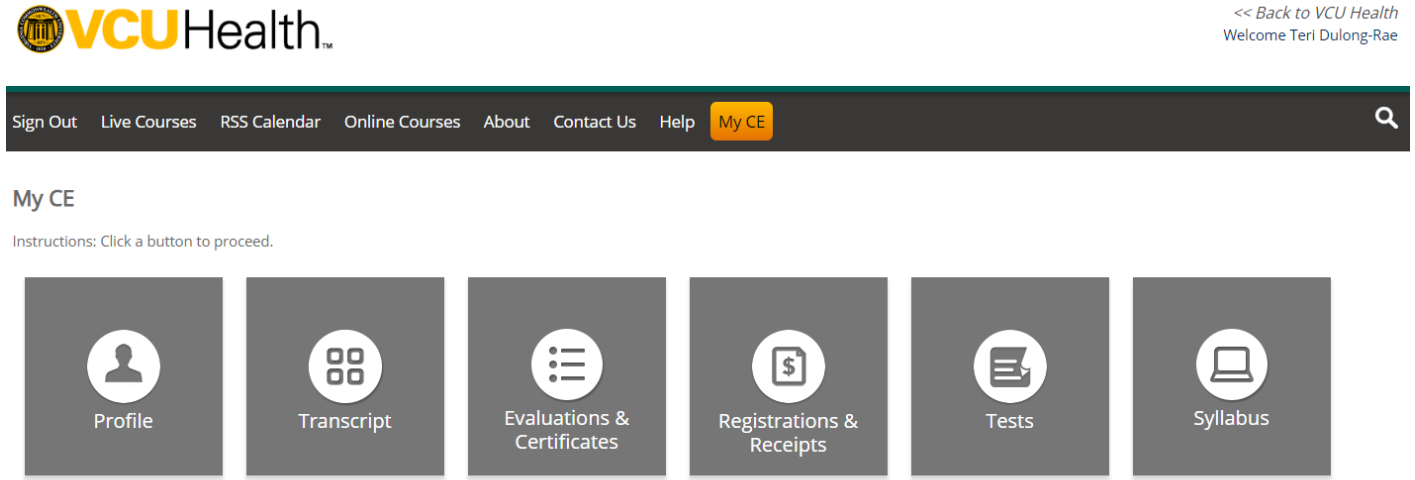

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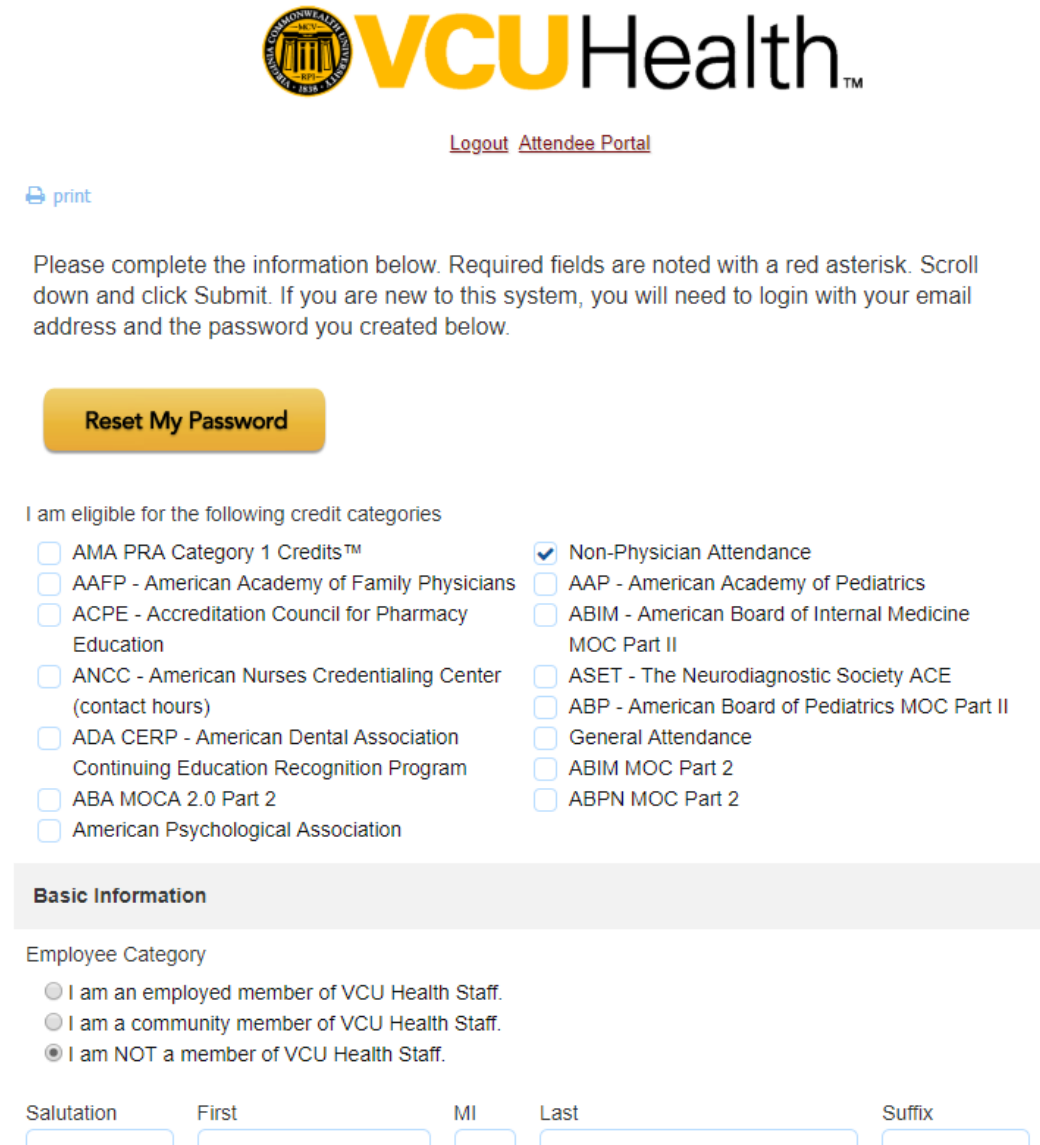

THANK YOU!

We hope to see you at our next ECHO

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RESEARCH ARTICLE

WILEY International Journal of Geriatric Psychiatry

The Oslo Study of Clonidine in Elderly Patients with Delirium; LUCID: a randomised placebo-controlled trial

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Objectives: The aim of this double-blinded randomised placebo-controlled trial was to investigate the efficacy of clonidine for delirium in medical inpatients greater than 65 years.

Methods: Acutely admitted medical patients greater than 65 years with delirium or subsyndromal delirium were eligible for inclusion. Included patients were given a loading dose of either placebo or clonidine; 75 μg every third hour up to a maximum of four doses to reach steady state and further 75 μg twice daily until delirium free for 2 days, discharge or a maximum of 7 days of treatment. The primary endpoint was the trajectory of the Memorial Delirium Assessment Scale (MDAS) for the 7 days of treatment. Presence of delirium according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria and severity measured by MDAS were assessed daily until discharge or a maximum of 7 days after end of treatment.

Results: Because of slower enrolment than anticipated, the study was halted early. Ten patients in each group were studied. The low recruitment rate was mainly due to the presence of multiple patient exclusion criteria for patient safety. There was no significant difference between the treatment group in the primary endpoint comparing the trajectory of MDAS for the 7 days of treatment using mixed linear models with log transformation, (P = .60). The treatment group did not have increased adverse effects.

Conclusions: No effect of clonidine for delirium was found, although the study was under powered. Further studies in less frail populations are now required.

KEYWORDS

delirium treatment, clonidine, RCT

1 | BACKGROUND

Delirium is an acute disturbance in attention, awareness, and cognition triggered mainly by acute medical disorders, trauma, surgery, or drugs. It affects at least 20% of hospitalised patients[1] and is associated with poor outcomes.[2] The pathogenesis is poorly understood, but one hypothesis is that delirium may in part result from exaggerated and/or prolonged stress responses.[3] No validated pharmacological treatment options exist,[4,5] but still medications are widely, although variably, used.[6,7]

Geriatric populations are poorly represented in drug trials,[8] despite their being the bulk of patients in clinical medicine. Ageism is a

*Karen R. Hov and Bjørn Erik Neerland shared first authorship

possible cause, but there are likely also other factors including heterogeneity because of different stages of aging, comorbidities, and polypharmacy. The lack of evidence informing medical decisions in older patients is a major challenge.

Dexmedetomidine is a parenterally administered alpha-2-adrenergic receptor agonist, which attenuates sympathetic nervous system activity[9] and shows promise as treatment of delirium in intensive care units (ICU),[10-15] and dexmedetomidine is now in clinical use for delirium in ICUs.[16] However, the vast majority of patients with delirium are outside of ICUs, where dexmedetomidine use is not feasible. An alternative agent could be orally administered clonidine. This drug has very similar pharmacological properties to dexmedetomidine[17] but lower alpha-2-adrenergic selectivity.[18] Clonidine in delirium is little studied, but a pilot study showed that the use of clonidine infusion during the weaning period after surgery for type-A aortic dissection might reduce the severity of delirium.[19]

The Oslo Study of Clonidine in Elderly Patients with Delirium (LUCID) aimed to investigate the potential superiority of clonidine vs placebo in decreasing delirium severity and duration in geriatric medical patients.[20] The primary endpoint was the trajectory of delirium severity over time (measured by Memorial Delirium Assessment Scale [MDAS]).

Key points

- This randomised placebo-controlled study aimed to investigate the effect of clonidine for delirium in geriatric medical patients.
- More than 4000 eligible patients were screened for inclusion.
- Ten patients in each group were studied.
- No effect of clonidine for delirium was found, although the study was under powered.

2 | METHODS

LUCID is a randomised, placebo-controlled, double-blinded, parallel group study with 4-month prospective follow-up.[20] Patients were recruited at the Oslo University Hospital, Oslo, Norway between April 2014 and February 2017. Independent data monitoring was performed. Acutely admitted medical patients greater than 65 years with delirium or subsyndromal delirium were eligible for inclusion. Included patients were randomised to treatment with oral clonidine or placebo for a maximum of 7 days. The goal was to include 100 patients, but according to the protocol, pharmacological analysis of clonidine and safety of the treatment would be assessed in the first 20 patients. As it turned out that inclusion rates were much lower than anticipated (for details on recruitment rates, see Results section and Figure 1), the principal investigator (T.B.W.) and study physicians (B.E.N. and K.R.H.) decided against further inclusion, and the study was halted. This paper presents the results of these 20 patients.

2.1 | Screening and inclusion

The main goal of the screening process was to find patients who fulfilled the selection criteria (see Table 1). Initially, all patients in the acute geriatrics ward were screened with a combination of the Single Question in Delirium (SQiD)[21] combined with two simple attention tests (reciting the days of the week and months of the year backwards). If any of these tests were positive, if the patient was drowsy or if the nurse and/or the treating physician for any other reason suspected delirium, formal ascertainment of delirium or subsyndromal delirium was performed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria.

Because of low inclusion rates, the screening sites were expanded from January 2015 to all patients greater than 65 years from the other medical wards. The screening was adjusted to initial information from staff and charts of any signs of delirium (ie, change in mental state, drowsiness/change in arousal, or other symptoms associated with delirium) or any knowledge of exclusion criteria present. If there were no known exclusion criteria and the patient was described to have symptoms suggestive of delirium or being at moderate to high risk of delirium development, the investigators (B.E.N. and K.R.H.) performed delirium diagnostic tests according to DSM-5 criteria as previously published.[20]

Due to the complexity of assessing both the inclusion and strict exclusion criteria, the ethics committee judged that the screening could be performed prior to consent, on condition that as soon as any positive exclusion criteria were found, no further confidential patient information was obtained.

2.2 | Randomisation and blinding

The block randomisation was based on computer-generated random numbers and was carried out by a statistician (E.S.). The randomisation schedule was distributed to the producer of the study medication, and capsules made accordingly. The randomisation was initially stratified with respect to whether or not the patient was admitted from a nursing home, in order to balance the groups with respect to pre-admission cognitive decline, an important prognostic factor. However, as the inclusion rate was slow and only two patients from nursing homes were eligible, to assist in reaching recruitment of the first 20 patients, the stratification was cancelled. This was a double-blinded study where the study physicians (B.E.N. and K.R.H.) who evaluated the primary endpoint (delirium), the patients, and the treating physicians all were blind to whether the patient is allocated to clonidine or placebo.

2.3 | Intervention

The study drug was produced and labelled by "Kragerø tablettproduksjon A/S," and each capsule (CAPSUGEL) contained either 75 μg Catapresan (clonidine hydrochloride) or placebo. After inclusion

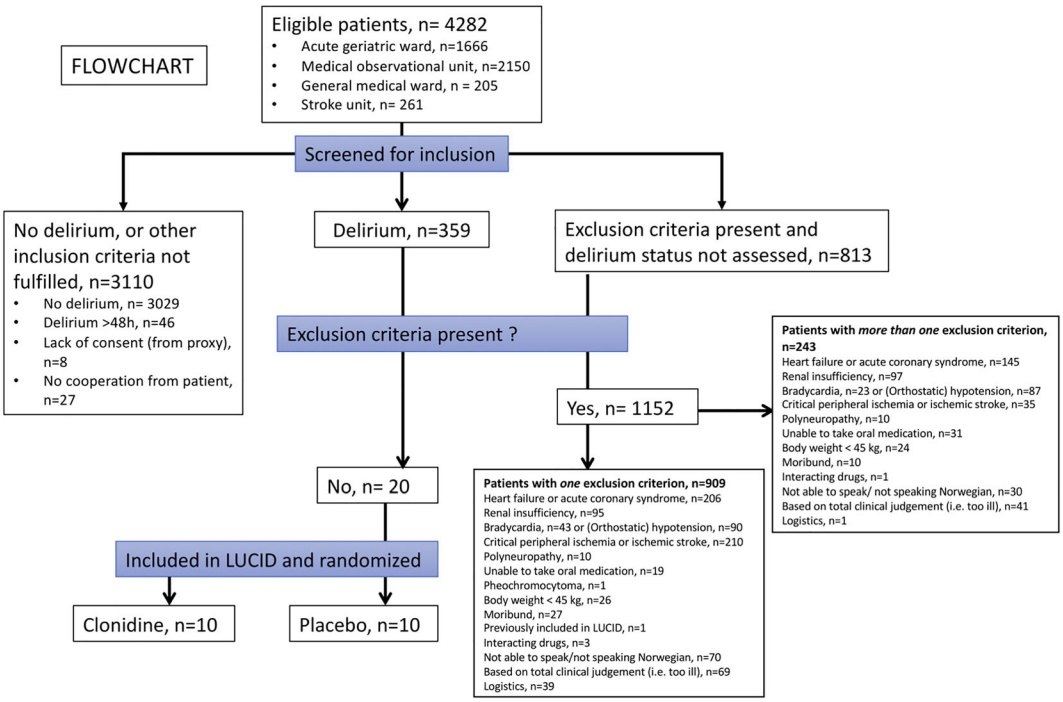

FIGURE 1 Flow chart of study screening, inclusions and exclusions [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Selection criteria

Inclusion criteria
• Patient >65 years old admitted to an acute medical ward
• Delirium or subsyndromal delirium within the last 48 h
• Signed informed consent from patient or relatives and expected cooperation of the patients for the treatment and follow-up must be obtained and documented
Exclusion criteria
• Symptomatic bradycardia, bradycardia due to sick-sinus-syndrome, second- or third-degree AV block (if not treated with pacemaker) or any other reason causing HR <50 bpm at time of inclusion
• Symptomatic hypotension or orthostatic hypotension, or a systolic blood pressure <120 mmHg at the time of inclusion
• Ischemic stroke within the last 3 mo or critical peripheral ischemia
• Acute coronary syndrome, unstable or severe coronary heart disease (symptoms at minimal physical activity; NYHA 3 and 4), and moderate to severe heart failure (NYHA 3 and 4). (Acute coronary syndrome is defined according to international guidelines)
• A diagnosis of polyneuropathy, phaeochromocytoma, or renal insufficiency (estimated GFR <30 mL/min according to the MDRD formula)
• Body weight <45 kg
• Considered as moribund on admission
• Unable to take oral medications
• Current use of tricyclic antidepressants, monoamine reuptake inhibitors, or ciclosporin
• Previously included in this study
• Adverse reactions to clonidine or excipients (lactose, saccharose)
• Not speaking or reading Norwegian
• Any other condition as evaluated by the treating physician
• Admitted to the intensive care unit

Abbreviations: AV, atrioventricular; HR, heart rate; NYHA, New York Heart Association; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

and randomisation to treatment group, patients were given a loading dose of one capsule every third hour up to a maximum of four doses. Further dosage was one capsule twice daily (8 AM and 8 PM) until delirium free for 2 days, discharge or a maximum of 7 days treatment, whichever came first. Blood pressure (BP) and heart rate (HR) were measured just before every dose for safety. The capsule was not given if the systolic BP (SBP) was less than 100 mmHg, or the HR is less than 50 beats per minute. Serum creatinine, blood glucose, ECG, a clinical assessment of hydration, and the Richmond Agitation Sedation Scale (RASS)[22] were scheduled for daily assessments for safety reasons. If

other medications were indicated for the treatment of delirium, the treating physician would prescribe this as was found necessarily, without interference from the study physicians. All patients received standard care following the ward routines.

2.4 | Outcomes

The objective was to explore the potential superiority of clonidine vs placebo in decreasing delirium duration and severity: measured by MDAS[23] in patients diagnosed with delirium or subsyndromal delirium (according to DSM-5[24]). The primary endpoint was the trajectory of delirium measured by MDAS over time. Several secondary endpoints were also assessed, as detailed in the published protocol.[20] With the early termination of the study and thus very low power for any analyses, all analyses were considered exploratory. The most important secondary endpoints were considered to be time to delirium resolution (both first resolution and final resolution), length of stay, and use of rescue medications.

2.5 | Data collection

All patients were assessed daily by a study physician for delirium diagnostics (according to DSM-5 criteria) and severity (MDAS). Scores were made based on a brief interview with tests of cognition, attention, and alertness including the digit span test (forward and backward), orientation, and delayed recall, the Observational Scale of Level of Arousal (OSLA),[25] and RASS.[22] Also information from staff, charts, and family members were obtained. All MDAS scores reflected the development from one MDAS score to the next (ie, the last 24 h). On some weekends, the on-call geriatrician would see the patients and perform the tests/interview before the DSM-5 and MDAS scores were filled out on Monday in cooperation with the study physicians and also using chart review from the weekend. Details of the diagnostic process have previously been published.[20]

Pre-existent functional and cognitive status were assessed by asking the patient's primary caregiver (the best available source) to complete questionnaires to assess the patient's functional and cognitive state 2 weeks prior to hospital admission. Functional status was assessed using the Barthel activities of daily living (ADL) Index[26] and the Nottingham Extended ADL Index (NEADL).[27] To ascertain prior long-term cognitive decline, we used the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[28] using a recently published cut-off of IQCODE greater than 3.82 for pre-existing cognitive impairment.[29] The severity and number of comorbidities were scored using the Cumulative Illness Rating Scale (CIRS).[30] The level of physiological disturbance was assessed by the Acute Physiology and Chronic Health Evaluation II (APACHE II).[31]

2.6 | Statistical methods

A statistical analysis plan (SAP) was developed (and published online at http://folk.uio.no/tbwyller/research.htm) prior to unblinding of the data. On the basis of power calculations and choice of statistical methods, the study aimed for 100 included patients; 100 patients would lead to approximately 80% power to detect a mean difference in MDAS score of 5, assuming SD = 9. The planned analysis using a mixed model would ensure a somewhat larger power. Therefore, when ending the study after 20 patients, it was not sufficiently powered to precisely estimate effects. It was thus not expected to be possible to draw conclusions about the primary outcome. However, the SAP stated that we would adhere to the original plan as described in the protocol but consider the analyses (of both primary and secondary endpoints) as exploratory. The statistician (E.S.) carried out the analyses blind to allocation.

TABLE 2 Characteristics of study participants, n = 20

Characteristic	Clonidine, n = 10	Placebo, n = 10
Age, years, median (range)	85 (73-94)	88 (66-95)
Female, n/N (%)	6/10 (60)	7/10 (70)
Body mass index, kg/m^2, median (range)	23 (19-29)	24 (17-28)
Creatinine at baseline, median (range)	78 (34-128)	88 (32-140)
Pre-existing cognitive impairment (IQCODE $\geq$ 3.82), n/N (%)	5/9[†] (55)	6/10 (60)
Barthel ADL Index, median (range)	18 (10-20)	16 (5-20)
Independent in ADL[‡], n/N (%)	4/10 (40)	3/10 (30)
The Nottingham Extended ADL Index (NEADL), median (range)	33 (17-60)	28 (1-48)
Admitted from nursing home, n/N (%)	0/10	2/10 (20)
Acute Physiology and Chronic Health Evaluation II (APACHE II), median (range)	10 (8-16)	11 (7-19)
Cumulative Illness Rating Scale (CIRS), total score	17 (8-21)	18 (7-31)

Abbreviation: IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; ADL, activities of daily living.

[†]IQCODE missing in one patient,

[‡]Barthel Index score $\geq$19.

For comparison between the groups of the repeated measures of continuous variables (ie, MDAS and OSLA), we used mixed linear models.[32] Estimated slopes for each individual's trajectory were based on all available data, thus tolerating a few missing single time-point evaluations. Data regarding our primary endpoint were available from all patients, and the three patients who died during the hospital stay or shortly after discharge were also included in all analyses. There was no linear relationship between the MDAS (and OSLA) scores and time, and data were log transformed to better fit a linear model. For time to resolution of delirium and length of stay, the Kaplan Meier method and the logrank test were applied.

Statistical analyses were performed in SPSS Statistics version 22 and 24 (IBM, Armonk NY) and Prism v7 (GraphPad Software Inc, La Jolla, CA, USA).

2.7 | Ethics

The study was undertaken in accordance with the Declaration of Helsinki. The data and plasma samples were collected after informed consent from the patient and/or proxy (if patient was lacking capacity to consent due to delirium and/or dementia), as approved by the Regional Committee for Ethics in Medical and Health Research (South-East Norway) REK: 2013/525. Due to the importance of rapid inclusion, the proxy would give verbal consent (by phone) before inclusion to the study, and written consent was obtained as soon as possible afterwards. None of our 20 patients had capacity to consent to this study, so next of kin gave consent in all cases. Still, all patients were informed to the level of their capacity, and all tests were voluntary at all times. ClinicalTrials.gov NCT01956604. EudraCT Number: 2013-000815-26. Approved by The Norwegian Medicines Agency.

3 | RESULTS

3.1 | Screening and inclusion

Of 4282 inpatients screened, 4262 were ineligible (see flowchart, Figure 1). Out of these, 3110 were considered to have no delirium, or other inclusion criteria were not fulfilled, while 1152 patients had at least one exclusion criterion present (delirium status unknown in 813 of these). Twenty patients fulfilled the selection criteria and were included in LUCID between April 2014 and February 2017 and randomised to either clonidine (n = 10) or placebo (n = 10). No patients were lost or excluded after inclusion, and all 20 patients are included in our analyses. Median age was 86 years (range 66-95), and 13 (65%) were women. See Table 2 for background characteristics.

3.2 | Primary endpoint

Comparing the trajectory of MDAS for the 7 days of treatment using mixed linear models with log transformation, there was no statistically significant difference in the reduction of log (MDAS score) over time (P = .60) between the two groups. See Figure 2 for all individual MDAS trajectories in both treatment groups.

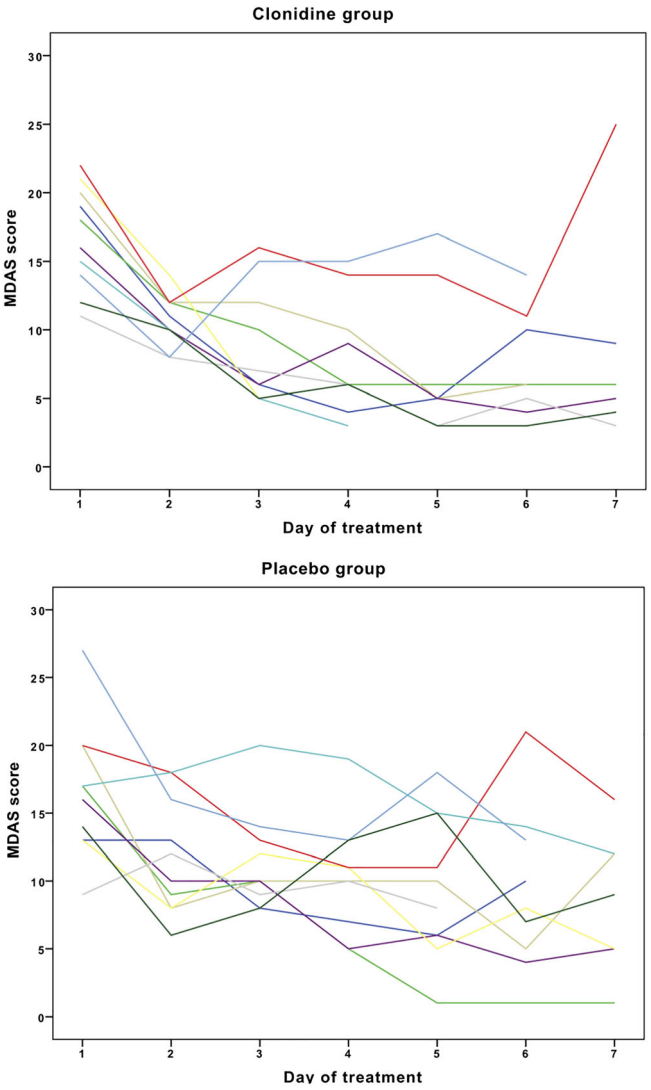

FIGURE 2 The figure shows the individual trajectories of the individual Memorial Delirium Assessment Scale (MDAS) scores in the clonidine and placebo groups (upper and lower panels of the figure, respectively) [Colour figure can be viewed at wileyonlinelibrary.com]

3.3 | Secondary endpoints

There was no difference in time to first delirium resolution (ie, first day without delirium) between the groups (placebo group median 3.0 [95% CI 1.8-4.2] vs clonidine group median 3.0 [95% CI 2.1-4.0]), P = 0.59. There was also no significant difference in time to final delirium resolution (ie, first delirium free day without known consecutive delirium episodes); placebo group median 8.0 (95% CI 4.7-11.3) vs clonidine group median 5.0 (3.8-6.3), P = 0.40. Median length of stay was 7 days in both groups. For the delirium element arousal (measured with OSLA), the trajectories were similar to those of MDAS, and using mixed linear models, there was no significant difference between the groups (P = 0.37). The use of rescue medications is described in Table 3. As the study was halted early and no effect of clonidine could be detected on primary or main secondary outcomes, no exploration of data from the 4-month follow-up was performed.

TABLE 3 Use of rescue medication

Rescue Medication	Clonidine, n = 10	Placebo, n = 10
Prticipants who received rescue medication, n/N (%)	4/10 (40)	6/10 (60)
No rescue medications	6 (60)	4 (40)
Only sedatives (benzodiazepines and/or clomethiazole)	2 (20)	4 (40)
Only antipsychotics	0	0
Both sedatives and antipsychotics	2 (20%)	2 (20%)

3.4 | Safety, haemodynamic responses, and plasma concentrations

Plasma concentrations of clonidine and haemodynamic responses were measured and have been reported.[33] Briefly, plasma concentration levels were within the higher end of our target range, suggesting that loading doses are not necessary to achieve adequate early therapeutic effect. There was extensive individual BP and HR variation in both the clonidine and placebo groups, but there were no episodes of clinically significant hypotension or bradycardia in any patient in any group.

3.5 | Other events

On the fifth day of treatment, one patient in the clonidine group developed a hypertensive pulmonary oedema (SBP 238 mmHg). According to the study protocol, the study drug was halted, and a report of a possible Serious Unexpected Serious Adverse Reaction (SUSAR) was filed routinely to The Norwegian Medicines Agency. The patient died two weeks later. The acute hypertensive episode was treated effectively, and hypertension was not a reoccurring problem when the patient's status deteriorated further. After careful consideration, it was assessed that the episode was not related to the study drug nor that withdrawing clonidine aggravated the situation. In the placebo group, two patients died during the hospital stay or shortly after discharge.

Regarding minor side effects, two patients in both the clonidine and the placebo group reported dry mouth. One patient in the clonidine group experienced a fall during the treatment, but it was not considered related to hypotension (there was no orthostatic hypotension found in this patient). There were no significant episodes of sedation or alterations in blood glucose in either treatment group.

4 | DISCUSSION

Enrollment in LUCID was more difficult than anticipated. The low recruitment rate was mainly due to a combination of a frail target population and the presence of rigorous exclusion criteria. After the 20th patient was included, an assessment by the principal investigator (T.B. W.) and study physicians (B.E.N. and K.R.H.) decided against further inclusion as the time frame to achieve 100 patients was clearly unrealistic. Additionally, with such a small percentage of eligible patients included, the results would not be considered generalizable to the population in question. It was, however, in line with the protocol to halt the trial after the first 20 patients to evaluate feasibility. The following results are considered exploratory.

There were no statistically significant differences between the treatment groups with regard to our primary endpoint (MDAS trajectory) or secondary endpoints (eg, time to delirium resolution). Because of the low power, however, the results do not imply that clonidine does not have a beneficial effect on delirium. Likewise, there is a possibility that clonidine is not effective. On the basis of our exploratory analysis, there is no trend in either direction. Thus, the study is inconclusive, and the main finding is that strict exclusion and inclusion criteria made the present study infeasible. Further evaluation of this drug in a more robust population and with altered exclusion and inclusion criteria is warranted.

As seen in the flowchart (Figure 1), there were many delirious patients, but the ineligibility rates were very high. Most commonly, exclusion criteria for patient safety were present, and several patients had more than one exclusion criterion. The ethics committee accepted that the screening could be performed prior to consent, provided that once it was recognised that a patient was not eligible for the study, no further confidential patient information could be obtained. Due to this, many patients being registered with one exclusion criterion might in fact have more than one criterion present. For the same reason, delirium status was unfortunately not assessed in all patients and is unknown for a large proportion of the patients not included. Our impression is that many of the patients who had to be excluded had in fact delirium. Even though no evidence exists regarding the need for dose adjustments based on renal dysfunction, such adjustment seems reasonable based on the renal elimination.[34]

The major recruiting problem was the high prevalence of exclusion criteria in our frail and multimorbid population. One solution could have been to adjust the exclusion criteria, but since the benefit of clonidine for delirium treatment is uncertain, it was not acceptable to take higher risks in order to improve recruitment. A lower dosage of clonidine could have been considered, but certain exclusion criteria were considered necessary for any dosage of clonidine. Moreover, lower dosages might not be expected to reveal any beneficial effect. So for future studies of clonidine for delirium, trials in more robust populations are probably more realistic; and feasibility studies in the chosen population would be helpful. Still, as the potential beneficial effect of clonidine in delirious patients is unknown, focus in such trials should be on feasibility and safety.

A strength of our study was the structured and comprehensive delirium diagnostics performed according to a published algorithm. However, this approach is work demanding. Balancing the difficult task of delirium diagnostics with what is doable must be considered for future studies. As inclusion rates are often low in delirium treatment trials, multicentre studies have often been more successful. The use of delirium detection tools already established in the wards might be feasible in such studies. Another practical issue is related to the need for informed consent. Our procedure with proxy consent by phone worked very well.

The overall impression from the clinical assessments was not that the exclusion criteria were too strict but rather that the population at hand was indeed very frail and multimorbid, as illustrated by a 15% short-term mortality. Thus, any introduction of new drugs needs to be well indicated and carefully considered regarding potential side effects.

The study included a real life control group in the assessment of hemodynamic changes. The patients were monitored very closely; safety and best care of the patients were a priority. As expected in this population, some evaluations are missing. Over all, because of strict exclusion criteria, the external validity of our findings is potentially limited.

In conclusion, enrollment in LUCID was considerable more difficult than anticipated, and the low inclusion rate was mainly because of the frail population and the presence of exclusion criteria for patient safety. The study was halted after 20 patients had been included, and no statistically significant difference between the clonidine and placebo was detected. It is however important to emphasize that this apparent lack of effect should not be misinterpreted as evidence of no therapeutic potential for clonidine in delirium. Further studies of clonidine for delirium are called for but should be performed in a more robust patient population.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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