Delirium in Advanced Cancer Patients:

The Top Things You Should Know

Dr. Lawrence Lee

MD, CCFP-PC
Assistant Clinical Professor, Div of Palliative Care Medicine, Dept of Oncology, Univ of Alberta
Physician Consultant, Edmonton Zone Palliative Care Program (EZPCP)

No Conflicts of Interest

Objectives

Using a delirium case study, participants will be able to:

-Identify and manage delirium

-Complete an opioid rotation

-Treat hypercalcemia of malignancy

-Describe the indications for and the process of initiating palliative sedation

Significance of Delirium

A Has a prevalence of 28-48% in patients admitted to a palliative care unit.

B Increases as death approaches

C Prevalence of 90% in the last week of life

D 1/3-2/3 of cases misdiagnosed, diagnosed late, or not diagnosed at all

E Is considered a palliative “emergency/urgency”

DSM-V criteria for delirium

A. Disturbance in ***attention*** (i.e., reduced ability to direct, focus, sustain, and shift attention) and ***awareness*** (reduced *orientation to the environment*)

B. The disturbance develops over a short period of time (usually hours to a few days), *represents an* ***acute change*** *from baseline attention and awareness*, and tends to ***fluctuate*** in severity during the course of a day.

C. An additional disturbance in ***cognition*** (e.g.memory deficit, disorientation, language, visuospatial ability, or perception).

D. Caused by a **general medical condition**

Why we miss delirium?

Contributing factors

- Fluctuating symptoms
- Hypoactive/hypoalert/mixed subtype
- Failure to systematically assess cognitive function
- Overlap with other syndromes
  - Depression
  - Dementia

CAM criteria for delirium

Confusion Assessment Method "AIDS"

+ **(A)cute** and fluctuating course
+ **(I)nattention**
+/- **(D)isorganized** thinking
+/- **(S)ensorium**/LOC is altered

BEST TOOL for identifying delirium?

>10 validated tools– no consensus

Main point

Use tool consistently and recognize limitations

Folstein MMSE: Assesses cognition but not other aspects of delirium (False negatives)

Hjermstad MJ et al. Palliat Med 2004; 18:494-506

REVERSIBILITY OF DELIRIUM

- Approximately 50% of episodes may be reversible (usually within 2-7 days)
- Sometimes causes are unclear
  - Underlying cancer
- Reversibility rate decreases with subsequent episodes

Lawlor PG et al. Arch Int Med 2000; 160: 786-794

Common reversible causes of delirium

Usually multifactorial (median 3 causes)

DIMS

(D)rugs
(I)nfection
(M)etabolic
(S)tructural

Common reversible causes of delirium

Drugs

Withdrawal from: EtOH, Nicotine, Benzos

Presence of:

- Opioids
- Benzodiazepines
- Antidepressants
- Anticholinergics
- Corticosteroids

Infection: Respiratory, UTI, cellulitis, sepsis

Common reversible causes of delirium (cont'd…)

Metabolic

- ↑Calcium
- ↓Sodium
- Renal failure/dehydration
- Hepatic failure
- Hypoxia
- Hypoglycemia

Structural: CNS metastases

Address underlying cause(s) in accordance with goals of care

- Address withdrawal
- Consider reducing or switching opioid
- Minimize psychotropic medications
- Consider antibiotics if infection suspected
- Identify and correct dehydration and metabolic abnormalities
- Correct hypoxia
- Consider steroids/RT if CNS metastases suspected/documented

Delirium Case Study

CASE

66 year old woman, retired teacher, living at home with husband

- Diagnosed with NSCLC w/ mets to liver and bone, no further treatments.
- No relief with ↑'ing doses of Morphine for chest pain due to cancer, lots of breakthroughs (extra doses) used

PMHx, PsychHx: nil **Meds:** Morphine, Lorazepam **Allergies:** NKDA

SHx: 50PY smoker, quit*15Y, no EtOH/rec drugs.

ROS: Pt is more confused*3/7. Difficulty swallowing pills, drinking poorly, has visual hallucinations, gets impulsive/restless at night. No symptoms/signs of pneumonia. Some dysuria.

O/E: Circumferential, forgets question, cachectic, dry mucous membranes, ↓AE R lung base, myoclonus

MMSE is 23/30 (expected 27/30), PPS40% (mainly sit/lie, mainly assistance)

Goals of Care: C1, would like to remain home as long as possible.

CASE

AIDS

DIMS

- **(D)rugs:**
- **(I)nfection:**
- **(M)etabolic:**
- **(S)tructural:**

Other Considerations

CASE: AIDS, DIMS

Other Considerations

66 year old woman, retired teacher, living at home with husband

- Diagnosed with NSCLC w/ **mets to liver** and bone, no further treatments.
- No relief with **↑'ing doses of Morphine** for chest pain due to cancer, lots of breakthroughs (extra doses) used

PMHx, PsychHx: nil **Meds: Morphine, Lorazepam** **Allergies:** NKDA

SHx: 50PY smoker, quit*15Y, no EtOH/rec drugs.

ROS: Pt is more **confused*3/7**. **Difficulty swallowing pills**, **drinking poorly**, has **visual hallucinations**, **gets impulsive/restless at night**. **No symptoms/signs of pneumonia. Some dysuria.**

O/E: **Circumferential, forgets question**, cachectic, **dry mucous membranes**, ↓AE R lung base, **myoclonus**

MMSE is **23/30 (expected 27/30)**, PPS40% (mainly sit/lie, mainly assistance)

Goals of Care: C1, would like to remain home as long as possible.

Edm Palliative Resources

Plan	How to…
Delirium, rule out reversible causes: • **Stop morphine and lorazepam** • **Order hydromorphone SC ATC +PRN** • Order haloperidol 1 mg SC q1h PRN for agitation	Obtaining SC medications: • Business Hrs- Market Drugs, Pharmacare Group • After Hrs- 24 hr Shoppers (Ellerslie+Namao) • Emergently After Hrs- EMS ATR
• **Get bloodwork+urinalysis/culture by home collections**	F: 780-452-5294, P: 780-453-9440 Fax requisiton to the above- indicate that pt is homebound
Homecare Support: • Insert SC site for SC medications • **Start hydration by hypodermoclysis (HDC)** • Teaching family to provide SC meds, give HDC • Services: AM + HS care, bath assist 2x/week • Equipment: walking aids, grab bars, hospital bed	Initiating homecare: anyone (physician order not required) can call community care access at: **780-496-1300**
Referring to Palliative Care • Community Consult Team Referral • Hospice • Hospice Pictures	Referral Process Hospice Admission Guidelines Virtual Tour

CASE: Opioid Rotation

Patient is taking morphine 20 mg PO q4h ATC + 10 mg PO q1h PRN

While lucid, the patient's pain was well controlled and she was requiring very few BTA.

Since getting confused, she has been moaning, groaning and restless. Family have perceived this as pain and have been treating this with ++BTA.

CASE: Opioid Rotation

	Step 1: Calculate the total of the daily dose of opioid	Step 2: Calculate equianalgesic dose of new opioid
Currently on: -morphine 20 mg PO q4h ATC -morphine 10 mg PO q1h PRN **Goal is:** -Rotate to another opioid & switch to the SC route -Oxycodone: no readily available SC formulation **-hydromorphone (HM) SC q4h + q1h PRN**	ATC: =20 mg * 6 =120 mg morphine PO/24h PRN: how many to include? Total daily dose (TDD) = 120 mg of PO morphine	**HYDROmorphone is 5x more potent than morphine therefore we need 5x less** TDD: =morphine PO 120 mg/5 =HM PO 24 mg

CASE: Opioid Rotation

Step 3: Decrease dose for incomplete cross-tolerance (~1/5 to 1/3)	Step 4: Calculate regular dose	Step 5: Order PRN doses
Total daily dose: 24 mg PO HM Dose reduction of: • 25% (1/4)= 6 mg 24-6 = 18 mg • 33% (1/3)= 8 mg 24-8 = 16 mg *Convert to SC Equivalents: SC/IV = 2x more potent than PO* 18/2= 9 mg HM TDD	HM SC 9 mg/6 = HM 1.5 mg SC q4h	**10% of total daily dose** = 10% of 9 mg = HM 0.9 mg SC q1h PRN for pain In the home, where pre-filled syringes are being provided, give half the q4h dose as PRN HM 1.5 mg SC q4h ATC HM 0.75 mg SC q1h PRN for pain

CASE: Opioid Rotation

		Equianalgesia	Equianalgesia
Potency relative to morphine	Opioid	PO equivalents	SC/IV*
1.5 to 2*	oxycodone	5-7.5 mg	2.5-3.75 mg
X			
5	HYDROmorphone	2 mg	1 mg
=	morphine	10 mg	5 mg
10	codeine	100 mg	50 mg

*Oxycodone is 1.5x more potent that morphine

*SC/IV = 2x more potent than PO

DELIRIUM and PAIN ASSESSMENT

- Patient's pain report is unreliable
- Need to distinguish pain from agitation
- Disinhibition → exaggerated pain expression

"And with 10 being the highest, you're sure you're only at a 6?"

Distinguishing pain from agitation

- Did the patient have the **pain before the delirium?**
- Is the patient able to **localize the pain** in a **consistent** manner?
- Does the **pain respond to analgesics**? Does it respond to neuroleptics?
- What is the patient's **level of consciousness**?

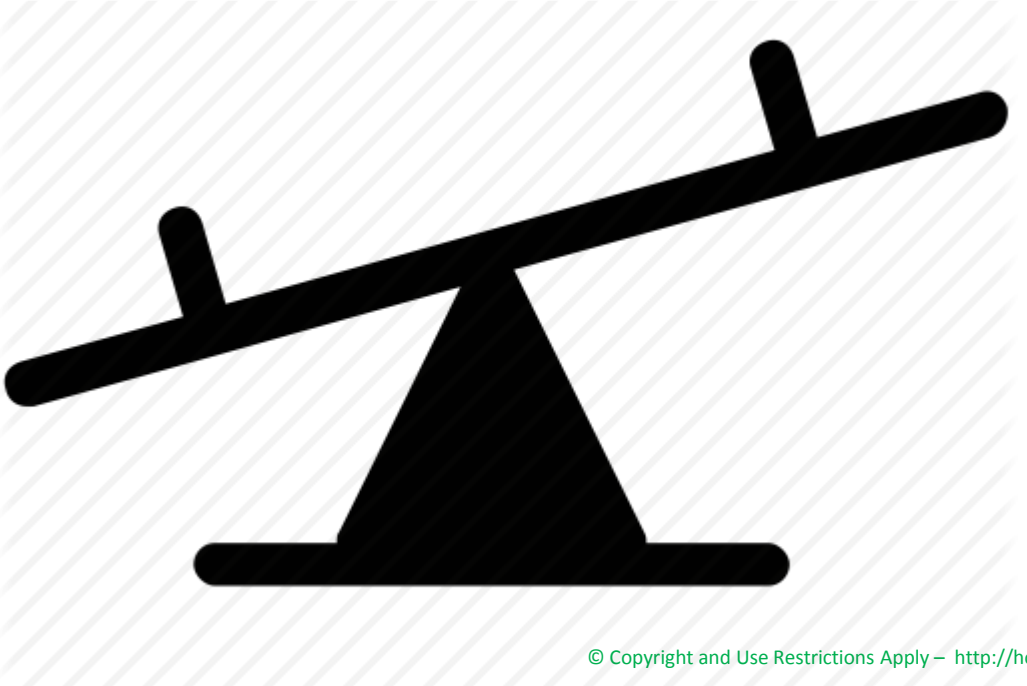
CASE: Opioid Rotation

Cross-Tolerance:

- a patient may have become tolerant to one of the side effects, such as somnolence, of a particular opioid, but when switched to the equianalgesic dose of another opioid the patient may once again experience initial somnolence
- therefore when switching from one opioid to another, decrease the dose of the new opioid by 20-30% because cross tolerance between opioids is not always complete

CASE: Opioid Rotation

Factors that influence whether you make a:		
Smaller Dose Reduction (20-25%)		**Larger Dose Reduction (33+%)**
Pain is well controlled	Pain Control	Pain is poorly controlled
Opioid toxicities are less severe	Severity of Toxicity	Opioid toxicities are more severe



CASE: Hypercalcemia

Bloodwork results generally unremarkable except for:

- Elevated Cr, abnormal liver enzymes (unchanged)
- **Calcium is 2.60**
- **Albumin is 25**

- How do we correct the calcium?

CASE: Hypercalcemia

Corrected Ca = serum Ca + (40-alb)*0.02

= 2.60+(40-25)*0.02

= 2.60+15*0.02

=2.60+0.30=**2.90** (N<2.60)

Pathophysiology of hypercalcemia of malignancy is due to PTH related peptide that causes mobilization of bony stores of calcium.

CASE: Hypercalcemia

Corrected Calcium	Severity	Treatment
2.65-2.80	Mild	Hydration: HDC 70 ml/hr (=limit) or add additional HDC site IV 100-200 ml/hr
2.80-3.00	Moderate	Hydration as above, add Bisphosphonate Pamidronate 60-90 mg in 500-1000 ml of NS IV given over 4-6 hours Clodronate 1500 mg in 500-1000 ml of NS IV given over 4-6 hours
3.00+	Severe	**Hydration & Bisphosponate as above, add Calcitonin** Calcitonin 100-200 units SC TID * 6 doses

Pamidronate must not be administered subcutaneously.

CASE: Hypercalcemia

Bloodwork:

- Obtain creatinine before administering a bisphosphonate (BisP)
- If renal impairment is present – especially prerenal – pre-hydrate the patient with N/S prior to administering the BisP
- Order electrolytes, calcium, urea and creatinine on the third day after administering the BisP to document a decrease in serum calcium
- Symptomatic hypocalcemia is very rare with bisphosphonates which inhibit osteoclast activity

Clodronate vs Pamidronate:

- Clodronate and Pamidronate are equally efficacious in decreasing the calcium however, the duration of effect of pamidronate may be more sustained (4 wks) vs clodronate (2 wks)

CASE: Hypercalcemia

Calcitonin:

- Calcitonin is a temporary option for rapid reduction in calcium levels but its effect is not sustained. It can be used while the patient is being hydrated in preparation for bisphosphonate administration.

Refractory Hypercalcemia:

- For refractory symptomatic hypercalcemia re-treatment with the same bisphosphonate or using a different bisphosphonate. If some cases, zoledronic acid (special access required, hypercalcemia must be refractory to pamidronate) is indicated.

Delirium- Symptomatic treatment: Non- Pharmacological

- Structure and routine
- Quiet, well-lit room
- Proximity to nursing station
- Visible clock and calendar
- Familiar objects and people
- Continuity of nursing staff
- Calm, respectful attitude
- Simple explanations

Delirium- Symptomatic treatment: Pharmacological

Mild: Haloperidol 1 mg PO/SC ATC + q1h PRN

Moderate: Methotrimeprazine (Nozinan) 6.25-25 mg SC ATC + q1h PRN

Use typical anti-psychotics because SC formulations are readily available unlike atypicals.

Severe: If refractory hyperactive delirium, consider **palliative sedation with continuous subcutaneous midazolam**

Delirium- Symptomatic treatment: Pharmacological

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

Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care: A Randomized Clinical Trial.

Agar MR[1], Lawlor PG[2], Quinn S[3], Draper B[4], Caplan GA[5], Rowett D[6], Sanderson C[7], Hardy J[8], Le B[9], Eckermann S[10], McCaffrey N[11], Devilee L[12], Fazekas B[12], Hill M[13], Currow DC[12].

CONCLUSIONS AND RELEVANCE: In patients receiving palliative care, individualized management of delirium precipitants and supportive strategies result in lower scores and shorter duration of target distressing delirium symptoms than when risperidone or haloperidol are added.

PALLIATIVE SEDATION

- Process of inducing/maintaining deep and permanent sleep in order to relieve refractory symptoms in pts who are close to death.

NOT EUTHANASIA, PAS, MAID

- Most common indications: intractable hyperactive delirium and dyspnea
- ?Risk of hastening death → No evidence!
- Midazolam: Benzodiazepine with short t1/2 → easily titratable by SC infusion

PALLIATIVE SEDATION

- Put 100 mg of midazolam in 100 ml of NS (concentration = 1 mg/ml)
- Bolus 2.5-5 mg SC midazolam
- Start continuous SC infusion of midazolam at 1-5 mg/hr then increase by 1 mg/hr q15min until deep sedation is achieved (no response to voice or physical stimulation).

Communicating with family about palliative sedation

- Discuss proactively
- Review understanding of illness/prognosis, goals of care
- Sedation used only if symptoms refractory to all other measures
- Patient will lose ability to communicate
- Usually irreversible, with death from underlying illness occurring within days

AHS Seniors Delirium Protocol

Alberta Health Services

Affix patient label within this box

Seniors Delirium Protocol

Confusion Assessment Method Score			
		Yes	**No**
For a diagnosis of delirium these two must be present → and →	Was the onset acute and/or does behaviour fluctuate?		
	Is there evidence of inattention? *(difficulty focusing, attention, shifting and keeping track)*		
and at least one of these → and/or →	Is there evidence of disorganized thinking? *(incoherent, rambling, illogical flow of ideas)*		
	Is there altered level of consciousness? *(i.e. hypoactive or hyperactive)*		
Management of delirium in older persons should always be individualized.		**Score**	/4

Adapted with permission. Copyright 2003, Sharon K. Inouye, M.D., MPH.

Alcohol Use

If alcohol use suspected, give the following
- ☐ Thiamine 100 mg IV/PO daily for 3 days
- ☐ Folic acid 5 mg po daily for _____ days
- ☐ Implement CIWA assessment and alcohol withdrawal protocol *(where available)*

Laboratory Tests, Diagnostic Imaging and Other Investigations

Laboratory Tests

☐ CBC and differential	☐ urinalysis	☐ random glucose	☐ sodium
☐ potassium	☐ chloride	☐ CO2	☐ creatinine
☐ urea	☐ calcium	☐ magnesium	☐ albumin
☐ ALP	☐ ALT	☐ bilirubin	☐ ABG

Cultures
- ☐ Urine for C and S ☐ MSU ☐ In/Out Catheter
- ☐ sputum for C and S ☐ blood cultures *(if temperature is 1.2 0C above normal)*

Consider performing the following tests if not completed in the last 6 weeks
☐ B12 ☐ TSH

Diagnostic Imaging *(check all that apply)*
- ☐ ECG ☐ Chest x-ray *(as indicated)* ☐ Flat Plate Abdomen *(as indicated)*
- ☐ CT head *(as indicated)* ☐ MRI head *(as indicated)*

☐ Other investigations *(specify)* _____

Orders

Vital Signs
q _____ h while awake

Maintain O2 saturations greater than or equal to 90%
☐ Initiate oxygen at 2 L/minute and titrate as appropriate *(caution if CO_2 retention)*

☐ Intake and output
If oral intake less than 1200 mL/24 hours
☐ push fluids or ☐ IV / ☐ Clysis _____ at _____ mL / hour for _____hours

Name of prescriber and designation *(print)*	Signature	Date *(yyyy-Mon-dd)*

09628(Rev2011-01) **White -** Chart **Canary -** Pharmacy Page 1 of 2

Online Palliative Resources

- Online Resources:
  - Prov Pall/EOL Care webpage: https://myhealth.alberta.ca/palliative-care
  - EZ Website: www.palliative.org
    - 99 Common Questions Handbook (pdf, free)
    - Alberta Hospice Pall Care Manual (pdf, free)
    - Palliative Care Tips
    - A Caregiver's Guide
  - Pallium Canada ($): Pocketbook, eBook, app
- Further Educational Opportunities (www.palliative.org):
  - LEAP (Learning Essential Approaches to Pall Care)
  - Annual Edm Palliative Care Conference (Oct)

QUESTIONS?