VCU Palliative Care ECHO*

August 8, 2019

Methadone Use in Palliative Care

*ECHO: Extension of Community Healthcare Outcomes

Continuing Medical Education

August 8, 2019| 12:00 PM | teleECHO Conference

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Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Continuing Nursing Education: 1.5 CE Contact Hours

VCUHealth is approved as a provider of continuing nursing education by the Virginia Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

Disclosures

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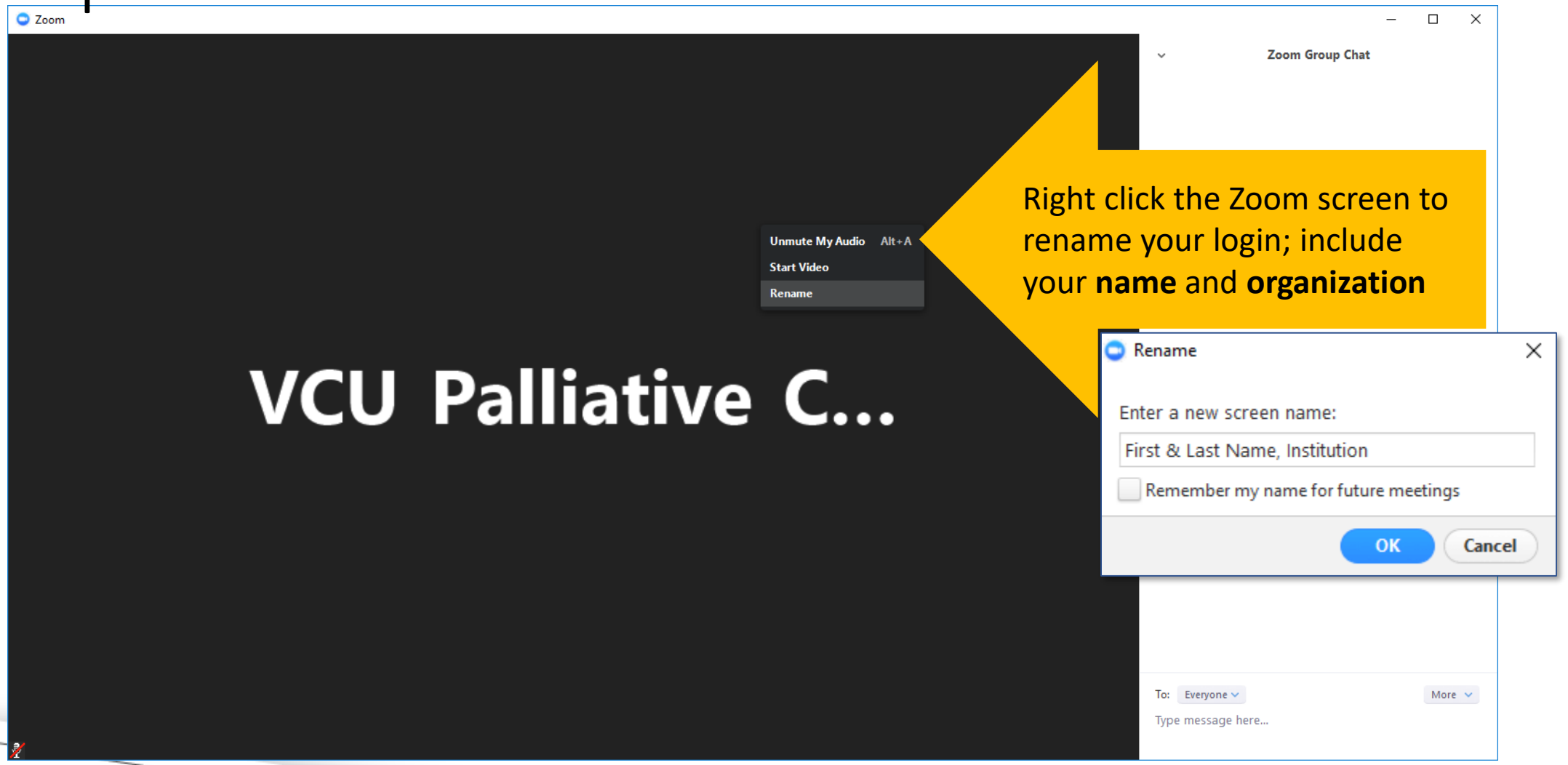
The following Planning Committee and Presenting Faculty Members report having no relevant financial relationships:

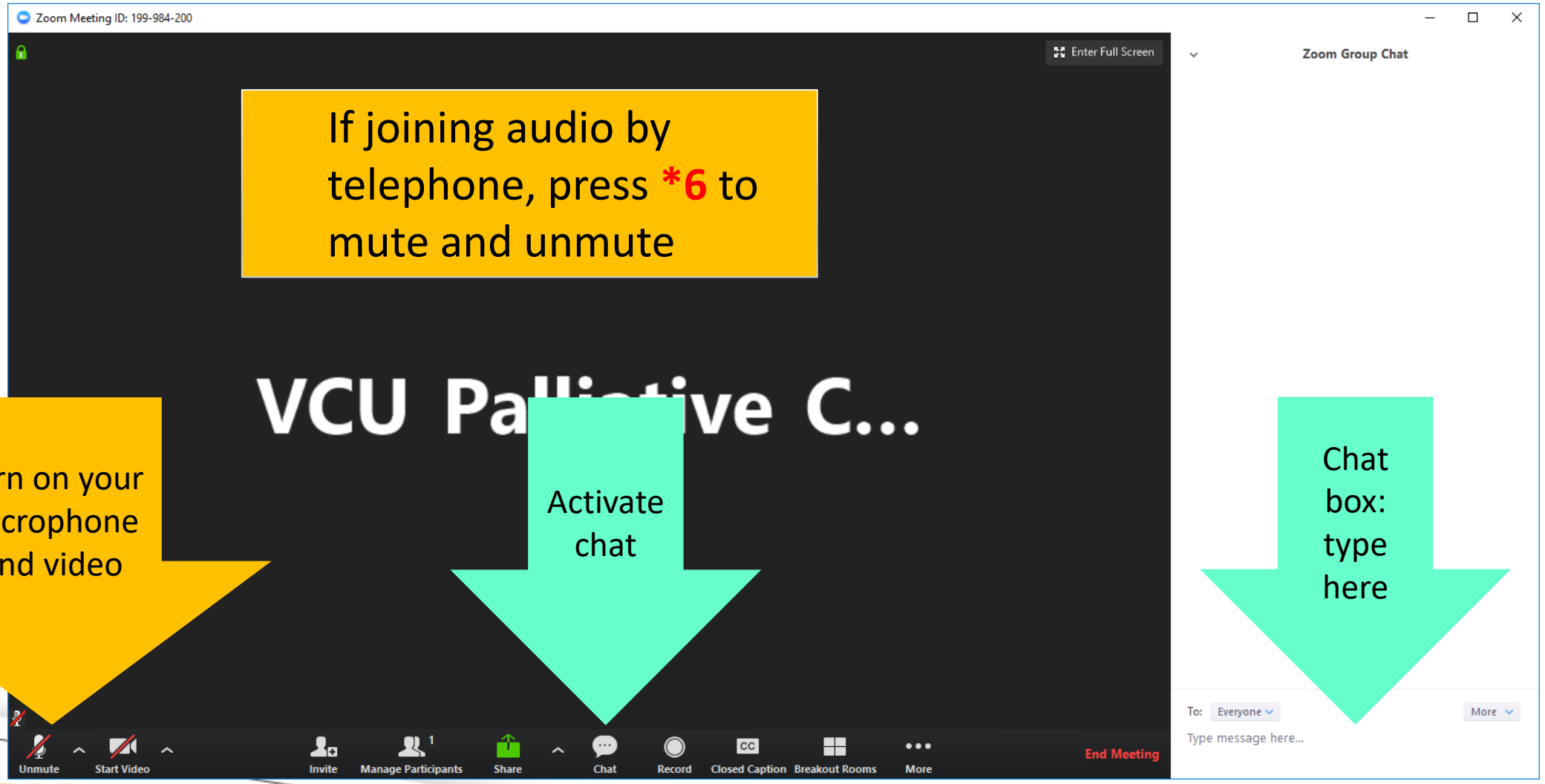
Egidio Del Fabbro, MD
Danielle Noreika, MD

No commercial or in-kind support was provided for this activity

Helpful Reminders



Helpful Reminders



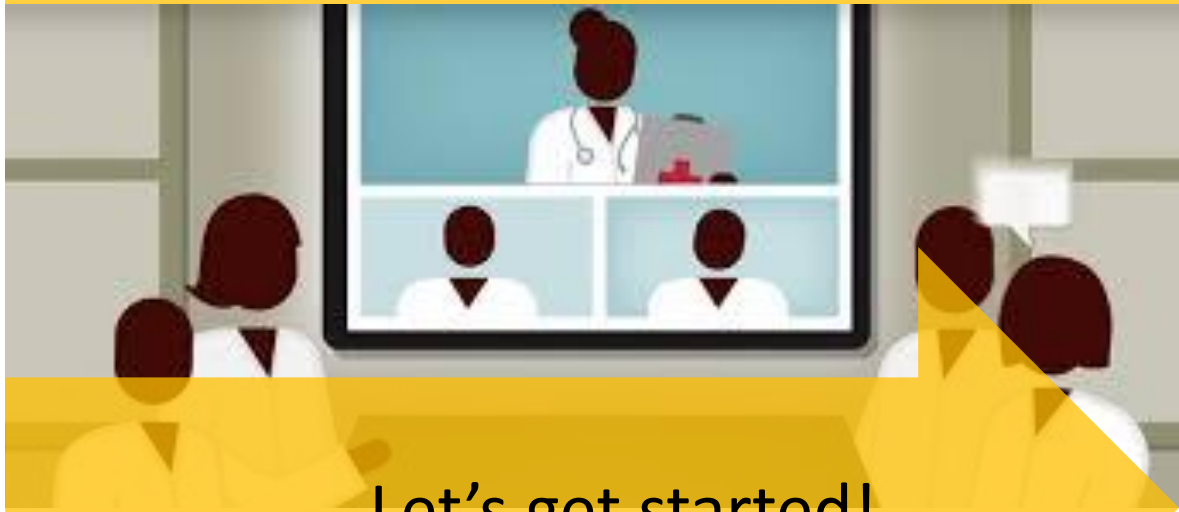
What to Expect

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

Methadone

Abused or Under-Used?

Egidio Del Fabbro, MD

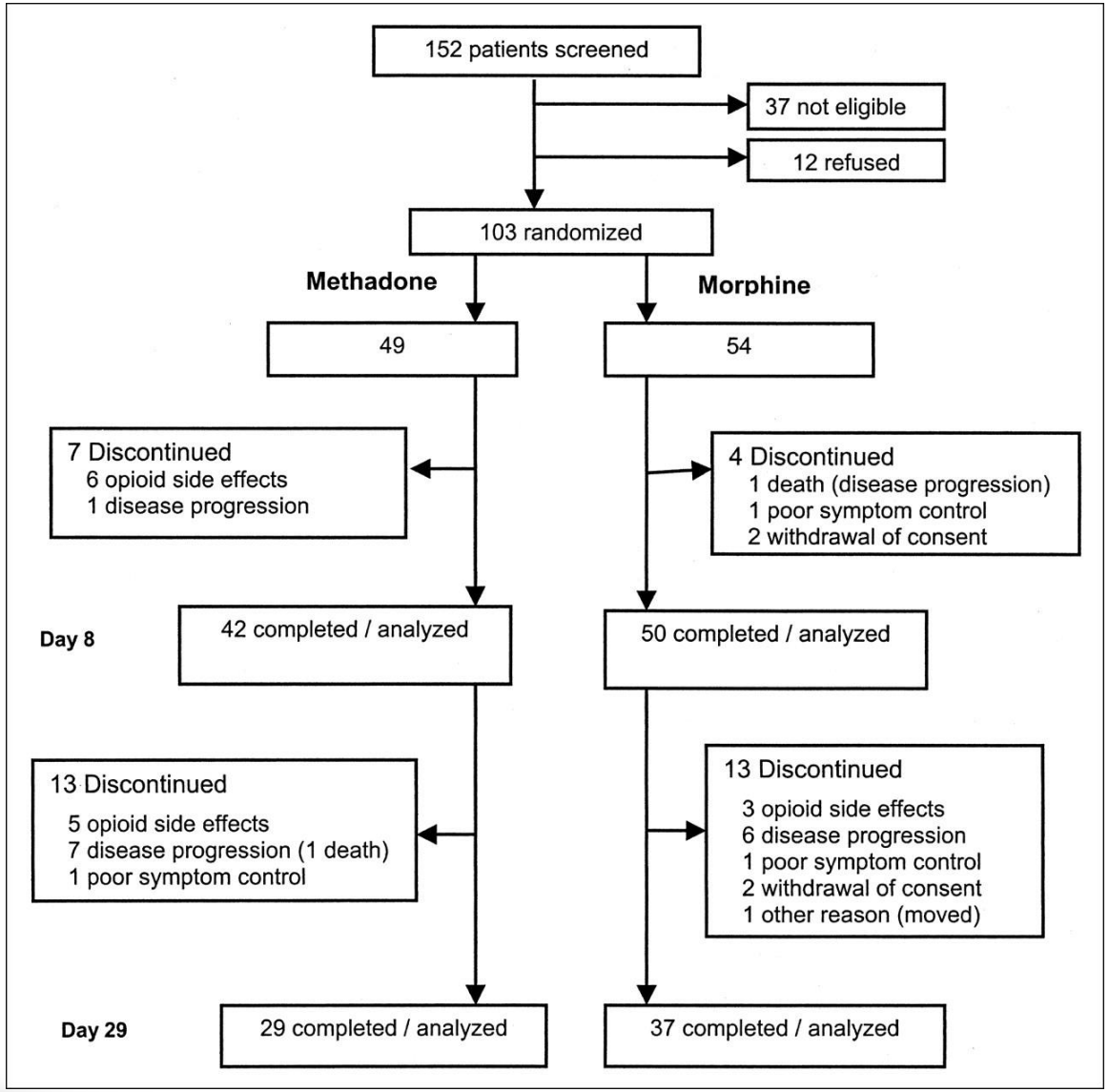
Properties

- High affinity for mu and delta receptors
- NMDA receptor antagonist
- Large inter-individual variation in pharmacokinetics
- Long ,variable half life can be more sedating
- Equi-analgesic variation from 1:1 to 10 :1 for morphine
- Drug Interactions
- Prolongs QTc

Convenient and effective in the management of pain in patients with cancer

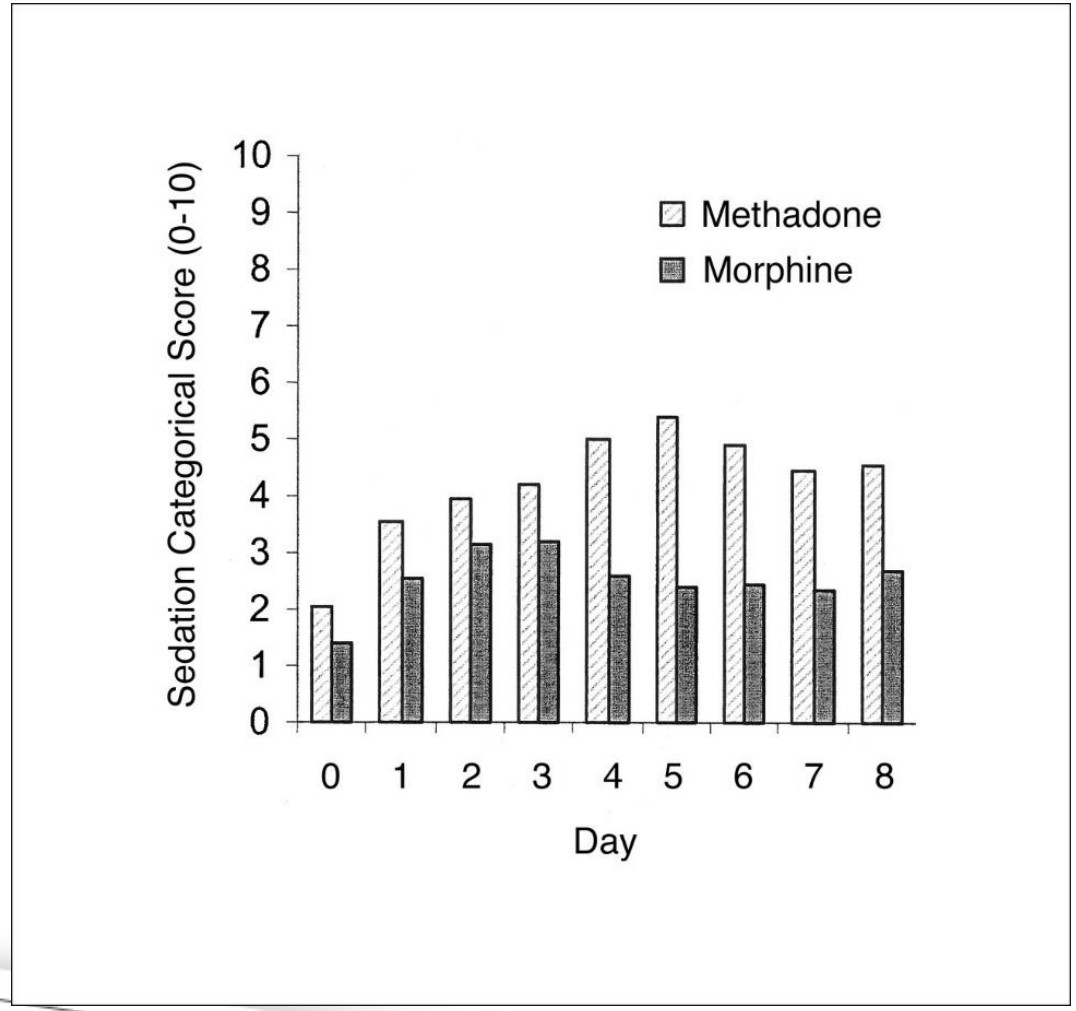
- Low cost
- Retrospective studies for neuropathic pain
- high oral bioavailability
- rapid onset of analgesic effect
- long half-life (resulting in less frequent dosing schedules)
- lack of active metabolites
- low rate of induction of tolerance
- Kidney failure and dialysis

Can methadone be used as first line therapy?



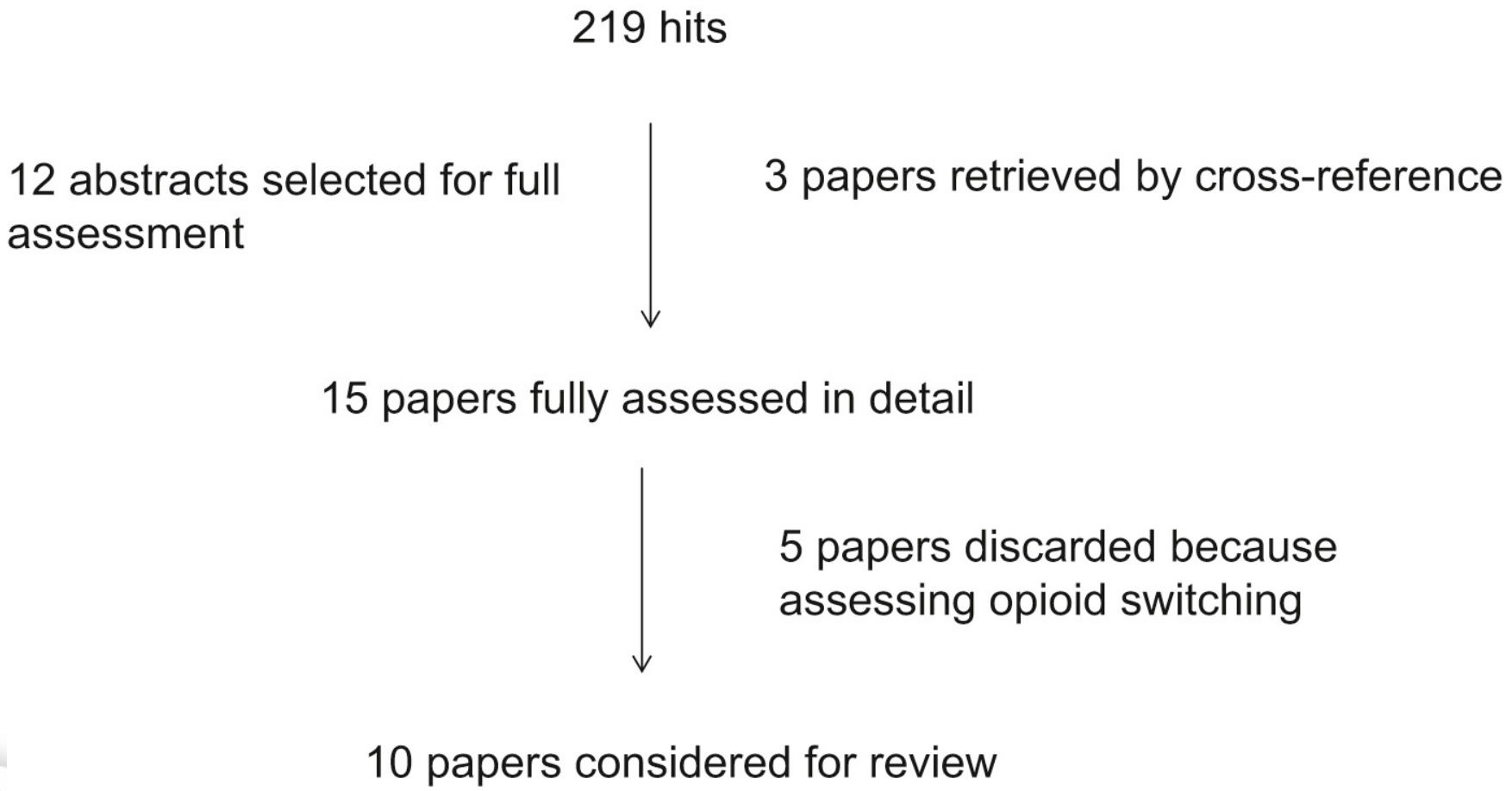
Bruera E, et al. *Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study.* J Clin Oncol. 2004 Jan 1;22(1):185-92.

Mean sedation scores for patients receiving methadone and morphine for baseline through day 8



Bruera E, et al. *Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study.* J Clin Oncol. 2004 Jan 1;22(1):185-92.

Methadone as a First-Line Opioid in Cancer Pain Management: A Systematic Review

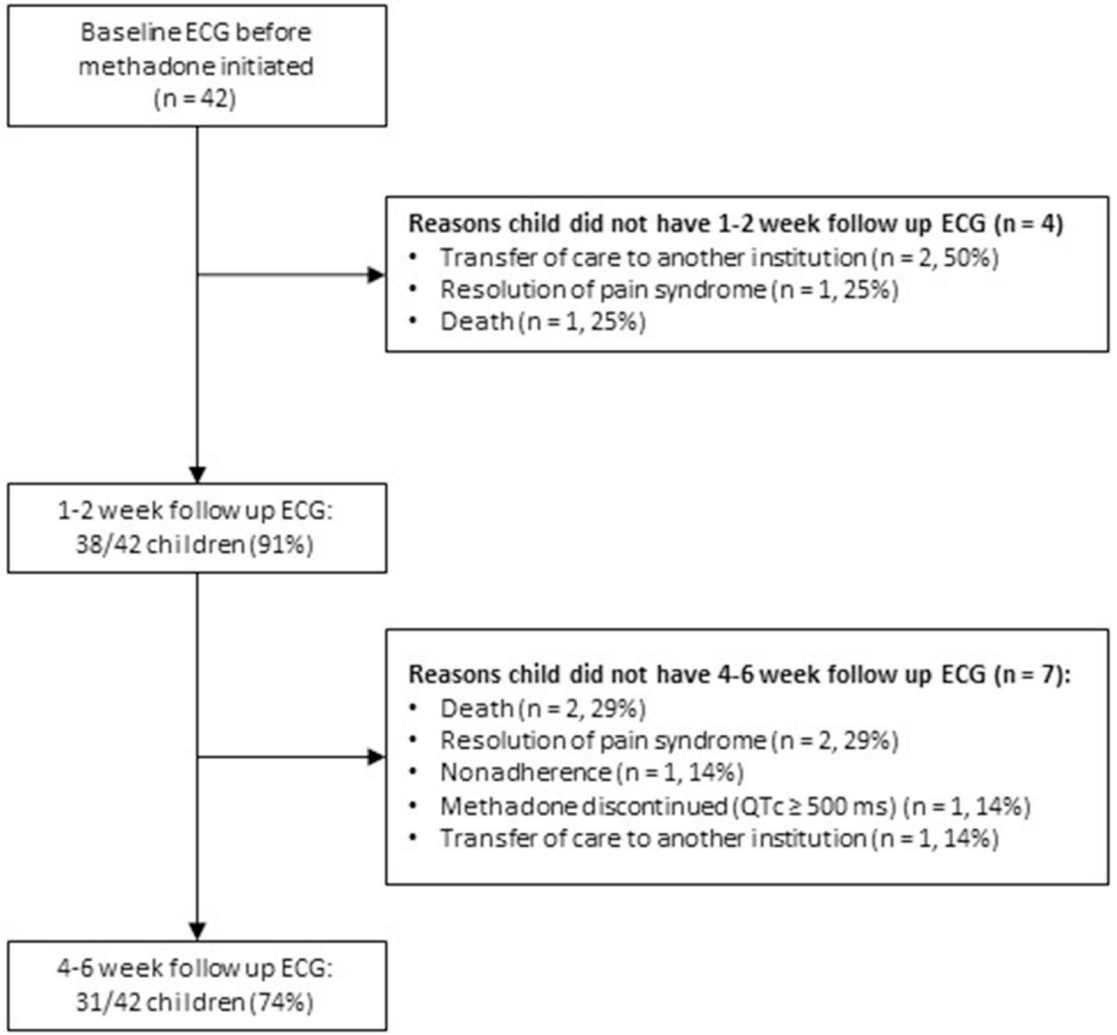


Mercadante S, Bruera E. Methadone as a First-Line Opioid in Cancer Pain Management: A Systematic Review. J Pain Symptom Manage. 2018 Mar;55(3):998-1003. doi: 10.1016/j.jpainsymman.2017.10.017.

Methadone

- Methadone doses seem to remain more stable in time with slow escalation indexes
- Methadone has been also initiated successfully as a first line drug in patients who were opioid naive

QTc Interval Prolongation in Pediatric and Young Adult Patients on Methadone for Cancer-Related Pain



Madden K, et al. J Pain Symptom Manage. 2019 Jun 11. pii: S0885-3924(19)30303-3. doi: 10.1016/j.jpainsymman.2019.05.021.

How to rotate over to methadone

Table 1

Summary of Main Methods of Rotation to Methadone

Rotation Method	Description
3DS	Day 1—30% of original opioid replaced with an equianalgesic dose of methadone given in three daily divided doses Days 2 and 3—dose of methadone is increased by 30% and dose of original opioid reduced by 30% each day
RC stop and go	Original opioid is discontinued Daily methadone dose is calculated according to evidence-based conversion ratios and given in three regular divided daily doses Regular methadone dose titrated to achieve effective analgesia It has been argued that a higher priming dose of methadone (20%–30% higher than as calculated using published conversion ratios) may be required initially[30]
AL stop and go	Original opioid is discontinued A fixed dose of methadone that is 1/10th of the actual or calculated morphine equivalent oral daily dose up to a maximum of 30 mg is calculated The fixed dose is taken orally as required but not more frequently than three hourly On Day 6, the methadone requirement of the previous two days is noted and converted into a regular q12-hourly regime
German model	Original opioid is discontinued Methadone is prescribed at a dose of 5–10 mg orally every four hours and every one hour as needed On Days 2–3, the dose of methadone is titrated up by 30% until analgesia is achieved. After 72 hours, methadone dosing is changed to an every eight-hour and every three-hour as-needed regime as the same dose as prescribed on Days 2–3. Methadone dose is titrated up until analgesia is achieved
Outpatient titration	Original opioid continued at same dose Methadone commenced at 5 mg orally every four hours and increased by 5 mg/dose every three days until improved analgesia is noted Original opioid then reduced by one-third, and the methadone dose increased according to breakthrough requirements. The original opioid dose is reduced, and the methadone dose increased accordingly over a variable period

3DS = three-day switch; RC = rapid conversion; AL = ad libitum.

McLean, Twomey. J Pain Symtom Manage. 2015

Methods of Rotation from Another Strong Opioid to Methadone for the Management of Cancer Pain: A Systematic Review of the Available Evidence

- Evidence mainly from uncontrolled observational studies, making causality difficult to establish. Studies heterogeneous in methodology and outcome measures.
- There was a trend toward excess AEs using the RC method, in comparison to the AL and 3DS methods
- The methodological quality of the AL studies was low. A direct comparison of AL and 3DS methods would be informative.

McLean, Twomey. J Pain Symptom Manage. 2015

Expert White Paper on Methadone

Table 1

Patient Selection for Methadone Therapy

Potentially Appropriate Candidates for Methadone in HPC	Potentially Inappropriate Candidates for Methadone in HPC
• Moderate to severe pain (especially as a second-line opioid choice) • Pain refractory to other opioids • True phenanthrene (e.g., morphine) allergy • Significant renal impairment • Need for a long-acting opioid (particularly as an oral concentrate solution) • High opioid tolerance • Poorly controlled opioid-induced adverse effects with other opioids • History of dysphagia, inability to swallow, or feeding tube placement	• Patient lives alone, or poor cognitive functioning, without a responsible caregiver • Lack of knowledgeable practitioner on transfer • History of opioid/medication nonadherence • History of substance misuse or SUD (patient or family) • Multiple risk factors for methadone toxicity (e.g., clinical instability, multiple transitions in care, history of transplant) • History of QTc prolongation or at high risk for such • Prognosis less than projected time to methadone steady state (i.e., five to seven days) • Obstructive or central sleep apnea • Determined to be medically inappropriate after risk assessment (see next section)

HPC = hospice and palliative care.

McPherson, et al. Safe and Appropriate Use of Methadone in Hospice and Palliative Care: Expert Consensus White Paper. J Pain Symptom Manage. 2019 Mar;57(3):635-645.e4. doi: 10.1016/j.jpainsymman.2018.12.001.

Expert White Paper on Methadone

Table 2

Precautions and Contraindications to Methadone Therapy

Risk Factor	Precaution	Contraindication	Applies to all Opioid Including Methadone	Applies Specifically to Methadone
Impaired liver function or liver failure	x		x	
Acute or unstable liver injury/damage	x (avoid use)		x (precaution)	x (contraindicated)
Active illicit drug use or misuse (cocaine, amphetamines, ephedrine, heroin, opioids)		x	x (overall risk)	x (additional risk of QTc prolongation)
Congenital QTc syndrome (patient or family)		x	(buprenorphine and methadone only)	x
Structural heart disease (congenital heart defects, history of endocarditis, or heart failure)[a]	x			x
Electrolyte abnormalities, or at risk for same (e.g., hypokalemia, hypomagnesemia)	x			x
Disordered breathing syndromes	x		x	
Paralytic ileus		x	x	

[a]See ECG monitoring section.

McPherson, et al. Safe and Appropriate Use of Methadone in Hospice and Palliative Care: Expert Consensus White Paper. J Pain Symptom Manage. 2019 Mar;57(3):635-645.e4. doi: 10.1016/j.jpainsymman.2018.12.001.

Expert White Paper on Methadone

Table 3
ECG Monitoring and Action Steps

Level of Vigilance	Goals of Care	Methadone Role	Baseline ECG	Follow-Up ECG
High	Curative, life-prolonging	First line	Obtain baseline ECG: • Positive risk factors[a] • Prior QTc >450 ms • History suggestive of prior ventricular arrhythmia Consider baseline ECG: • No risk factors • QTc <450 ms in the previous year Recommendation: • QTc >500 ms—do not use methadone • QTc 450–499 ms—consider alternate opioid (or correct reversible causes of QTc prolongation and reassess)	Obtain ECG within two to four weeks: • Positive risk factors • Prior ECG with QTc > 450 ms • History of syncope Obtain additional ECG: • TDD methadone reaches 30–40 mg • TDD methadone reaches 100 mg • New risk factors or signs/symptoms suggesting arrhythmia Recommendation: • QTc > 500 ms—switch to alternative opioid or reduce methadone dose • QTc 450–499 ms—consider switching to alternative opioid or reduce methadone dose
Moderate	Curative, life-prolonging	Second line	• Discuss risks and benefits with patient/family in light of goals of care	• Reinitiate discussion of risks/benefits if goals of care change
	Comfort measures only	First line	• Routine baseline ECG monitoring not recommended; may consider ECG depending on patient's risk status, wishes, and goals of care (e.g., curative) • Document informed consent if no ECG • If ECG obtained, follow recommendations above	• Routine follow-up ECG monitoring not recommended; may consider ECG depending on patient's risk status, wishes, and goals of care • Document informed consent if no ECG • If ECG obtained, follow recommendations above
Low	Comfort measures only	Second line	• No ECG unless compelling indication • If ECG obtained, follow recommendations above	• No ECG unless compelling indication • If ECG obtained, follow recommendations above

[a]Clinical risk assessment is always indicated and may alter recommendation for ECG monitoring. Risk factors include hypokalemia, hypomagnesemia, impaired liver function, structural heart disease (congenital heart defects, history of endocarditis, or heart failure), and genetic predisposition including patient or family history of congenital QTc syndrome, use of QTc-prolonging medications.[3]

McPherson, et al. Safe and Appropriate Use of Methadone in Hospice and Palliative Care: Expert Consensus White Paper. J Pain Symptom Manage. 2019 Mar;57(3):635-645.e4. doi: 10.1016/j.jpainsymman.2018.12.001.

Questions

Case Presentation

Referral from Oncology

- 59 year male with Multiple Myeloma
- LE numbness and burning pain
- Dorsum and plantar pain, worse after standing
- Cannot sleep more than 30 minutes at a time
- Taken off bortezemib because of painful sensory neuropathy
- No thalidomide Rx

Labs

- BUN=30 Creatinine=2.32
- Total Protein=5.5 Albumin =3.7 IgG elevated
- CBC normal except for mild thrombocytopenia
- Bone survey=moderate degenerative changes ,no lytic lesions
- EKG QTc=410

Management Trials

- Gabapentin 300mg bid
- 300mg t.i.d causes muscle twitching and jolts
- Duloxetine trial by oncology, alprazolam for insomnia
- wife observed personality changes, an increase in anxiety, and irrational thoughts
- Capsaicin and topical lidocaine ineffective

Initial Palliative Care Outpatient Visit

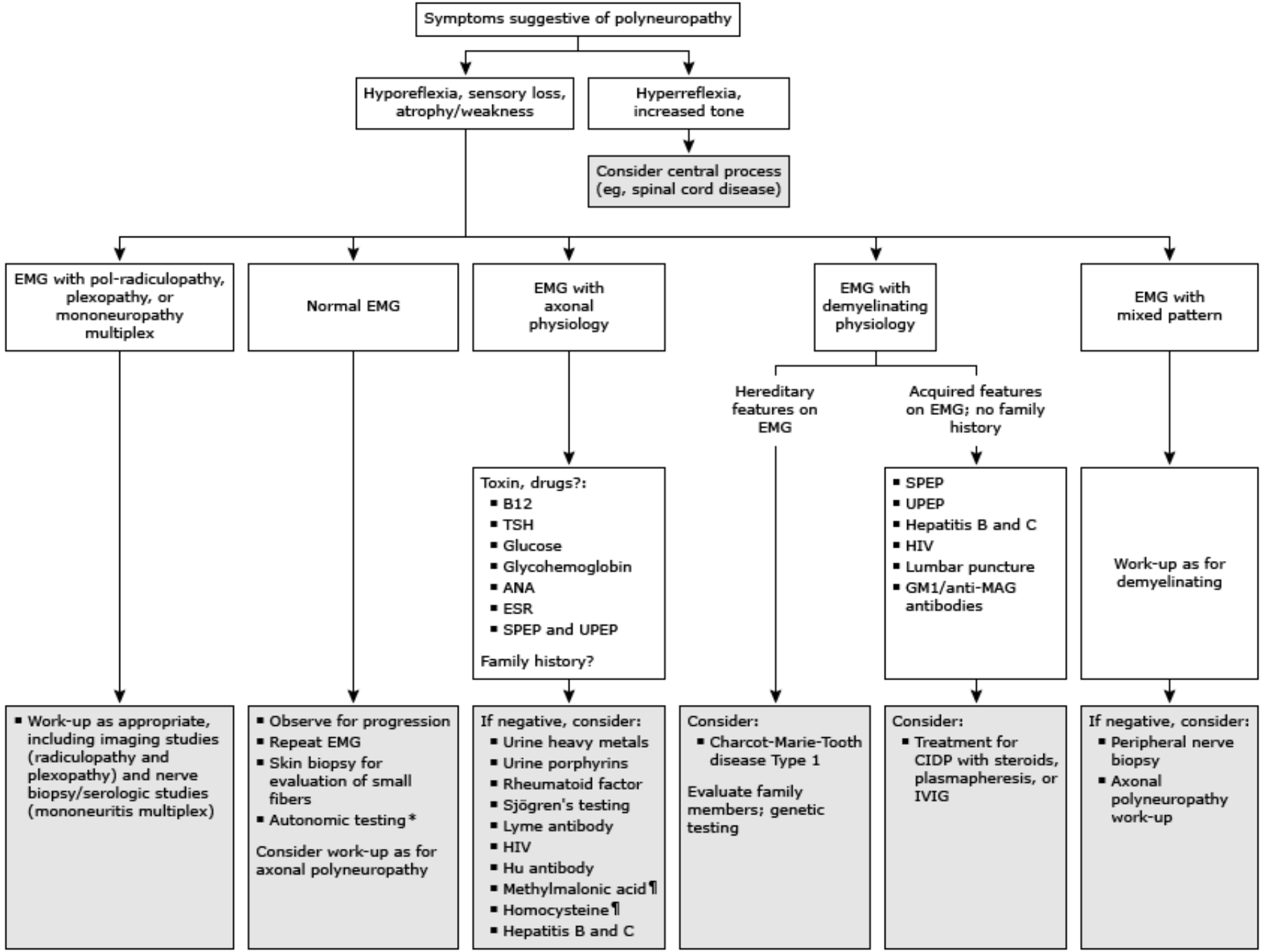
- Pain: 2/10.
- Fatigue: 4/10.
- Nausea: 0/10.
- Depression: 0/10.
- Anxiousness: 0/10.
- Drowsiness: 2/10.
- Appetite: 0/10.
- Wellbeing: 0/10.
- Shortness of breath: 0/10.
- Sleep: 2/10.

Add methadone 2.5mg q12h po ,discontinued benzo ,and follow-up 4 weeks later

- Pain: 1/10.
- Fatigue: 2/10.
- Nausea: 0/10.
- Depression: 0/10.
- Anxiousness: 0/10.
- Drowsiness: 2/10.
- Appetite: 1/10.
- Wellbeing: 0/10.
- Shortness of breath: 1/10.
- Sleep: 1/10.

- Wean to 300mg then discontinued gabapentin
- Increase methadone to 5mg bid
- Follow up in 4 weeks ,pain still 1/10
- Quality of life improved ,more active
- ‘life altering’ ‘able to smile for the first time since pain started’
- Sustained relief for at least 14 months so far

UPtoDATE


Symptoms suggestive of polyneuropathy
Hyporeflexia, sensory loss, atrophy/weakness
Hyperreflexia, increased tone
Consider central process (eg, spinal cord disease)
EMG with pol-radiculopathy, plexopathy, or mononeuropathy multiplex
Normal EMG
EMG with axonal physiology
EMG with demyelinating physiology
EMG with mixed pattern
Hereditary features on EMG
Acquired features on EMG; no family history
Toxin, drugs?:
B12
TSH
Glucose
Glycohemoglobin
ANA
ESR
SPEP and UPEP
Family history?
SPEP
UPEP
Hepatitis B and C
HIV
Lumbar puncture
GM1/anti-MAG antibodies
Work-up as for demyelinating
Work-up as appropriate, including imaging studies (radiculopathy and plexopathy) and nerve biopsy/serologic studies (mononeuritis multiplex)
Observe for progression
Repeat EMG
Skin biopsy for evaluation of small fibers
Autonomic testing*
Consider work-up as for axonal polyneuropathy
If negative, consider:
Urine heavy metals
Urine porphyrins
Rheumatoid factor
Sjögren's testing
Lyme antibody
HIV
Hu antibody
Methylmalonic acid¶
Homocysteine¶
Hepatitis B and C
Consider:
Charcot-Marie-Tooth disease Type 1
Evaluate family members; genetic testing
Consider:
Treatment for CIDP with steroids, plasmapheresis, or IVIG
If negative, consider:
Peripheral nerve biopsy
Axonal polyneuropathy work-up

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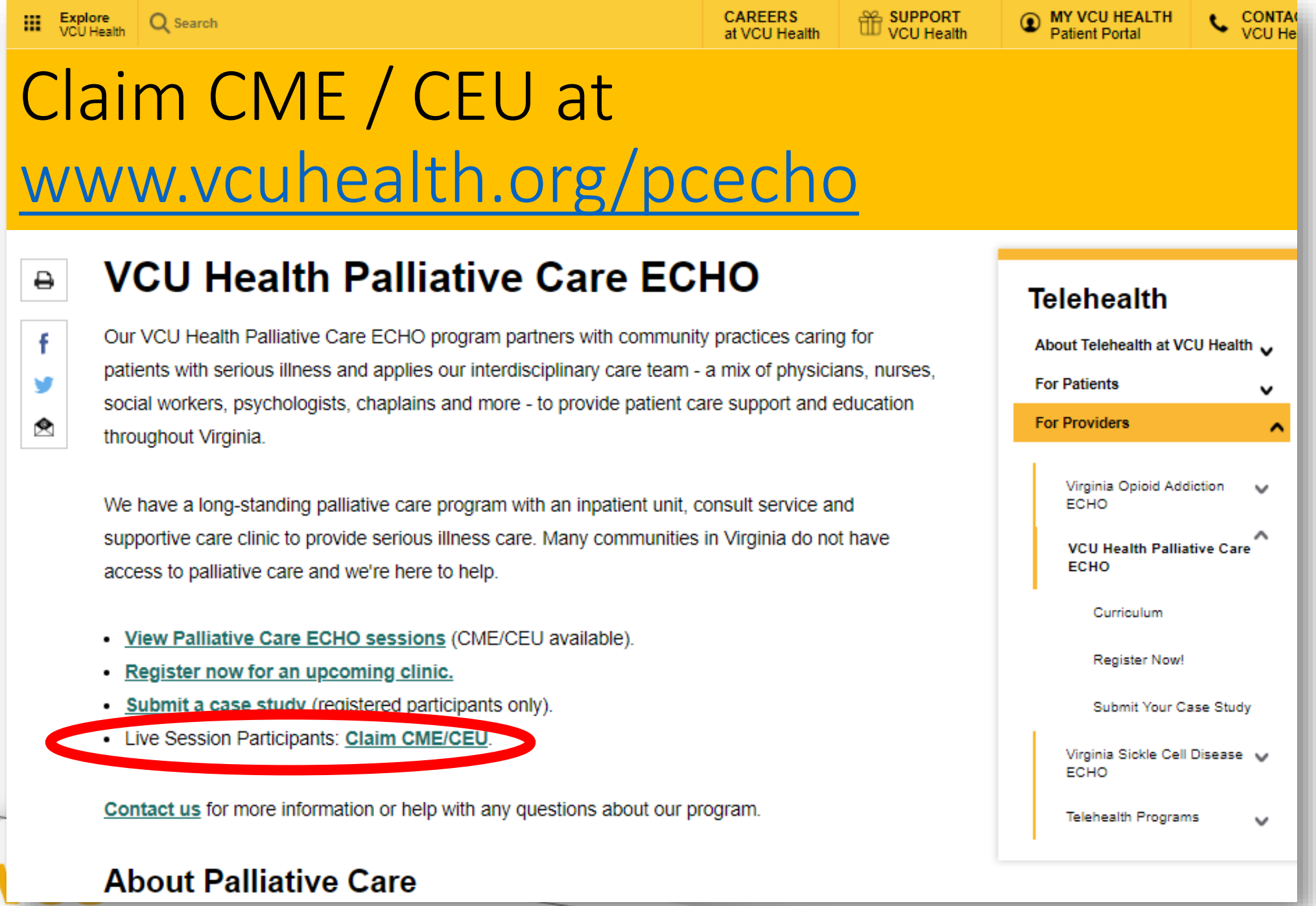

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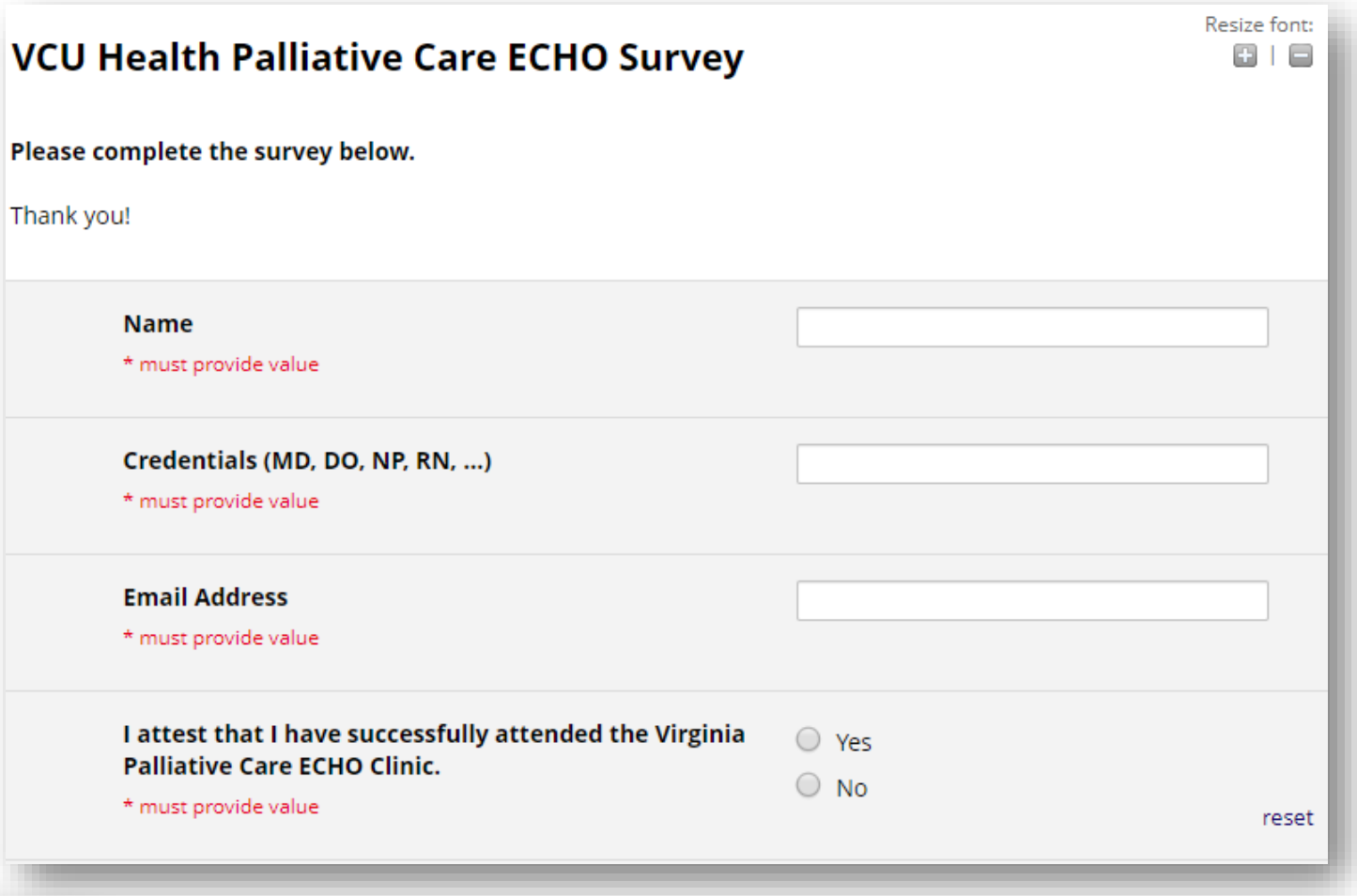

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VCU Health Palliative Care ECHO Survey

Please complete the survey below.

Thank you!

Name

* must provide value

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

* must provide value

Email Address

* must provide value

I attest that I have successfully attended the Virginia Palliative Care ECHO Clinic.

* must provide value

Yes

No

reset

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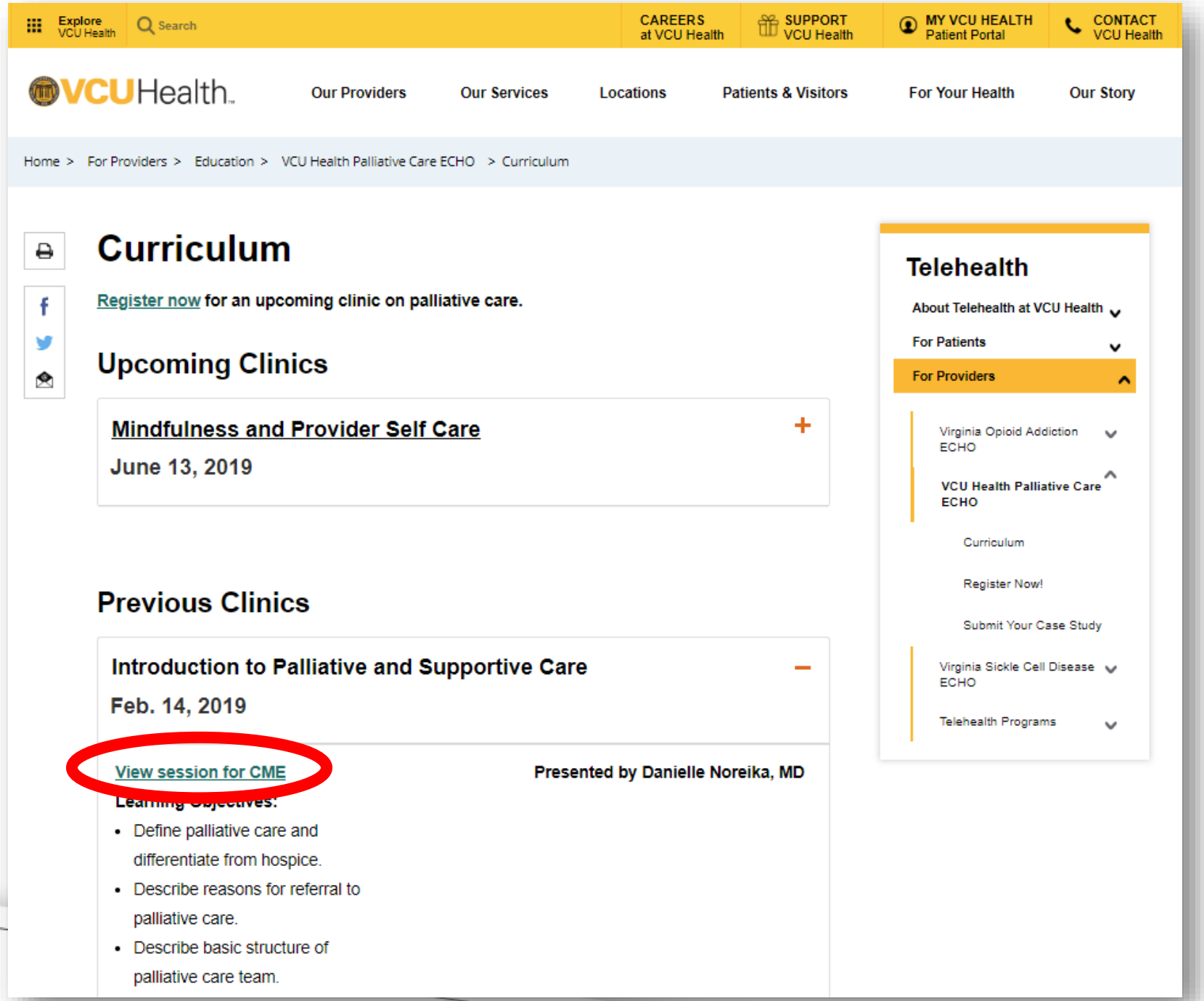
Virginia Commonwealth University



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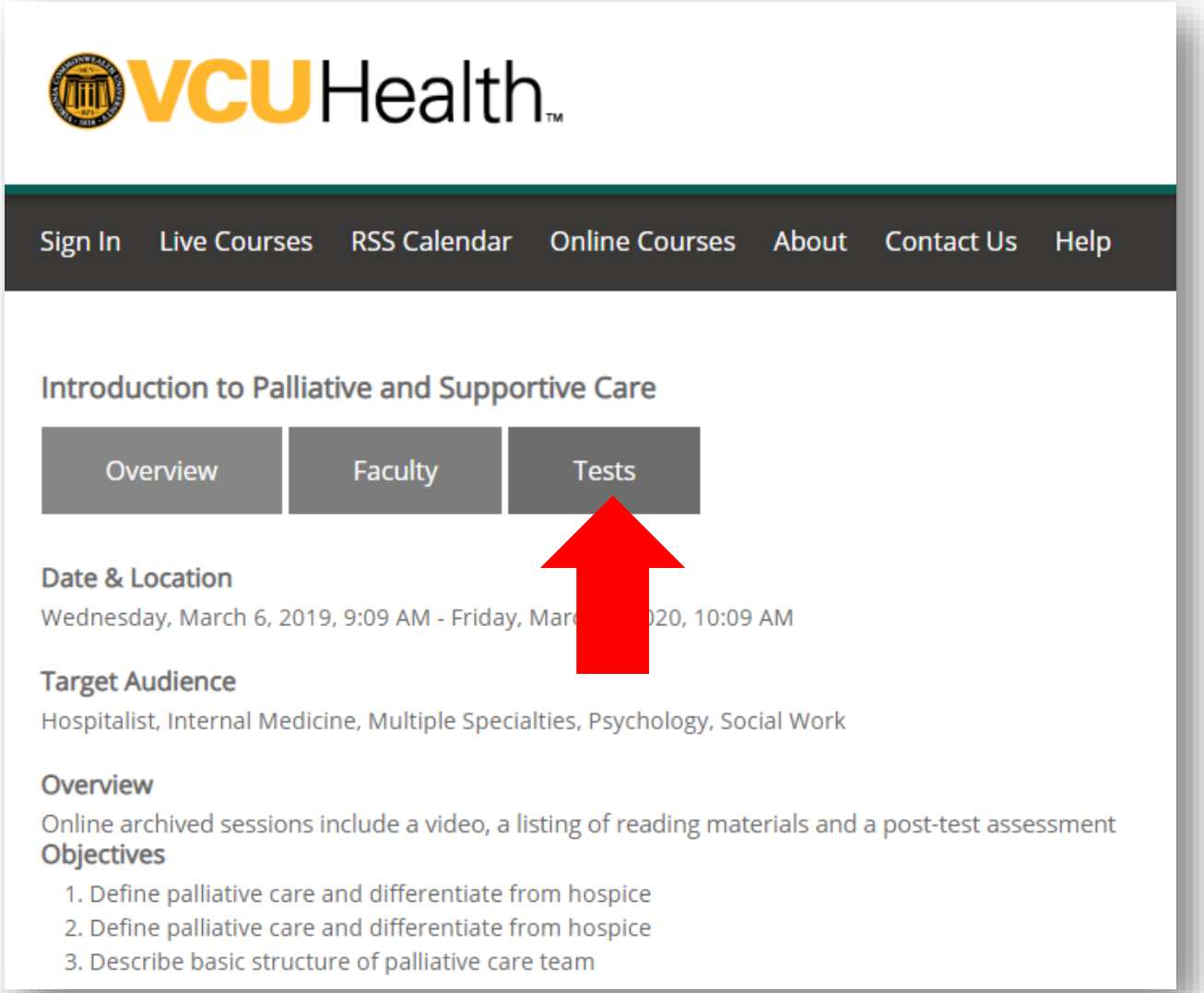
Click “Tests” to view video of the session and take a short quiz for continuing education credit



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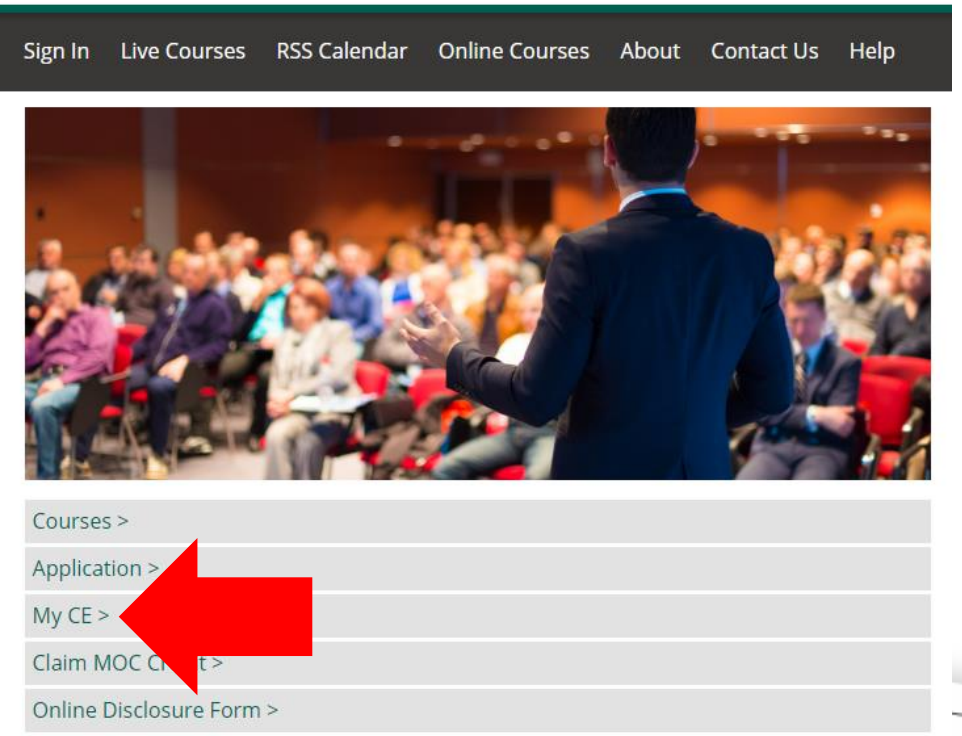
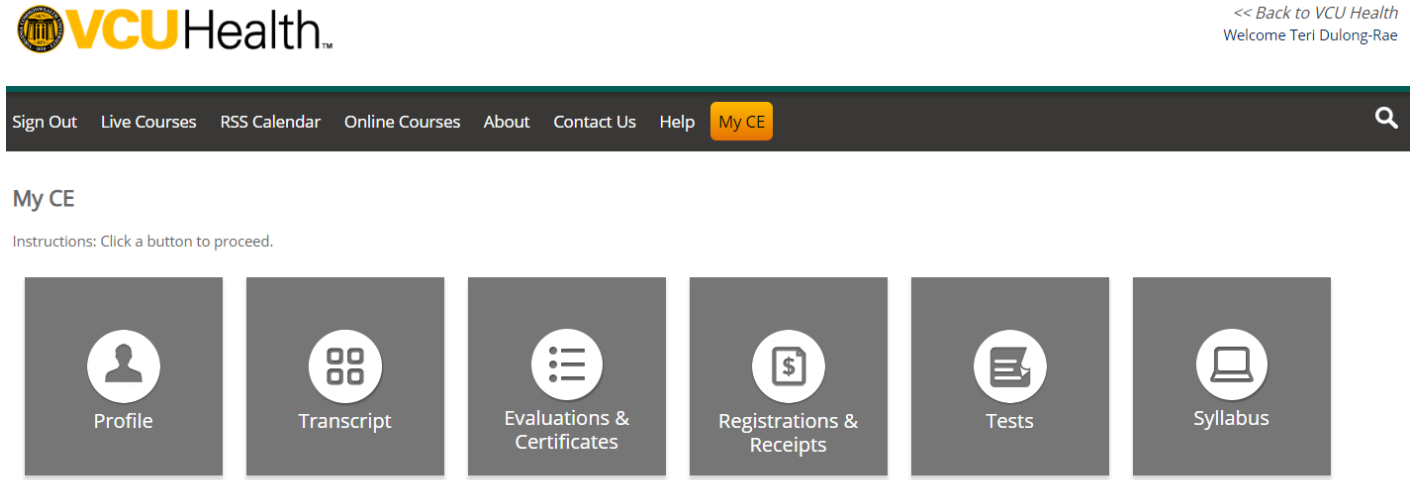
- Log in with the email you used to register for our ECHO session





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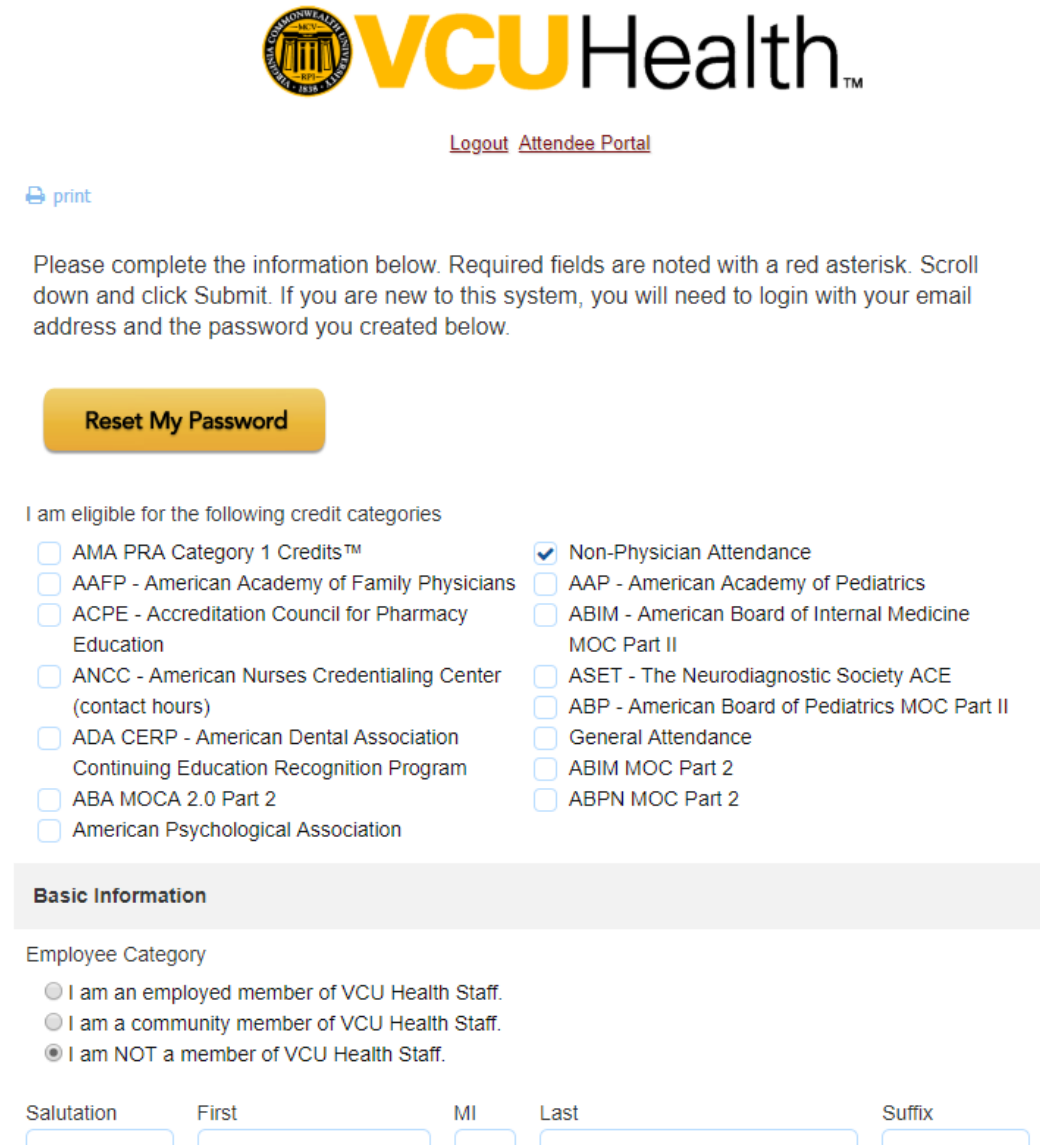

THANK YOU!

We hope to see you at our next ECHO