JOURNAL OF PALLIATIVE MEDICINE
Volume 21, Number 3, 2018

DOI: 10.1089/jpm.2017.0475

Levorphanol for Treatment of Intractable Neuropathic Pain in Cancer Patients

Akhila Reddy, MD,[1,*] Amy Ng, MD,[1,*] Tarun Mallipeddi,[2] and Eduardo Bruera, MD[1]

Abstract

Neuropathic pain in cancer patients is often difficult to treat, requiring a combination of several different pharmacological therapies. We describe two patients with complex neuropathic pain syndromes in the form of phantom limb pain and Brown-Sequard syndrome who did not respond to conventional treatments but responded dramatically to the addition of levorphanol. Levorphanol is a synthetic strong opioid that is a potent N-methyl-D-aspartate receptor antagonist, mu, kappa, and delta opioid receptor agonist, and reuptake inhibitor of serotonin and norepinephrine. It bypasses hepatic first-pass metabolism and thereby not subjected to numerous drug interactions. Levorphanol's unique profile makes it a potentially attractive opioid in cancer pain management.

Keywords: Brown-Sequard syndrome; cancer; cancer pain; levorphanol; neuropathic pain; phantom limb pain

Introduction

One-third of cancer patients who experience pain also experience neuropathic pain[1] and about half the patients with cancer who suffer from neuropathic pain also have nociceptive pain.[2] Most neuropathic pain exists as mixed pain in combination with nociceptive pain. Treatment of neuropathic pain is often challenging. Several drugs such as gabapentinoids, duloxetine, amitriptyline, opioids, and topical agents have been studied with mixed results.[3,4] Guidelines and findings of studies involving noncancer neuropathic pain syndromes are often extrapolated into treatment of neuropathic pain in cancer patients.[4] Cancer-related neuropathic pain may be chemotherapy related, radicular pain from tumor involvement, postsurgical neuropathic pain, postherpetic neuralgia, and other kinds of neuropathic pain.[4–7] Neuropathic pain in cancer patients may also exist as rare conditions such as phantom limb pain (PLP) and Brown-Sequard syndrome (BSS).

PLP is defined as a painful sensation originating in the amputated limb that usually develops within days after amputation.[8] It is estimated that 50% of people with limb amputations develop PLP.[8] It is usually described as shooting, shocking, burning, tingling, aching, and pins and needles-like sensation in the absent limb.[8] Peripheral nerve ending changes, structural reorganization of spinal cord and primary somatosensory cortex, and increased sensitization of spinal cord may be the neurological basis for PLP.[8,9] Because the pathophysiology of PLP is not clearly understood, the treatment options are mainly based on clinical experience.[9] There are case series showing that tramadol and methadone may be helpful. Antidepressants, antiepileptics, ketamine, calcitonin, memantine, spinal cord stimulator, ablation of spinal cord dorsal root, anterolateral cordotomy, and sympathectomy, have shown mixed results.[9,10] Treatments such as transcutaneous electrical nerve stimulation and mirror therapy have shown modest benefit.[8–10]

BSS like PLP is a difficult to treat cause of neuropathic pain. BSS refers to an injury of the spinal cord where one side is damaged more than the other, resulting in ipsilateral weakness and position sense loss, but with contralateral pain and temperature sensation loss below the affected level of spinal cord.[11] This is because motor fibers of the corticospinal tracts cross at the junction of the medulla and spinal cord and ascending dorsal column (vibration and position sensation) crosses above the spinal cord in the medulla. Whereas the spinothalamic tract carries pain, temperature, crude touch sensations from the contralateral side of the body.[12] BSS can be caused by both traumatic and nontraumatic causes.[12,13] BSS has also been reported as a delayed complication of

[1]Department of Palliative, Rehabilitation, and Integrative Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas.
[2]Candidate for Bachelor of Arts in Biological Basis of Behavior, University of Pennsylvania, Class of 2018, Philadelphia, Pennsylvania.
*These authors contributed equally to this work.
Accepted December 20, 2017.

stereotactic body radiotherapy in cancer patients.[14,15] Along with physical therapy, several treatment regimens are proposed with only modest efficacy for BSS such as high-dose steroids, hyperbaric oxygen, pentoxyphylline, anticoagulation, vitamin E, and bevacizumab.[11,13–18]

We present two patients with PLP and BSS who did not respond to conventional treatments but demonstrated major improvement after the addition of levorphanol.

Case Description

Patient 1

A woman in her 30s was diagnosed with osteosarcoma involving the right-sided proximal humerus with metastasis to the scapula. She underwent radical resection of the right proximal humerus with reconstruction. During the postoperative period, morphine was ineffective and was later switched to hydromorphone. Unfortunately, she developed recurrent disease in the right axilla, shoulder, chest wall, and upper arm. She complained of constant ''achy'' pain (intensity of 8 out of 10 on the Edmonton Symptom Assessment System [ESAS][19] pain score) in the right shoulder with radiation down the arm. At times, she also described combination of burning with pins and needle sensation. Tramadol 50 mg tablets four times a day and later hydromorphone 2 mg tablets six times a day were ineffective for her pain, leading to the initiation of hydromorphone extended-release 16 mg once daily with hydromorphone immediate release 4 mg tablets prescribed for breakthrough pain every four hours as needed. Gabapentin 300 mg once daily at bedtime was also initiated. This regimen controlled her pain (intensity of 3 out of 10 ESAS pain score).

Further progression in disease led to right-sided forequarter amputation. During the postoperative period, her pain was initially well managed with intravenous hydromorphone infusion and changed to home regimen of oral hydromorphone extended-release. Shortly afterward, she developed worsening in her pain. The achy pain in the area of the right upper extremity was now replaced by constant ''tingling and shooting pain'' sensation (7 out of 10 ESAS pain score) at the site of amputated limb, causing her significant distress. She was diagnosed with PLP. During this time, the combination of hydromorphone extended-release 16 mg once daily, hydromorphone 4 mg six times a day, and gabapentin 300 mg three times a day was ineffective. A trial of increase in gabapentin resulted in drowsiness, prompting a decrease back to previous dose. An opioid rotation to methadone was not pursued due to potential interaction with an antineoplastic agent. Levorphanol was initiated at 2 mg every eight hours scheduled with hydromorphone 4 mg every four hours as needed for breakthrough pain. A week later, she reported the PLP had almost completely resolved (intensity of 0–1 out of 10 ESAS pain score). She reported no side effects. For the next several months, the patient continued to report excellent control of the PLP. She ran out of levorphanol for a period of three days, which resulted in the recurrence of severe PLP. Despite taking hydromorphone 4 mg every four hours around-the-clock and continuing gabapentin, she remained with uncontrolled pain until she was restarted on levorphanol. At that point her ESAS pain intensity returned back to previous levels of 0–1 out of 10.

Patient 2

A woman in her 40s was diagnosed with metastatic right-sided breast cancer to lymph nodes and thoracic vertebra. She underwent chemotherapy, right-sided modified radical mastectomy, axillary lymph node dissection, postmastectomy radiation to the right-sided chest wall, and stereotactic radiation to the metastatic disease on the thoracic vertebral body. Approximately one year later, she began to experience a burning sensation over the mid back area. Magnetic resonance imaging of the spine revealed a syrinx and myelomalacia with enhancement and enlargement of the cord centrally and to the left at the site of the radiation. Shortly afterward, she developed weakness in the left leg associated with loss of balance and foot drop along with tingling, burning, and numbness in her right lower extremity. She developed abnormal sensation to sharp stimulus, light touch, or vibration in the right lower extremity. She was diagnosed with BSS. High-dose dexamethasone was prescribed without any benefit. She continued to have severe neuropathy in the right lower extremity and progressive weakness prompting intensification in her physical therapy. Although the burning sensation over the mid back resolved, the severe neuropathic pain in her right lower extremity (5–10 out of 10 on the ESAS pain item) was intractable to tramadol, hydrocodone, hydromorphone, methadone, pregabalin, gabapentin, duloxetine, venlafaxine, nortriptyline, amitriptyline, and other drugs such as accutane, pentoxifylline, and supplementation with high-dose B and E vitamins. She was on 1200 mg of gabapentin three times a day, venlafaxine extended-release 75 mg once daily, and hydrocodone/acetaminophen 10/325 mg taken every six hours scheduled and still complained of uncontrolled pain. She was started on a low dose of levorphanol at 1 mg taken every eight hours scheduled with continuation of hydrocodone/acetaminophen 10/325 mg taken as needed. At one-month follow-up, she experienced drastic improvement in her pain, burning, and tingling sensation (2 out of 10 on the ESAS pain item). This improvement persisted at subsequent follow-ups for the next several months. She rarely required the use of any hydrocodone and was later discontinued. She continued to use gabapentin and venlafaxine.

Discussion

Despite recent advances in cancer pain management, neuropathic pain remains one of the most challenging symptoms to treat.[4,20–24]Neuropathic pain often is a predictor of poor overall response to opioid analgesics in cancer patients.[22,23,25–27] Our team used levorphanol, a rarely prescribed opioid to successfully treat intractable neuropathic pain syndromes in the form of PLP and BSS in two patients.

Levorphanol, a synthetic strong opioid, was approved in the United States in the 1950s. It is an agonist at the mu, kappa, and delta opioid receptors, reportedly more potent than methadone. It is a very potent N-Methyl-D-aspartate receptor antagonist, more so than methadone and perhaps even ketamine.[28,29] It is also a reuptake inhibitor of both serotonin and norepinephrine (perhaps weaker than methadone).[28,30–32] It has no known cardiac corrected QT (QTc) prolongation effects.[28] It bypasses first-pass metabolism in the liver by the cytochrome P450 enzymes and hence subjected to negligible drug interactions as compared with methadone.[30]

Levorphanol undergoes glucoronidation through UDP-glucuronosyltransferase to levorphanol-3-glucoronide, which is renally excreted. Owing to its unique profile, it may be an attractive drug to treat complex pain syndromes, opioid-induced hyperalgesia, neuropathic pain, and refractory pain syndromes.[28,30–36] Side effects for levorphanol are similar to those of other opioids. It has a shorter half-life than methadone (11–16 hours vs. 8–60 hours),[30,31,34,37] and accumulates at a slower pace reaching a steady state in approximately three days. It appears to have a safer profile than methadone and yet possesses the desirable unique properties of methadone.[31,38,39]

The accurate opioid rotation ratio (ORR) from other opioids to levorphanol is unknown. It is estimated that levorphanol is approximately six to eight times more potent than morphine.[32,34] Our two patients had an ORR from morphine equivalent daily dose (MEDD) to levorphanol of 13.3 and 20. Patient 1's MEDD was 80 mg (16 mg hydromorphone × 5) and was rotated to 6 mg of levorphanol/day with an ORR of 13.3 (MEDD/levorphanol mg = 80/6 = 13.3). Similarly, patient 2's MEDD was 60 mg (40 mg hydrocodone × 1.5) and was rotated to 3 mg of levorphanol/day with an ORR of 20 (MEDD/levorphanol mg = 60/3 = 20). Studies investigating the ORR of other opioids to levorphanol are clearly required to safely and efficiently conduct opioid rotations.

Limited data exist regarding the efficacy of levorphanol in cancer pain management. In adults with chronic neuropathic pain, higher doses of levorphanol (average 9 mg/day) were more effective than lower doses of levorphanol (2.7 mg/day) in reducing the intensity of neuropathic pain.[35] Seventy-four percent (23/31) of patients with chronic nonmalignant pain who did not respond to other opioids and adjuvants including methadone responded to levorphanol.[34] There are case reports of its efficacy in intractable nociceptive cancer pain.[33] Well-designed randomized controlled trials are needed to study the effect of levorphanol on cancer-related nociceptive, neuropathic, and mixed pain syndromes, along with unique scenarios such as PLP and BSS. Our two patients were fortunate that levorphanol was covered by their health insurance plan and available in their local pharmacy. Unfortunately, levorphanol is not readily available in most pharmacies and may require a significant period of time to enable the pharmacy to place an order and acquire the drug before dispensing to the patient. Proactive planning by both the prescriber and the patient is hence required to ensure there are no interruptions in drug use. Moreover, regional differences in availability of levorphanol may exist. In addition to drug availability issues, the lack of training and familiarity with levorphanol, limited data on its use in cancer patients, and availability of cheaper and newer opioids make levorphanol a ''forgotten opioid.''[37] The dramatic improvement in neuropathic pain after the addition of levorphanol in our two patients calls for more research and revival of this opioid in cancer pain management.

Acknowledgment

The authors thank the two patients who allowed them to report their journey to achieving successful cancer pain management.

This case series was presented at the 15th World Congress of the European Association for Palliative Care, May 18–20, 2017.

Author Disclosure Statement

No competing financial interests exist.

References

1. Roberto A, Deandrea S, Greco MT, et al.: Prevalence of neuropathic pain in cancer patients: Pooled estimates from a systematic review of published literature and results from a survey conducted in 50 Italian Palliative Care Centers. J Pain Symptom Manage 2016;51:1091.e4–1102.e4.
2. Caraceni A, Portenoy RK: An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. Pain 1999;82:263–274.
3. Hershman DL, Lacchetti C, Dworkin RH, et al.: Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2014;32:1941–1967.
4. Piano V, Verhagen S, Schalkwijk A, et al.: Treatment for neuropathic pain in patients with cancer: Comparative analysis of recommendations in national clinical practice guidelines from European countries. Pain Pract 2014;14: 1–7.
5. Boogaard S, Heymans MW, de Vet HC, et al.: Predictors of persistent neuropathic pain—A systematic review. Pain physician 2015;18:433–457.
6. Smith EM, Pang H, Cirrincione C, et al.: Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: A randomized clinical trial. JAMA 2013;309:1359–1367.
7. Pachman DR, Watson JC, Loprinzi CL: Therapeutic strategies for cancer treatment related peripheral neuropathies. Curr Treat Options Oncol 2014;15:567–580.
8. Luo Y, Anderson TA: Phantom limb pain: A review. Int Anesthesiol Clin 2016;54:121–139.
9. Weeks SR, Anderson-Barnes VC, Tsao JW: Phantom limb pain: Theories and therapies. Neurologist 2010;16:277–286.
10. Alviar MJ, Hale T, Dungca M: Pharmacologic interventions for treating phantom limb pain. Cochrane Database Syst Rev 2016;10:CD006380.
11. Wong CS, Fehlings MG, Sahgal A: Pathobiology of radiation myelopathy and strategies to mitigate injury. Spinal Cord 2015;53:574–580.
12. Diaz E, Morales H: Spinal cord anatomy and clinical syndromes. Semin Ultrasound CT MR 2016;37:360–371.
13. Mendoza JE: Brown-Séquard syndrome. In: Kreutzer JS, DeLuca J, Caplan B, eds. *Encyclopedia of Clinical Neuropsychology*. New York, NY: Springer New York, 2011, pp. 460–460.
14. Sahgal A, Ma L, Gibbs I, et al.: Spinal cord tolerance for stereotactic body radiotherapy. Int J Radiat Oncol 2010;77: 548–553.
15. Gerszten PC, Burton SA, Ozhasoglu C, et al.: Radiosurgery for benign intradural spinal tumors. Neurosurgery 2008;62: 887–895; discussion 895–886.
16. Psimaras D, Tafani C, Ducray F, et al.: Bevacizumab in late-onset radiation-induced myelopathy. Neurology 2016; 86:454–457.
17. Karadag-Saygi E, Cubukcu-Aydoseli K, Aydoseli A, Akyuz G: Brown-Sequard syndrome caused by cervical disc herniation: Case report and review. Neurosurg Quart 2010;20:46–47.

18. Glantz MJ, Burger PC, Friedman AH, et al.: Treatment of radiation-induced nervous system injury with heparin and warfarin. Neurology 1994;44:2020–2027.
19. Bruera E, Kuehn N, Miller MJ, et al.: The Edmonton Symptom Assessment System (ESAS): A simple method for the assessment of palliative care patients. J Palliat Care 1991;7:6–9.
20. Finnerup NB, Attal N, Haroutounian S, et al.: Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. Lancet Neurol 2015;14:162–173.
21. Bennett MI: Effectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: Systematic review. Palliat Med 2011;25:553–559.
22. Fainsinger RL, Nekolaichuk C, Lawlor P, et al.: An international multicentre validation study of a pain classification system for cancer patients. Eur J Cancer 2010;46:2896–2904.
23. Brunelli C, Kaasa S, Knudsen AK, et al.: Comparisons of patient and physician assessment of pain-related domains in cancer pain classification: Results from a large international multicenter study. J Pain 2014;15:59–67.
24. Fallon MT: Neuropathic pain in cancer. BJA 2013;111: 105–111.
25. Knudsen AK, Brunelli C, Klepstad P, et al.: Which domains should be included in a cancer pain classification system? Analyses of longitudinal data. Pain 2012;153: 696–703.
26. Cherny NI, Thaler HT, Friedlander-Klar H, et al.: Opioid responsiveness of cancer pain syndromes caused by neuropathic or nociceptive mechanisms: A combined analysis of controlled, single-dose studies. Neurology 1994;44: 857–861.
27. Caraceni A, Hanks G, Kaasa S, et al.: Use of opioid analgesics in the treatment of cancer pain: Evidence-based recommendations from the EAPC. Lancet Oncol 2012;13: e58–e68.
28. Gudin J, Fudin J, Nalamachu S: Levorphanol use: Past, present and future. Postgrad Med 2016;128:46–53.
29. Stringer M, Makin MK, Miles J, Morley JS: d-Morphine, but not l-morphine, has low micromolar affinity for the non-competitive N-Methyl-D-aspartate site in rat forebrain. Possible clinical implications for the management of neuropathic pain. Neurosci Lett 2000;295:21–24.
30. Codd EE, Shank RP, Schupsky JJ, Raffa RB: Serotonin and norepinephrine uptake inhibiting activity of centrally acting analgesics: Structural determinants and role in antinociception. J Pharmacol Exp Ther 1995;274:1263–1270.
31. Pham TC, Fudin J, Raffa RB: Is levorphanol a better option than methadone? Pain Med 2015;16:1673–1679.
32. Prommer E: Levorphanol: Revisiting an underutilized analgesic. Palliat Care 2014;8:7–10.
33. McNulty JPMFF: Levorphanol for excruciating pain from oral cancer: A case report. Int J Pharm Compd 2007;11:212–218.
34. McNulty JP: Can levorphanol be used like methadone for intractable refractory pain? J Palliat Med 2007;10:293–296.
35. Rowbotham MC, Twilling L, Davies PS, et al.: Oral opioid therapy for chronic peripheral and central neuropathic pain. N Engl J Med 2003;348:1223–1232.
36. Chapman V, Dickenson AH: The combination of NMDA antagonism and morphine produces profound antinociception in the rat dorsal horn. Brain Res 1992;573:321–323.
37. Prommer E: Levorphanol: The forgotten opioid. Support Care Cancer 2007;15:259–264.
38. Ray WA, Chung CP, Murray KT, et al.: Out-of-hospital mortality among patients receiving methadone for noncancer pain. JAMA Intern Med 2015;175:420–427.
39. Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: A clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. J Pain 2014; 15:321–337.

Address correspondence to:
Akhila Reddy, MD
Department of Palliative, Rehabilitation, and Integrative Medicine
The University of Texas MD Anderson Cancer
1515 Holcombe Boulevard, Unit 1414
Houston, TX 77030

E-mail: asreddy@mdanderson.org

VCU Palliative Care ECHO*

March 28, 2019

Basics of Cancer Pain Management

*ECHO: Extension of Community Healthcare Outcomes

Continuing Medical Education

February 28, 2019 | 12:00 PM | teleECHO Conference

Physicians: VCU Health Continuing Medical Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. VCU Health Continuing Medical Education designates this live activity for a maximum of 1 ***AMA PRA Category 1 Credits™.***

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

Disclosures

February 28, 2019 | 12:00 PM | teleECHO Conference

In compliance with the Accreditation Council for Continuing Medical Education (ACCME) *Standards for Commercial Support of CME*, VCU Health Continuing Medical Education discloses all relevant relationships which program faculty and planners report having with "any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients." VCU Health Continuing Medical Education has procedures to resolve any apparent conflicts of interest.

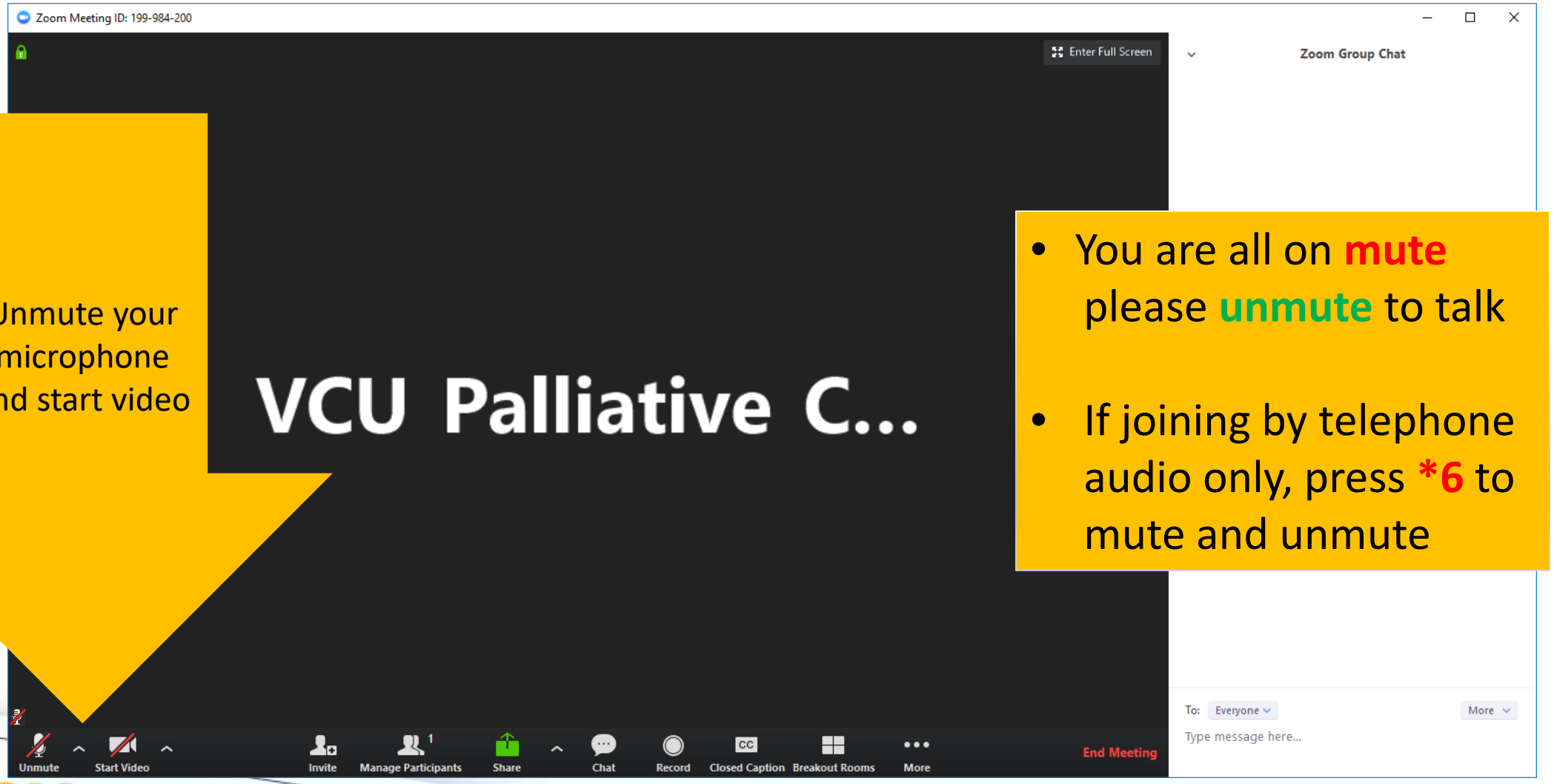
The following Planning Committee and Presenting Faculty Members report relevant financial relationships to disclose:

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

Danielle Noreika, MD
Egidio Del Fabbro, MD

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

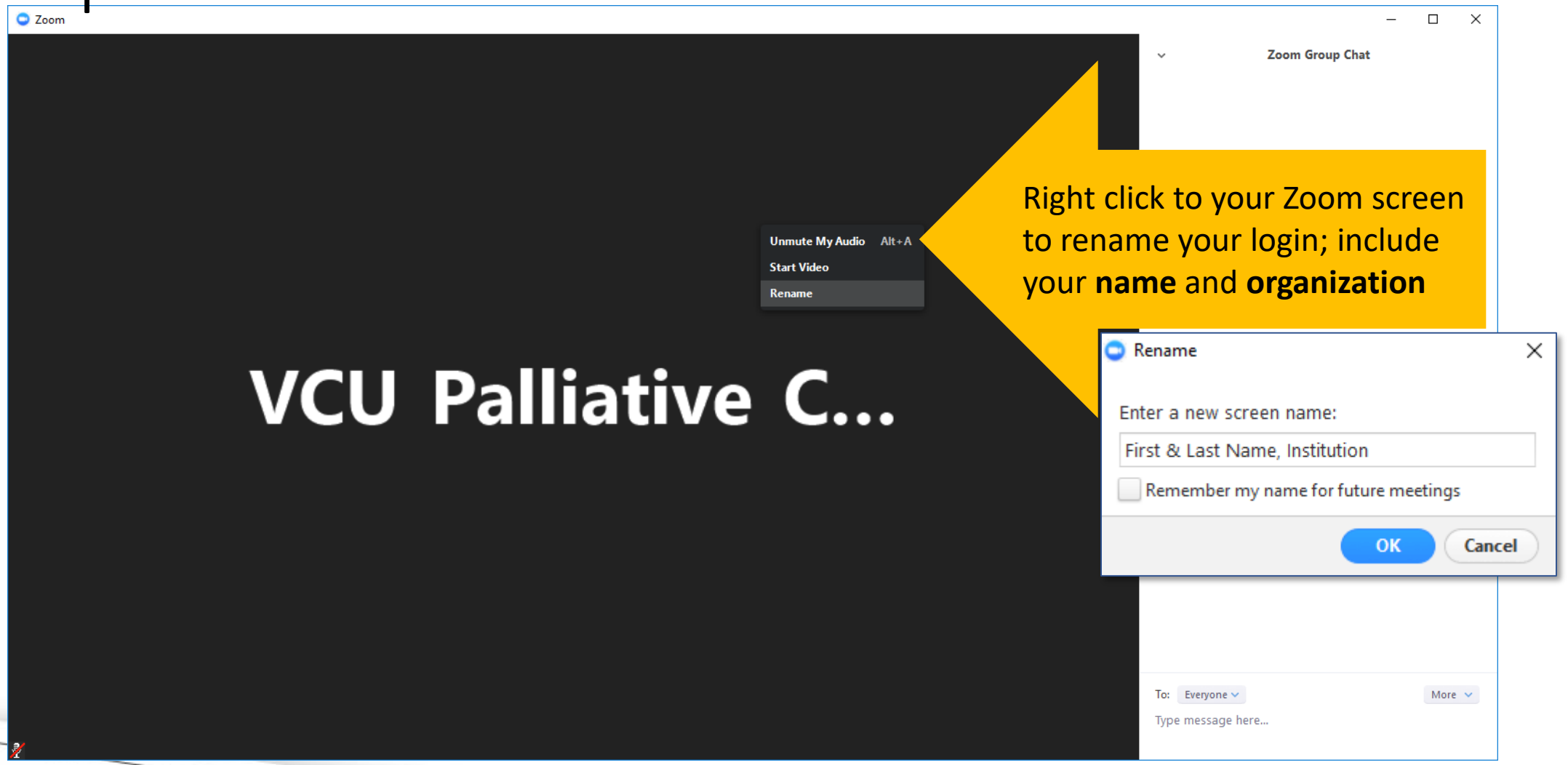
Helpful Reminders



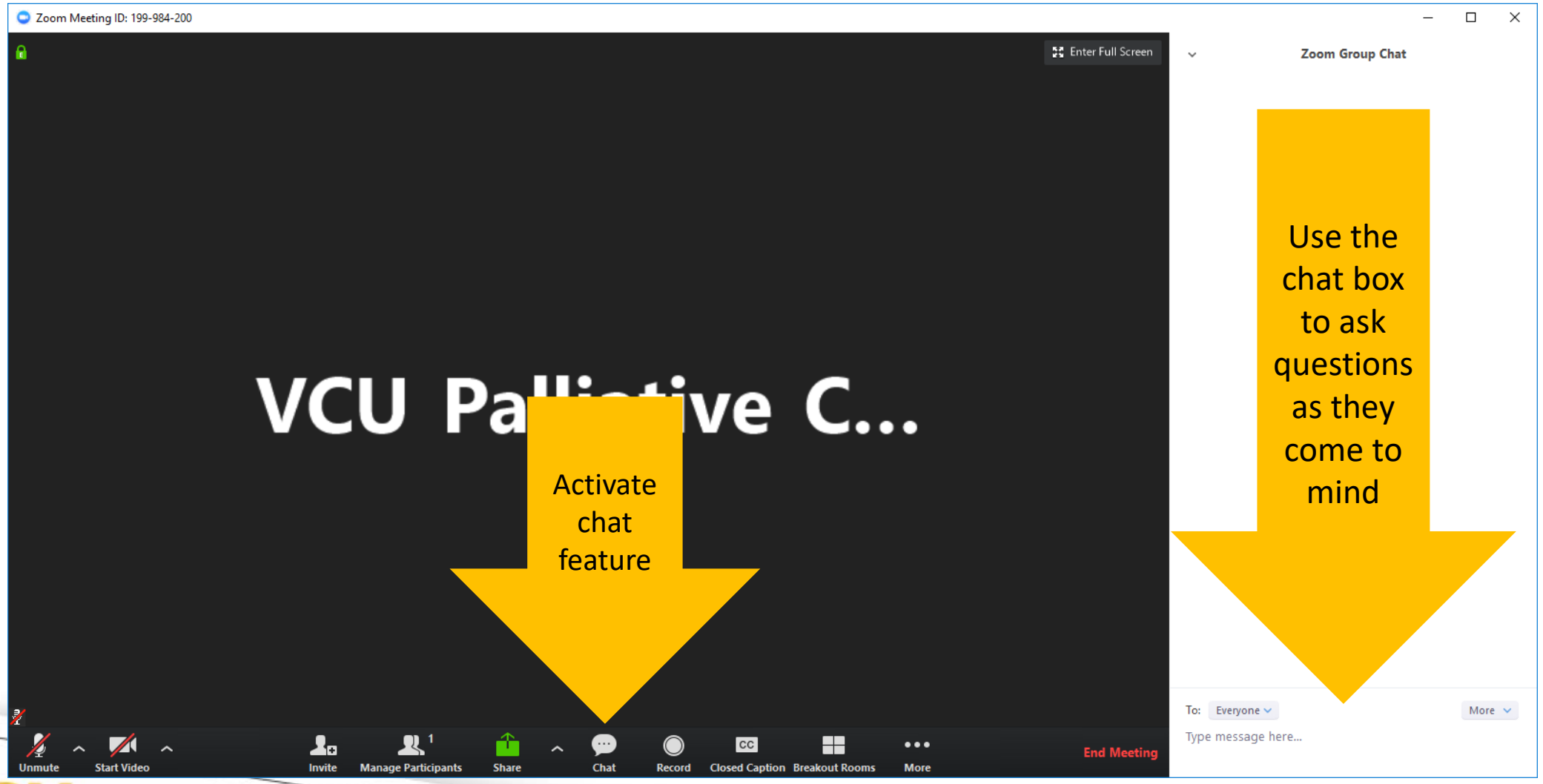
Unmute your microphone and start video

- You are all on **mute** please **unmute** to talk
- If joining by telephone audio only, press ***6** to mute and unmute

Helpful Reminders



Helpful Reminders



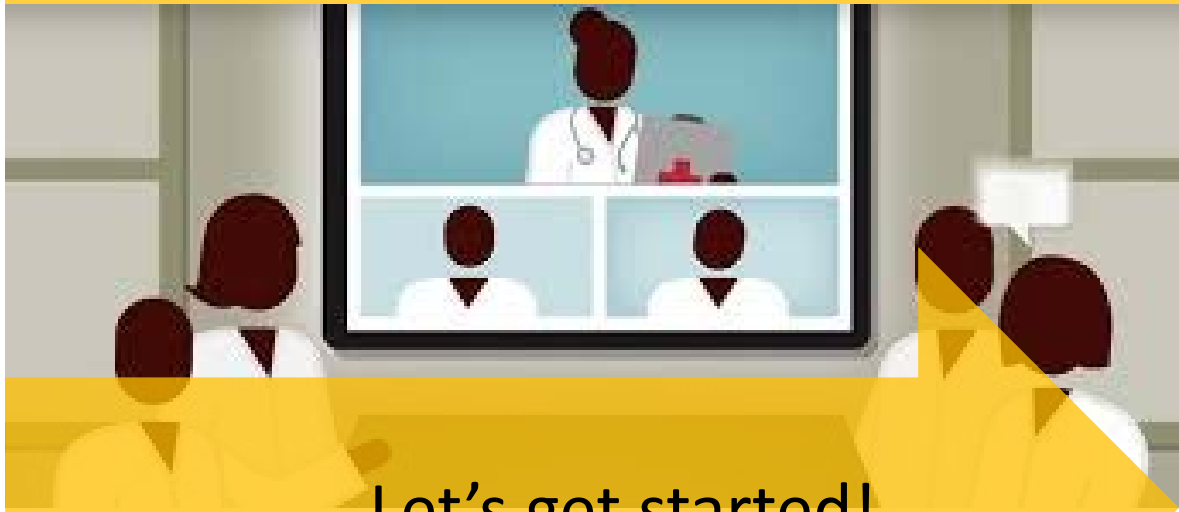
What to Expect

I. Didactic Presentation
   20 minutes + Q&A

II. Case Discussions (x2)
   - 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 Director	Danielle Noreika, MD, FACP, FAAHPM Medical Director/Fellowship Director VCU Palliative Care
Clinical Experts	Egidio Del Fabbro, MD – VCU Palliative Care Chair Jason Callahan, MDiv – Palliative Care Specialty Certified Tamara Orr, PhD, LCP – Clinical Psychologist Diane Kane, LCSW – Palliative Care Specialty Certified Felicia Hope Barner – RN Candace Blades, JD, RN – Advance Care Planning Coordinator Brian Cassel, PhD – Palliative Care Outcomes Researcher
Support Staff Program Manager Practice Administrator IT Support	 Teri Dulong-Rae / Bhakti Dave, MPH David Collins, MHA Frank Green

Spoke Participant Introductions

Name and Institution

Basics of Cancer Pain Management

Egidio Del Fabbro, MD

March 28, 2019

Objectives

The participant will be able to:

1) Define basic evaluation of pain assessment in cancer patients
2) Differentiate cancer pain from non-cancer pain assessment
3) Define broad strategies of cancer pain management

Overview of Opioids and Cancer-Related Pain

Egidio Del Fabbro MD
Chair, Palliative Care Program
Virginia Commonwealth University
Massey Cancer Center

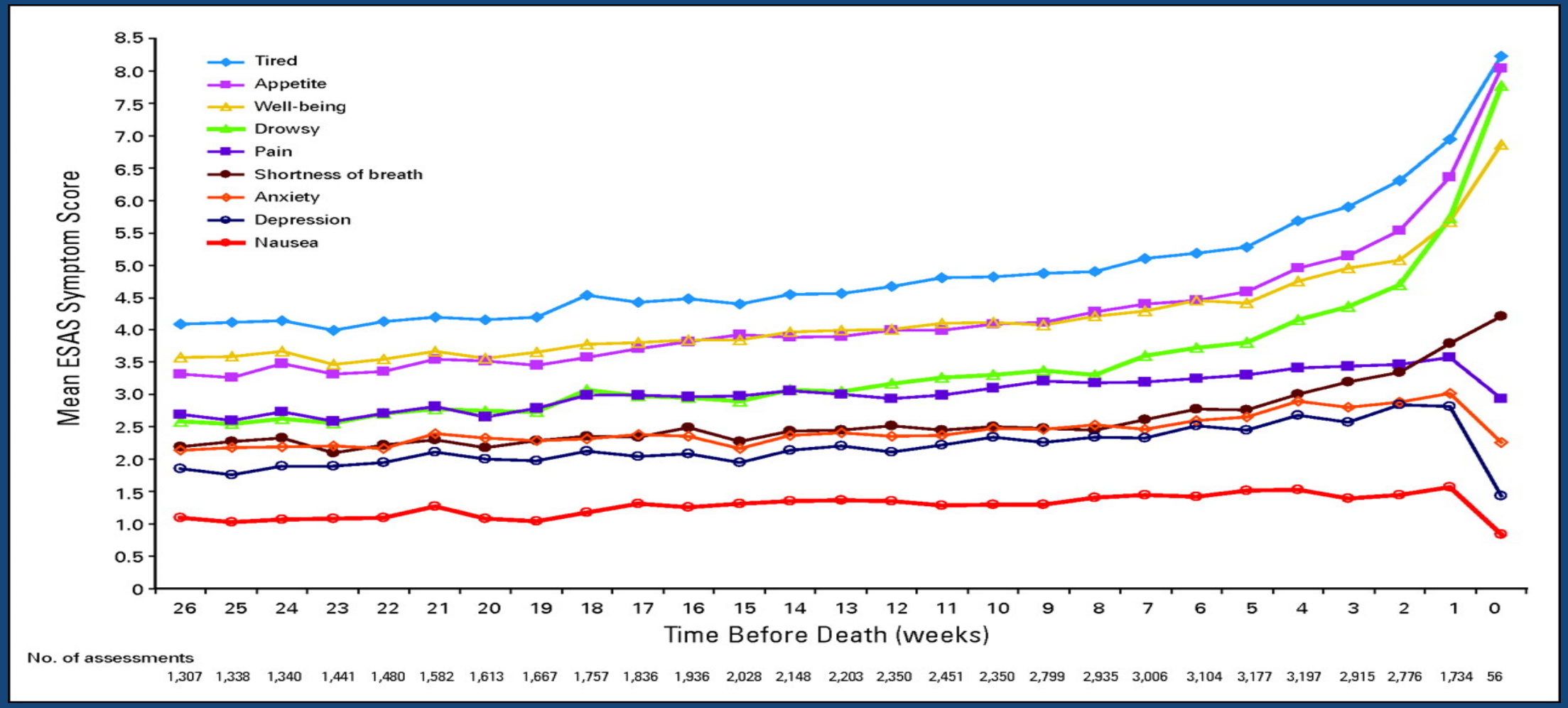
Overview

- Assessment
- Education
- Risk Mitigation
- Harm Reduction
- Opioid side-effects

Edmonton Symptom Assessment Scale

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
Not tired	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
Not nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
Not depressed	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
Not anxious	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
Not drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
Best appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible appetite
Best feeling of well-being	0	1	2	3	4	5	6	7	8	9	10	Worst possible feeling of well-being
No shortness of breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
Other =Insomnia	0	1	2	3	4	5	6	7	8	9	10	

Mean ESAS scores over time of 10752 patients



Hsien Seow et al. JCO 2011;29:1151-1158

Pain Interference – Short Form 8a (PROMIS)

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ91	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ222	How much did pain interfere with work around the home?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ313	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your enjoyment of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ125	How much did pain interfere with the things you usually do for fun?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ366	How much did pain interfere with your enjoyment of social activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ347	How much did pain interfere with your household chores?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ138	How much did pain interfere with your family life?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Validated Risk Assessment Tools

Acronym of tool[α]	Number of questions	Completion	Time to complete
SOAPP®-R	24 items	Self-report	< 10 minutes
DIRE	7 items	Clinician administered	< 5 minutes
ORT	5 items	Clinician administered	< 5 minutes
COMM	40 items	Self-report	< 10 minutes
CAGE	4 items	Either	< 5 minutes
PDUQ	42 items	Clinician administered	20 minutes
STAR	14 items	Self-report	< 5 minutes
SISAP	5 items	Clinician administered	< 5 minutes
PMQ	26 items	Self-report	< 10 minutes

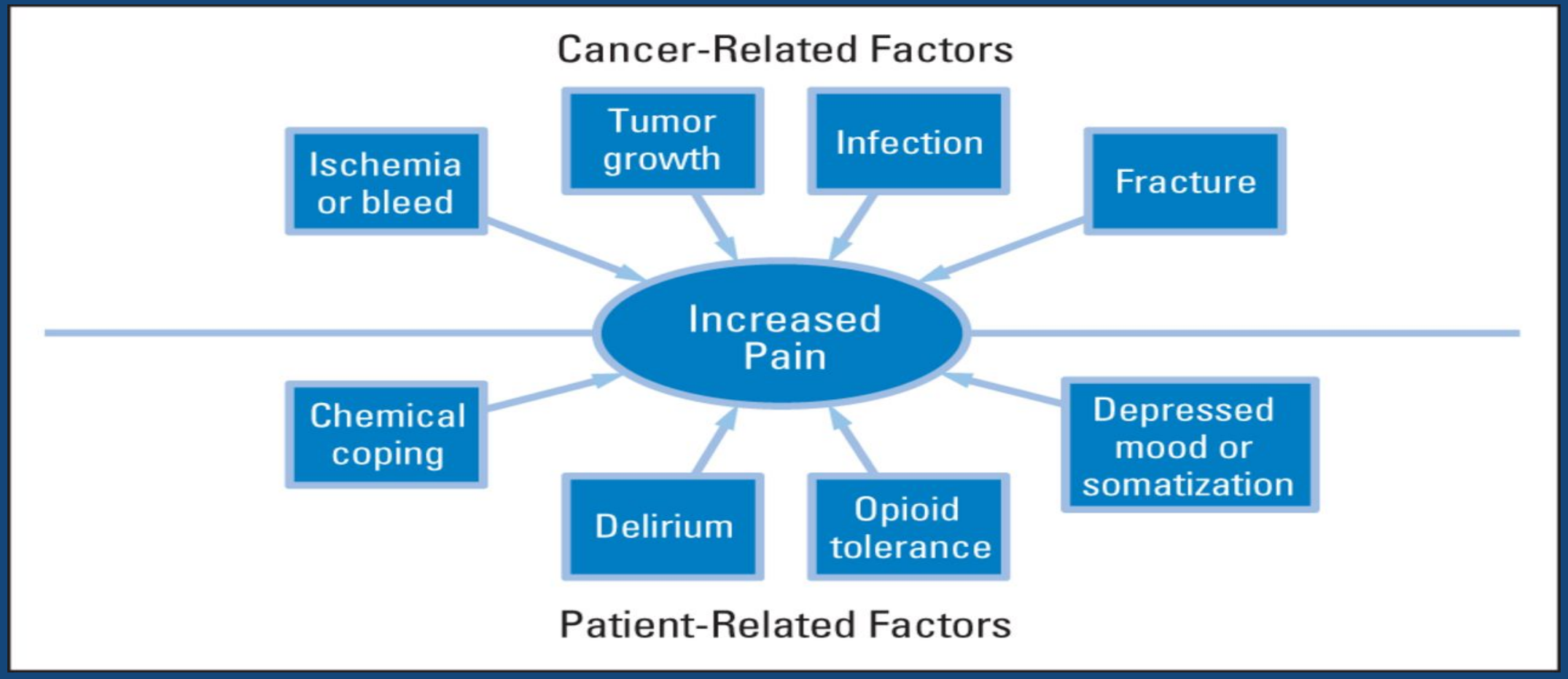
α - SOAPP®-R (Screener and Opioid Assessment for Patient's in Pain-revised); DIRE (Diagnosis, Intractability, Risk, and Efficacy); ORT (Webster's Opioid Risk Tool); COMM (Current Opioid Misuse Measure); CAGE (Cut-down, Annoyed, Guilt, Eye-opener); PDUQ (Prescription Drug Use Questionnaire); STAR (Screening Tool for Addiction Risk); SISAP (Screening Instrument for Substance Abuse Potential); PMQ (Pain Medication Questionnaire)

Identifying and assessing risk of opioid abuse in cancer: an integrative review

- 691 articles using search terms
- 34 case studies, case series, retrospective observational studies, narrative reviews
- screening questionnaires for opioid abuse or alcohol, urine drug screens to identify opioid misuse or abuse, prescription drug-monitoring programs, universal precautions
- 7 opioid specific 13 CAGE questionnaire to assess the risk of “chemical coping”
- Screening questionnaires one in five may be at risk of opioid-use disorder
- Several studies demonstrated associations between high-risk patients and clinical outcomes, such as aberrant behavior, prolonged opioid use, higher morphine-equivalent daily dose, greater health care utilization, and symptom burden

Substance Abuse and Rehabilitation *Carmichael, Morgan , Del Fabbro 2016*

Cancer- and patient-related factors contributing to pain

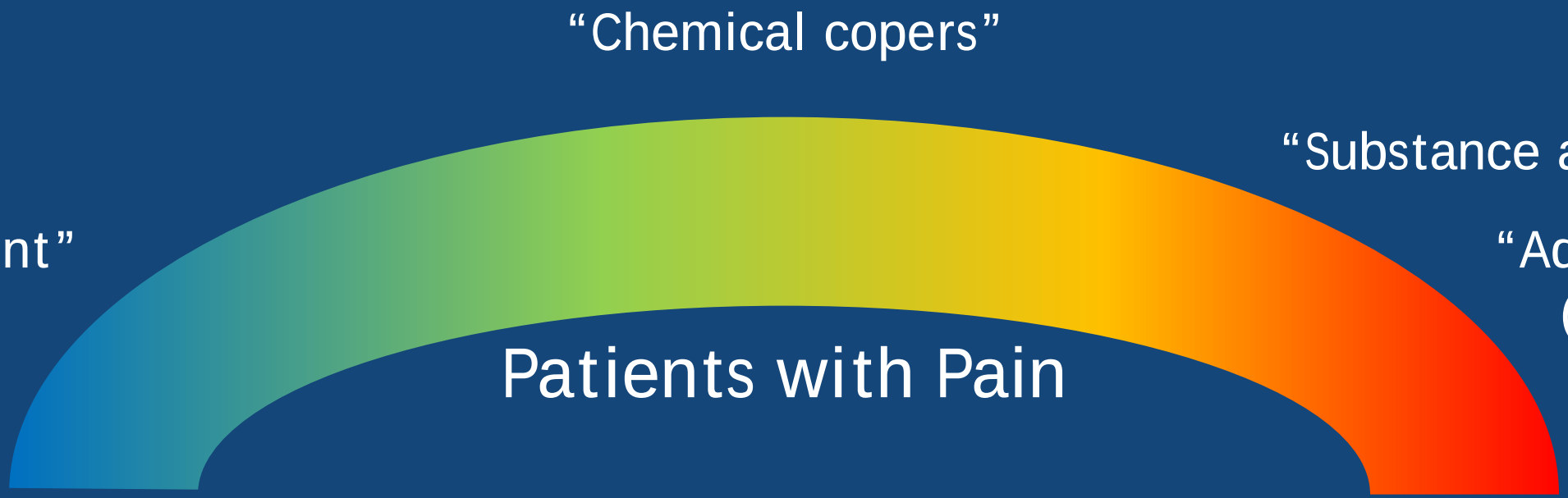


Del Fabbro E JCO 2014;32:1734-1738

JOURNAL OF CLINICAL ONCOLOGY
Official Journal of the American Society of Clinical Oncology

All addicts are Chemical Copers, but not all Chemical Copers are addicts

Population is Heterogeneous



Adapted from: Passik, Kirsch. *Exp Clin Psychopharmacol* 2008

Complications of chemical coping

- Opioid induced neurotoxicity
- Combining drugs of abuse
- Overdose
- Death
- Medico legal problems
- Addiction
- Poor quality of life, increased symptom burden
- Diversion

Bruera Pain 1989,Bruera JPSM 1995,Fainsinger JPSM 2005, Bohnert JAMA 2005,Walton PHR 2015,

Opioid use after Curative-intent Surgery

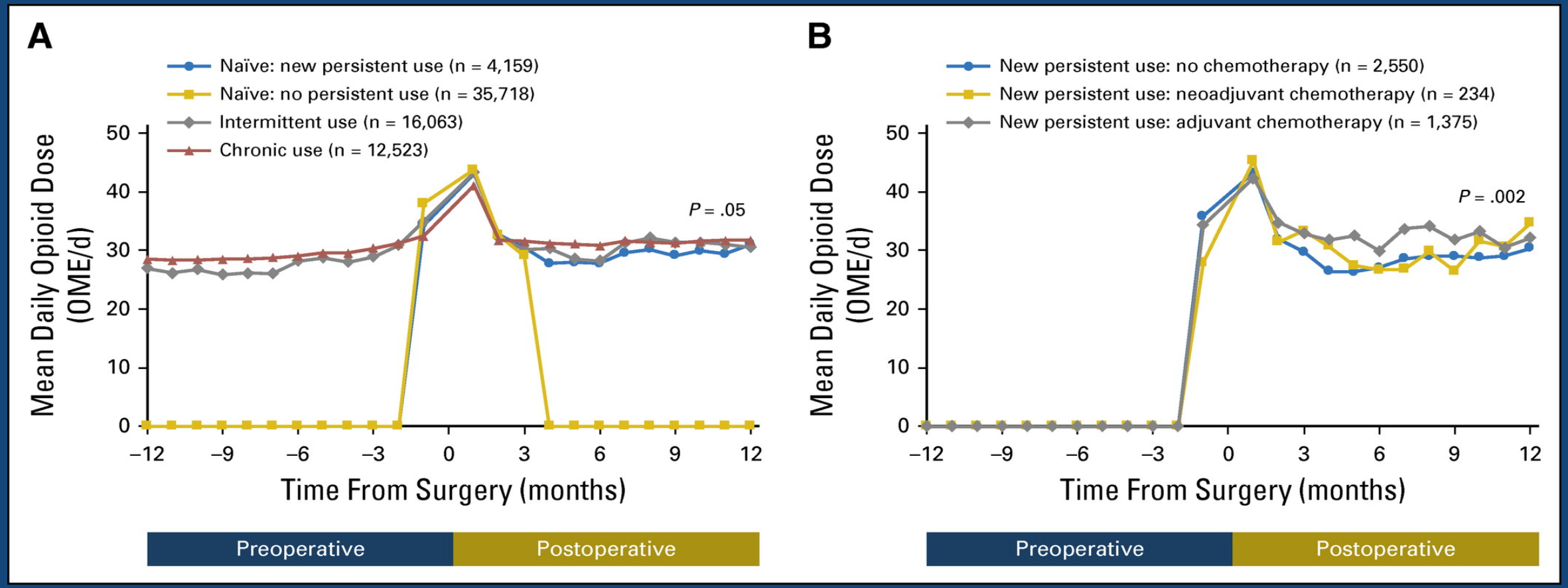


Fig 2. (A) Trajectory of daily opioid dose stratified by perioperative opioid use. Mean daily opioid dose for each group was calculated every 30 days from 1 year before surgery to 1 year after surgery, while adjusting for preoperative opioid prescriptions, initial opioid prescribed, procedure type, adjuvant and neoadjuvant therapy, and patient characteristics. One year after surgery, patients who developed new persistent opioid use continued filling opioid prescriptions with daily doses similar to intermittent and chronic opioid users (P = .05). (B) Trajectory of daily opioid dose stratified by timing of chemotherapy. Patients who developed new persistent opioid use and received adjuvant chemotherapy had higher daily opioid doses compared with those who received no chemotherapy (P = .002). All groups, however, continued filling prescriptions with high daily doses, equivalent to five to six tablets per day of 5-mg hydrocodone. OME, oral morphine equivalent

Jay Soong-Jin Lee et al *JCO* **2017,** 35, 4042-4049.

Management
Who should be referred to a multidisciplinary clinic?

- High doses
- Complex e.g. cancer pain + treatment related pain+chronic pain
- Complex opioid regimen
- Aberrant behavior

Aberrant behaviors associated with opioid misuse

- Request opioid refill earlier
- use of street drugs
- abnormal urine drug test
- excessive dose increase
- resistance to changes in opioids
- impaired functioning in daily activities
- lost or stolen opioid
- seeking opioids from multiple providers
- request for specific opioids
- Family concerned about patient's inappropriate opioid use
- Tampering or forging opioid prescriptions

Universal Precautions for patients with cancer

Table 1. Approach to Managing Opioid Risk and Chemical Coping in Patients With Cancer Based on Universal Precautions

Step	Description
1	Differential diagnosis: identify tumor-related causes of pain and patient-related factors influencing pain perception and expression
2	History of risk factors for chemical coping: tobacco use, depression, history of substance abuse, personality disorder, somatization, sexual abuse
3	Screening instrument at first visit to identify those at high risk (eg, CAGE, SOAPP, ORT, STAR)
4	Informed consent including patient education about addiction, tolerance, and opioid adverse effects and treatment plan that de-emphasizes opioids as sole treatment for pain
5	Opioid agreement (written or verbal) that includes outline of patient obligations (eg, receive opioids prescriptions from single provider, no early refills, random UDS)
6	Pre- and postassessment of pain level and function; routine assessment of four As: analgesia, activities of daily living, adverse effects, and aberrant behavior[38]
7	Psychological support, motivational interviews, and increased vigilance and structure for those at high risk for opioid misuse (eg, pill counts, shorter intervals between visits); consider integrated comanaged model with interdisciplinary palliative care or chronic pain team
8	Periodically review differential diagnosis; contribution of tumor- and patient-related factors to pain may have changed (eg, patients with no evidence of disease should receive stable scheduled dose or tapered opioids, whereas patients with progressive advanced cancer will require additional breakthrough-dose opioids)
9	Documentation of all prescriptions, office visits, agreements, and instructions
10	Ethical concerns: discharging patient with advanced cancer and substance misuse; comanagement with substance abuse specialists should be initial step

NOTE. Data adapted.[35,36,37]
Abbreviations: ORT, Opioid Risk Tool; SOAPP, Screener and Opioid Assessment for Patients With Pain; STAR, Screening Tool for Addiction Risk; UDS, urine drug screen.

Del Fabbro JCO 2014
J Clin Oncol 32: 1734-1738

Management Strategies

Key Domains

1. Education
2. Harm reduction
3. Managing psychological & spiritual distress
4. Risk mitigation

Education

Printed

Digital

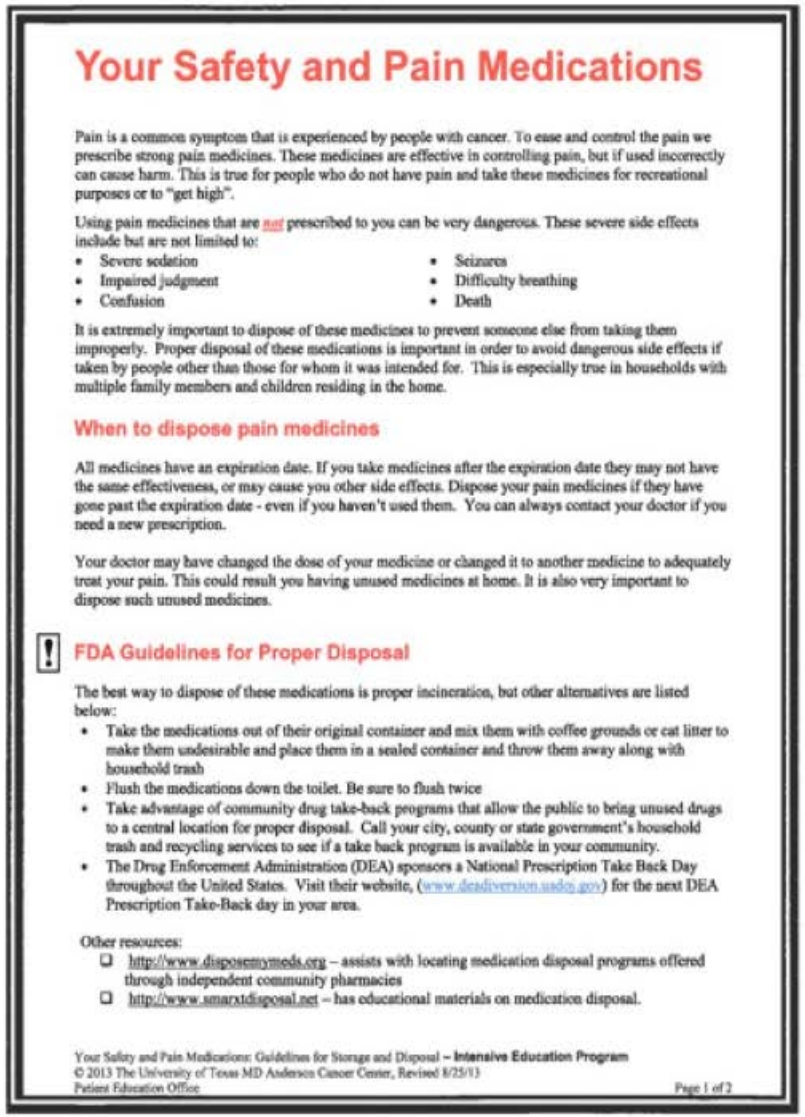
Social Media

Reddy Oncologist 2014,De La Cruz Oncologist 2017

Management Strategies

Education

- Proper opioid disposal methods (76% vs. 28%; p ≤ .0001)
- Share opioids with someone else (3% vs. 8%; p = .0311)
- Practice unsafe use of opioids (18% vs. 25% p = .0344)
- Danger of opioids when taken by others (p = .0099)
- Unused medication at home (38% vs. 47%; p = .0497)
- Keep medications in a safe place (hidden, 75% vs. 70%; locked, 14% vs. 10%; p = .0025)



Your Safety and Pain Medications

Pain is a common symptom that is experienced by people with cancer. To ease and control the pain we prescribe strong pain medicines. These medicines are effective in controlling pain, but if used incorrectly can cause harm. This is true for people who do not have pain and take these medicines for recreational purposes or to "get high".

Using pain medicines that are *not* prescribed to you can be very dangerous. These severe side effects include but are not limited to:

- Severe sedation
- Impaired judgment
- Confusion
- Seizures
- Difficulty breathing
- Death

It is extremely important to dispose of these medicines to prevent someone else from taking them improperly. Proper disposal of these medications is important in order to avoid dangerous side effects if taken by people other than those for whom it was intended for. This is especially true in households with multiple family members and children residing in the home.

When to dispose pain medicines

All medicines have an expiration date. If you take medicines after the expiration date they may not have the same effectiveness, or may cause you other side effects. Dispose your pain medicines if they have gone past the expiration date - even if you haven't used them. You can always contact your doctor if you need a new prescription.

Your doctor may have changed the dose of your medicine or changed it to another medicine to adequately treat your pain. This could result you having unused medicines at home. It is also very important to dispose such unused medicines.

FDA Guidelines for Proper Disposal

The best way to dispose of these medications is proper incineration, but other alternatives are listed below:

- Take the medications out of their original container and mix them with coffee grounds or cat litter to make them undesirable and place them in a sealed container and throw them away along with household trash
- Flush the medications down the toilet. Be sure to flush twice
- Take advantage of community drug take-back programs that allow the public to bring unused drugs to a central location for proper disposal. Call your city, county or state government's household trash and recycling services to see if a take back program is available in your community.
- The Drug Enforcement Administration (DEA) sponsors a National Prescription Take Back Day throughout the United States. Visit their website, (www.deadiversion.usdoj.gov) for the next DEA Prescription Take-Back day in your area.

Other resources:

- ☐ http://www.disposemymeds.org – assists with locating medication disposal programs offered through independent community pharmacies
- ☐ http://www.smarxtdisposal.net – has educational materials on medication disposal.

Proper Storage

Storing your pain medicines properly is just as important as disposal, because of the dangers of drug abuse as well as the severe harm that these medications can cause. Take the following steps to prevent improper use of these medications:

- You want to make sure they are out of reach to children and pets.
- Store the medications where they are not visible to others besides yourself or a designated caregiver who helps manage your medications.
- If you live in an unsafe neighborhood, keep your medications under lock and key.
- Keep track of the number of medications that you have used. Report any missing medications to law enforcement authorities.
- Do not tell people that you are taking strong pain medications.

Do's and Don'ts of Pain Medication Use

Do	Don't
• Always take pain medicine only as directed. Never change how you take the medicine, in any way, or take other medicines without first asking the doctor who prescribed your pain medicine.	• Never cut, chew, crush, or dissolve extended release pain medicine tablets or capsules. We may ask you to halve some immediate release tablets.
• Only get prescriptions for pain medicine from our supportive care center.	• Never cut a pain patch and do not expose a pain patch to a source of heat, like a heating pad, while the patch is attached to your skin.
• If you must get pain medicine anywhere else, such as in an emergency or from a dentist, you must tell our supportive care center nurses.	• Never share, sell, or trade your pain medicine with anyone. Never use someone else's medicines for pain or any other condition.
• All other doctors should be told of the pain medicines you are taking and that supportive care is prescribing them to you.	• Never use pain medicines to help you sleep, or combine pains with any sleep-aid drugs, such as tranquilizers or sedatives.
• We routinely ask for testing of your urine, saliva, or blood for drugs. You also may be asked to bring the unused portions of all drugs that you have been prescribed to clinic.	• Never use illegal drugs, such as cocaine, heroin, crystal meth, or others. Marijuana, even where legal, or alcohol — wine, beer, or hard liquor — may not be used without your pain medicine prescriber's permission.
• Only ask for pain medicine refills during regular office or clinic hours. Early refills for a replacement for lost, stolen, or spoiled pain medicine may not be allowed, depending what happened.	• Do not drive a car or operate dangerous equipment while taking pains until you know how you react to the medicine and your pain prescriber says it is okay.

Reddy et al. *Oncologist* 2017

Management Strategies
Harm Reduction

- Opioid prescription
  - Use long-acting opioids and limit IR
  - methadone and buprenorphine
  - Rotate to lower equianalgesic dose
  - Avoid demand PCA, use basal and clinician bolus only
  - Non –opioids for pain
- Selective Naloxone use?
  - For high risk of overdose?
  - Parenteral (IV, IM, SC; 0.4-1 mg), nasal (1 mg per nostril)
  - Caregivers need to be taught; repeat if no response
  - More research needed on outcomes

Kirsh et al. Palliat Supp Care 2007
Wermeling Drug Deliv and Tranls Res 2013
Strang et al. Drug Alcohol Depend 2016

Outpatient Opioid Rotation

- 120/512 (23%) underwent opioid rotation (OR)
- Uncontrolled pain (83%) most common indication
- 74/114 (65%) patients had a successful OR
- OR= improved pain, wellbeing, insomnia and depression
- Fentanyl transdermal to methadone most common
- MEDD decreased in patients with successful OR (P=0.04)

Reddy, The Oncologist, 2013

Comorbid psychiatric conditions & psychological interventions

- Co-occurring opioid use disorder and chronic pain
  >90% co-morbid psychiatric conditions
- Cognitive behavioral therapy, mindfulness based therapy
- Relaxation techniques, biofeedback, and distraction techniques
- Brief motivational interviewing

Management Strategies

Compassionate High Alert Team (CHAT) Program

Arthur Oncologist 2017

Triggers

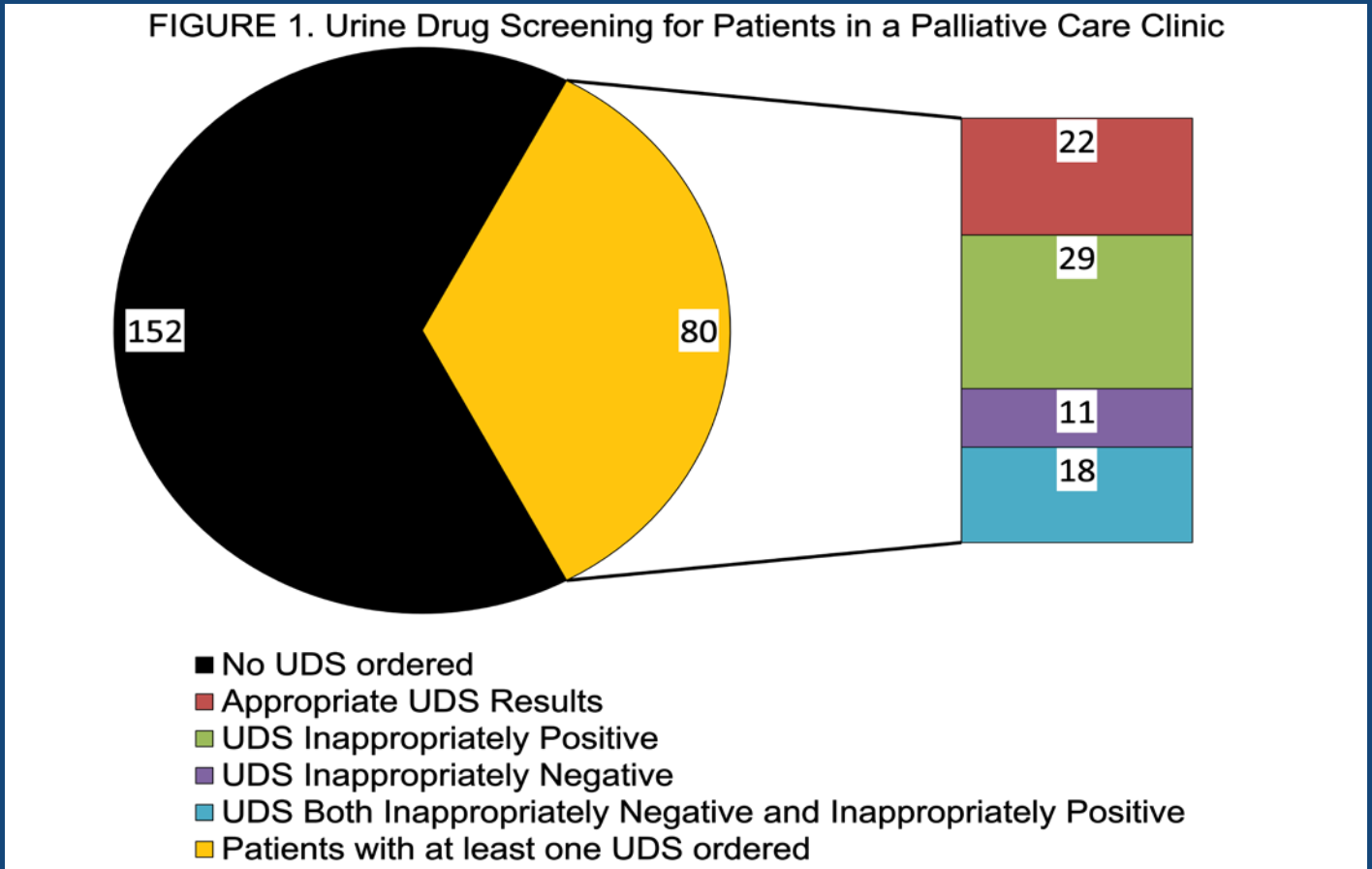
- Abnormal UDS results
- Multiple early refills requested
- Running out of opioids early
- Lost prescriptions
- medications multiple providers

Approach

- Education about safe opioid use
- Longitudinal counseling
- Sensitive communication
- Frequent monitoring
- Structured documentation
- Personalized treatment
  Logistical and caregiver support

Are Oncology patients at risk?
Urine drug screen (UDS) findings in a supportive care clinic

Rauenzahn, Cassel, Del Fabbro MASCC 2015



Opioids & sex-hormones
In Cancer patients low Testosterone is associated with

- Higher Opioid dose *Bruera 2004, Dev 2014*
- Fatigue, depression, poor HRQoL scores *Strasser 2006*
- Poor appetite, increased IL-6,ghrelin *Garcia 2006*
- Decreased survival *Del Fabbro JPSM 2010*

Opportunities for improved pain Mx

- Education of patients, family, providers (pamphlets –social media)
- Screening with brief questionnaire
- Psychological support, brief motivational interviewing
- Opioid sparing interventions rotation, modify PCA's
- Long acting opioids, Non-Opioids & Non-pharmacologic for pain
- Methadone role in rotation, combination Rx for neuropathic pain
- Risk mitigation with UDS,PMP
- 'Adapted' Universal precautions –no evidence despite gold standard
- Testosterone and Opioids

egidio.delfabbro@vcuhealth.org

Case Presentation

Cynthia Straub, Bon Secours

Case 1: Pain and Symptom Management

Are there any other pain management ideas I didn't use before Palliative Sedating this patient?

Patient Presentation
ECHO
3/28/19
Cynthia Straub, FNP-C, ACHPN

BON SECOURS MERCY HEALTH

80 y/o Female

- diagnosed with bladder cancer 12/2016.
- s/p bladder resection (no chemotherapy due to age and toxicity of Cisplatin)
- patient opted not to seek immunotherapy as she has Polymyalgia Rheumatica in remission
- 2/2017 evaluated at UVA and signed on for Phase III clinical trial of atezolizumab vs. Observation as adjuvant therapy for muscle-invasive bladder cancer after surgery. Began c/o right hip pain and found to have metastatic disease, undergone intra medullary nailing of the proximal right femur

4/5/2017
admitted to MRMC

- intractable back pain

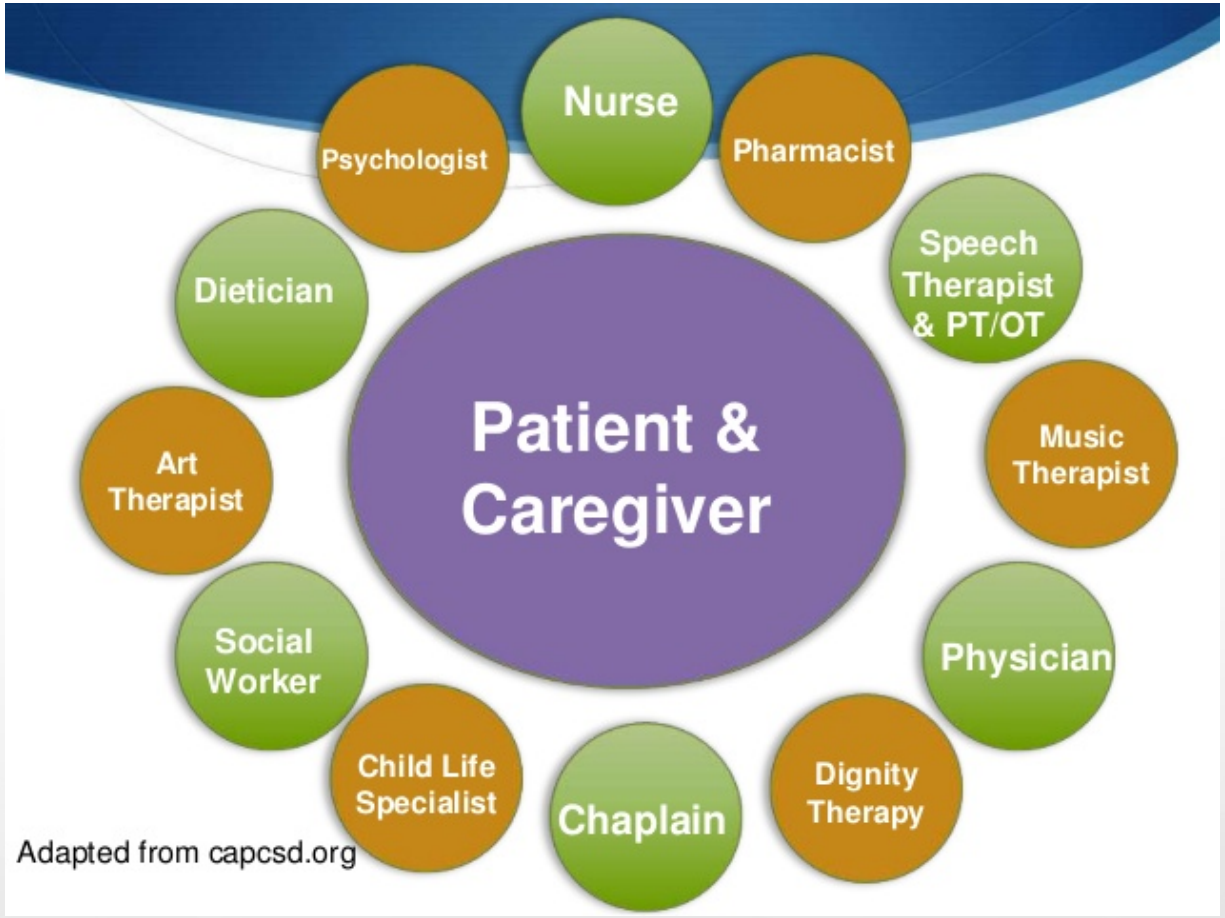
- scheduled for XRT on day of admission to help stabilize the bone in and around the metallic fixation hardware.

- MRI L-Spine: metastatic disease with superior endplate compression fracture at L3, transcortical spread at L3 demonstrated into anterior and left lateral epidural space especially within subarticular zone, subtle transcortical spread also suggested in the left anterior epidural space at S2.

HOW WOULD YOU MANAGE HER PAIN?

- 1. PCA Dilaudid (later changed to Fentanyl)
- 2. Decadron 4mg IV QD (increased to every 12 hours)
- 3. Specialty Mattress
- 4. Asked radiation to add single fraction to L-spine
- 5. Asked IR to evaluate for Kyphoplasty
- 4/7/17:
- 6. added Methadone, Toradol, lidoderm, Ativan

HOW WOULD YOU MANAGE HER PAIN?



4/10/17

- unable to undergo XRT due to pain
- patient expresses that she does not want to be a burden, wants to be able to ambulate. PT/OT assessment.

4/11/17

- meeting with patient, family, Palliative and Hospice interdisciplinary team to discuss pain management and end of life care.
- escalate treatment for anxiety

4/12/17

- add IV Ketamine

4/12/17 - 4/14/17

- titrating Ketamine up.
- no relief

- 4/14/17 Palliative Sedation
- Discussed expectations, family time.
- "what's taking so long?"

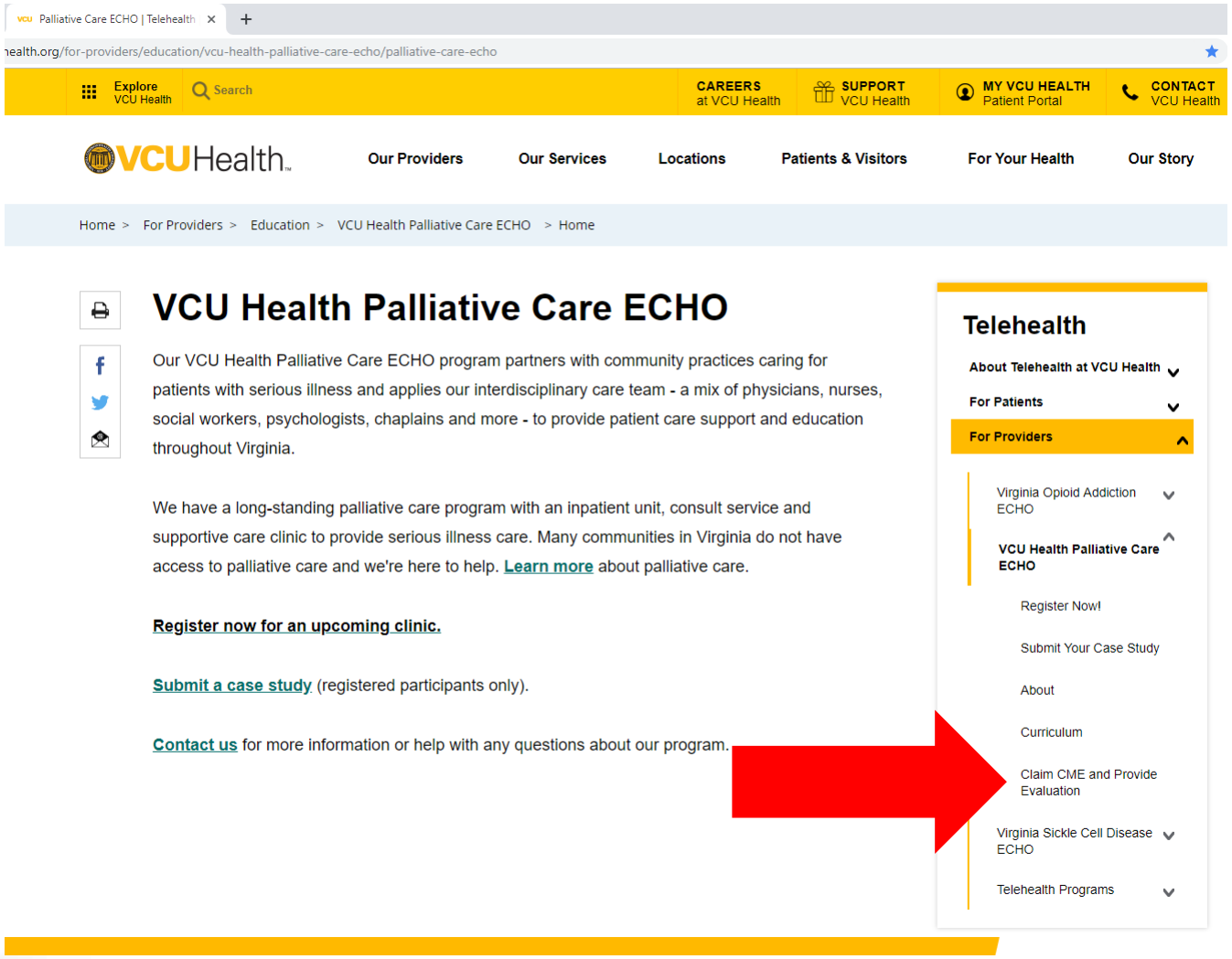
- 4/15/17 pt died

Accessing CME credit

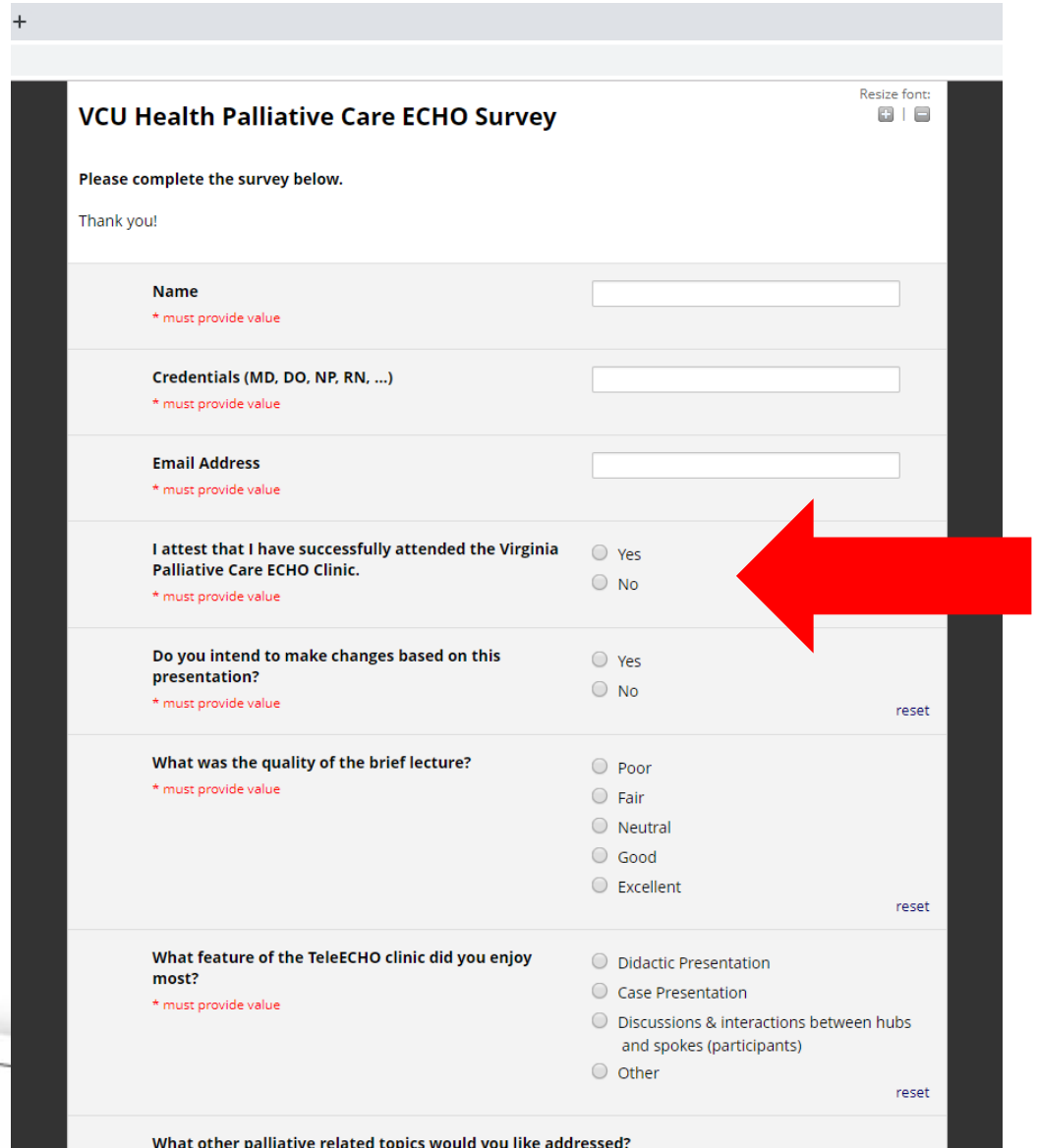
Submit your evaluation to claim your CME

After our live ECHO session, visit www.vcuhealth.org/pcecho

Click “Claim CME and Provide Evaluation”



Submit your evaluation to claim your CME



VCU Health Palliative Care ECHO Survey

Resize font:

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

Do you intend to make changes based on this presentation?
* must provide value
- Yes
- No

reset

What was the quality of the brief lecture?
* must provide value
- Poor
- Fair
- Neutral
- Good
- Excellent

reset

What feature of the TeleECHO clinic did you enjoy most?
* must provide value
- Didactic Presentation
- Case Presentation
- Discussions & interactions between hubs and spokes (participants)
- Other

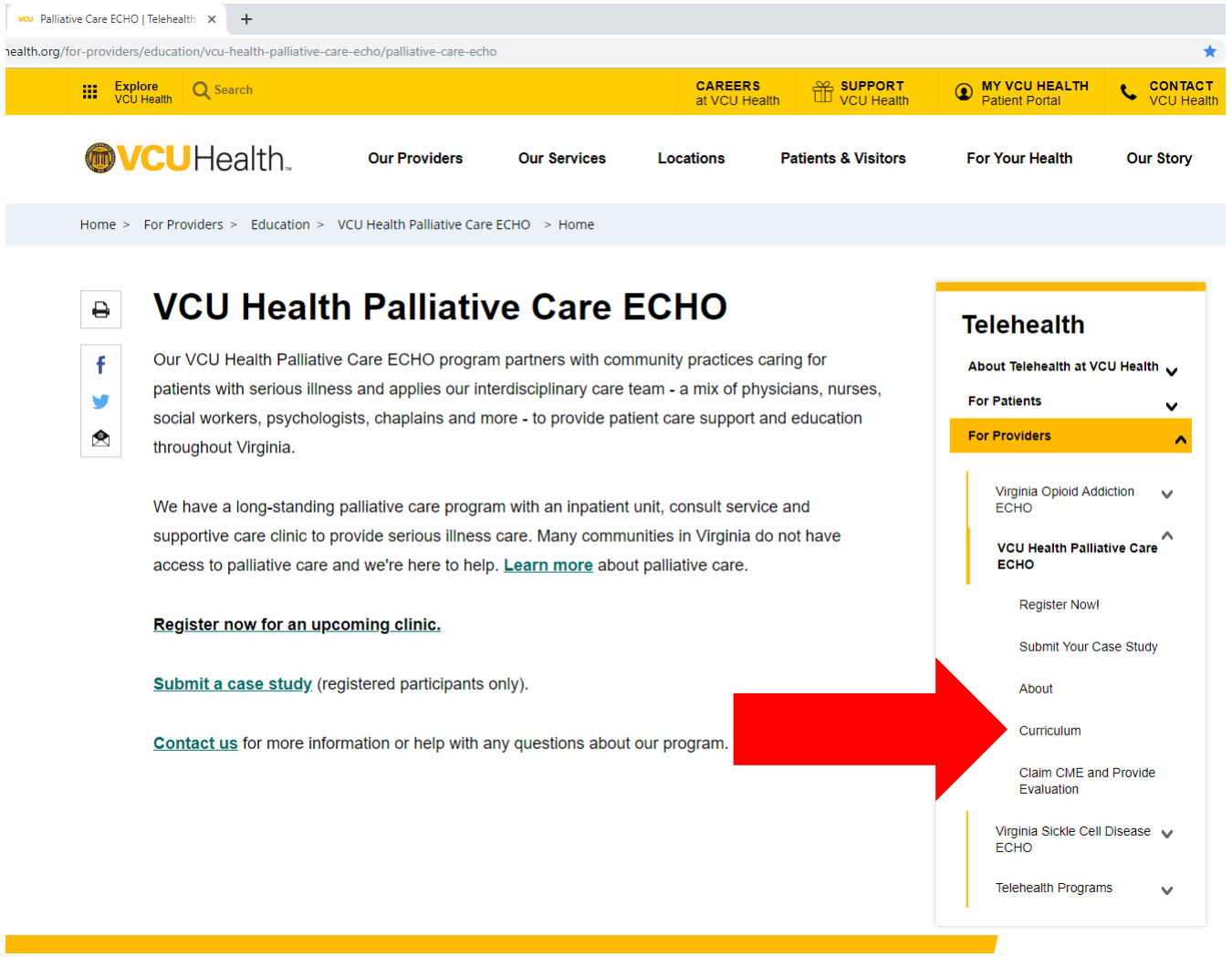
reset

What other palliative related topics would you like addressed?

View previously recorded ECHOs for CME

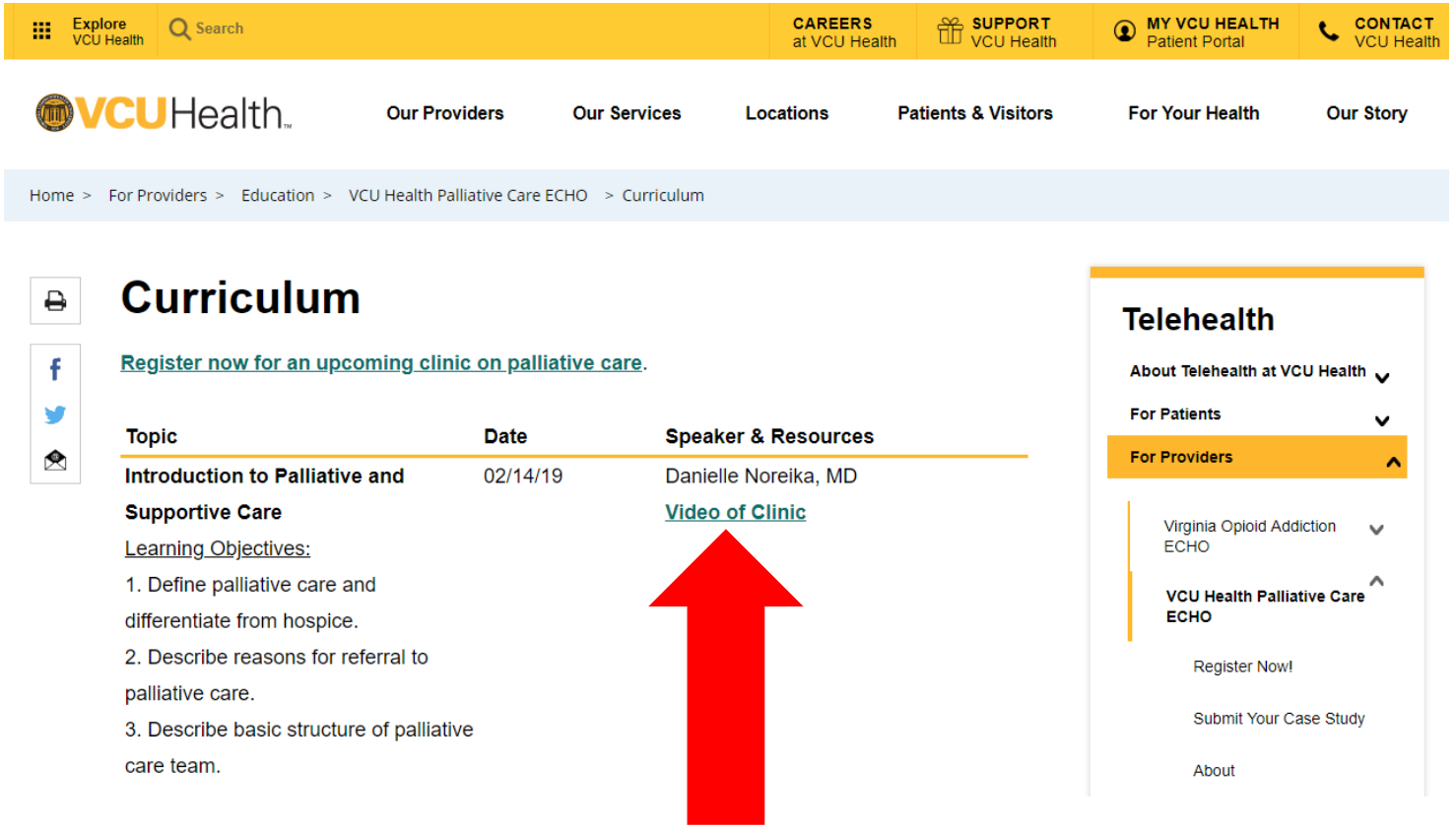
To view previously recorded sessions and claim credit, visit www.vcuhealth.org/pcecho

Click “Curriculum”



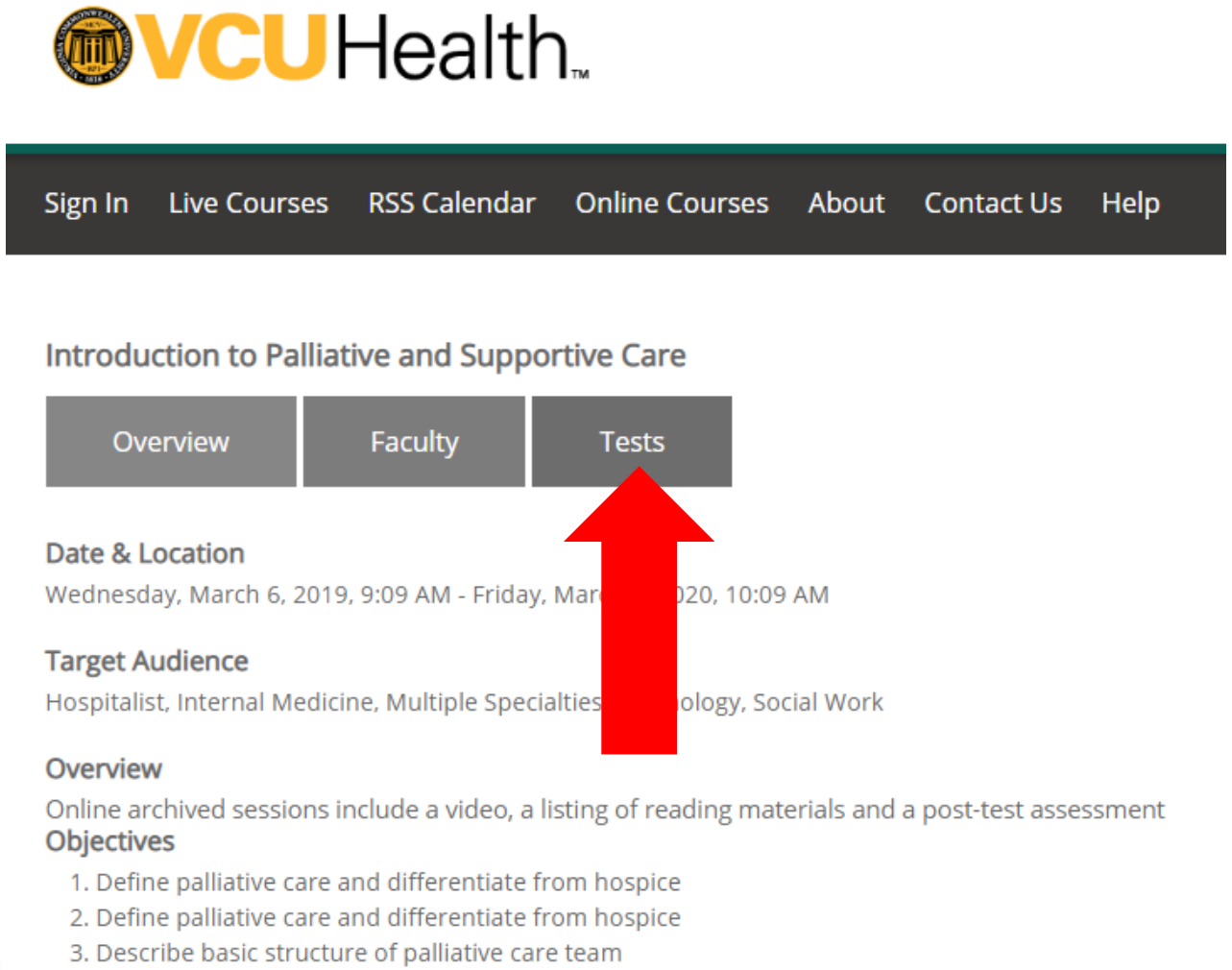
View previously recorded ECHOs for CME

Select the session you would like to view



View previously recorded ECHOs for CME

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



THANK YOU!

We hope to see you at our next ECHO