Delirium in Advanced Cancer Patients:
The Top Things You Should Know

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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)

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

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

DIMIS

(D)rugs:

(I)nfection:

(M)etabolic:

(S)tructural:

Other Considerations
CASE: AIDS, DIMS

Other Considerations

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## Edm Palliative Resources

### Plan

<table>
<thead>
<tr>
<th>Delirium, rule out reversible causes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Stop morphine and lorazepam</td>
</tr>
<tr>
<td>• Order hydromorphone SC ATC +PRN</td>
</tr>
<tr>
<td>• Order haloperidol 1 mg SC q1h PRN for agitation</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>How to...</th>
</tr>
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<tbody>
<tr>
<td>Obtaining SC medications:</td>
</tr>
<tr>
<td>• Business Hrs- Market Drugs, Pharmacare Group</td>
</tr>
<tr>
<td>• After Hrs- 24 hr Shoppers (Ellerslie+Namao)</td>
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<td>• Emergently After Hrs- EMS ATR</td>
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| Get bloodwork+urinalysis/culture by home collections |

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<th>Homecare Support:</th>
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<tbody>
<tr>
<td>• Insert SC site for SC medications</td>
</tr>
<tr>
<td>• Start hydration by hypodermoclysis (HDC)</td>
</tr>
<tr>
<td>• Teaching family to provide SC meds, give HDC</td>
</tr>
<tr>
<td>• Services: AM + HS care, bath assist 2x/week</td>
</tr>
<tr>
<td>• Equipment: walking aids, grab bars, hospital bed</td>
</tr>
</tbody>
</table>

| Initiating homecare: anyone (physician order not required) can call community care access at: 780-496-1300 |

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<th>Referring to Palliative Care</th>
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<tbody>
<tr>
<td>• Community Consult Team Referral</td>
</tr>
<tr>
<td>• Hospice</td>
</tr>
<tr>
<td>• Hospice Pictures</td>
</tr>
</tbody>
</table>

### How to...

- F: 780-452-5294, P: 780-453-9440
- Fax requisition to the above- indicate that pt is homebound

- Initiating homecare: anyone (physician order not required) can call community care access at: **780-496-1300**
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

<table>
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<tr>
<th>Currently on:</th>
</tr>
</thead>
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<tr>
<td>- morphine 20 mg PO q4h ATC</td>
</tr>
<tr>
<td>- morphine 10 mg PO q1h PRN</td>
</tr>
</tbody>
</table>

**Goal is:**
- Rotate to another opioid & switch to the SC route
- Oxycodone: no readily available SC formulation
- Hydromorphone (HM) SC q4h + q1h PRN

### Step 1: Calculate the total of the daily dose of opioid

<table>
<thead>
<tr>
<th>ATC:</th>
</tr>
</thead>
<tbody>
<tr>
<td>= 20 mg * 6</td>
</tr>
<tr>
<td>= 120 mg morphine PO/24h</td>
</tr>
</tbody>
</table>

### Step 2: Calculate equianalgesic dose of new opioid

<table>
<thead>
<tr>
<th>PRN: how many to include?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total daily dose (TDD) = 120 mg of PO morphine</td>
</tr>
</tbody>
</table>

**HYDROMorphone is 5x more potent than morphine therefore we need 5x less**

<table>
<thead>
<tr>
<th>TDD:</th>
</tr>
</thead>
<tbody>
<tr>
<td>= morphine PO 120 mg/5</td>
</tr>
<tr>
<td>= HM PO 24 mg</td>
</tr>
</tbody>
</table>
**CASE: Opioid Rotation**

<table>
<thead>
<tr>
<th>Step 3: Decrease dose for incomplete cross-tolerance (~1/5 to 1/3)</th>
<th>Step 4: Calculate regular dose</th>
<th>Step 5: Order PRN doses</th>
</tr>
</thead>
</table>
| Total daily dose: 24 mg PO HM | 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 |
| 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* |  |  
HM 1.5 mg SC q4h ATC  
HM 0.75 mg SC q1h PRN for pain |
| 18/2= 9 mg HM TDD |  |  |
### CASE: Opioid Rotation

<table>
<thead>
<tr>
<th>Potency relative to morphine</th>
<th>Opioid</th>
<th>PO equivalents</th>
<th>SC/IV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 to 2*</td>
<td>oxycodone</td>
<td>5-7.5 mg</td>
<td>2.5-3.75 mg</td>
</tr>
<tr>
<td>X</td>
<td>HYDROmorpheone</td>
<td>2 mg</td>
<td>1 mg</td>
</tr>
<tr>
<td>10</td>
<td>codeine</td>
<td>100 mg</td>
<td>50 mg</td>
</tr>
</tbody>
</table>

*Oxycodone is 1.5x more potent that morphine

*SC/IV = 2x more potent than PO
DELIРИUM 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:

<table>
<thead>
<tr>
<th>Smaller Dose Reduction (20-25%)</th>
<th>Larger Dose Reduction (33+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain is well controlled</td>
<td>Pain is poorly controlled</td>
</tr>
<tr>
<td>Opioid toxicities are less severe</td>
<td>Opioid toxicities are more severe</td>
</tr>
<tr>
<td>Pain Control</td>
<td>Severity of Toxicity</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Corrected Calcium</th>
<th>Severity</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.65-2.80</td>
<td>Mild</td>
<td>Hydration: HDC 70 ml/hr (=limit) or add additional HDC site IV 100-200 ml/hr</td>
</tr>
<tr>
<td>2.80-3.00</td>
<td>Moderate</td>
<td>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</td>
</tr>
<tr>
<td>3.00+</td>
<td>Severe</td>
<td>Hydration &amp; Bisphosphonate as above, add Calcitonin Calcitonin 100-200 units SC TID * 6 doses</td>
</tr>
</tbody>
</table>

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

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

Agar MR¹, Lawlor PG², Quinn S³, Draper B⁴, Caplan GA⁵, Rowett D⁶, Sanderson C⁷, Hardy J⁸, Le B⁹, Eckermann S¹⁰, McCaffrey N¹¹, Devilee L¹², Fazekas B¹², Hill M¹³, Currow DC¹².

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

Confusion Assessment Method Score

For a diagnosis of delirium these and/or two must be present

- 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. hypactive or hyperactive)

Management of delirium in older persons should always be individualized.

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 14 days
- Implement CiWA assessment and alcohol withdrawal protocol (where available)

Laboratory Tests, Diagnostic Imaging and Other Investigations

Laboratory Tests

- CBC and differential
- Potassium
- Urea
- ALP
- Cultures
- Urine for C and S
- Sputum for C and S

- Urinalysis
- Chloride
- Calcium
- ALT
- MSU
- Blood cultures (if temperature is 1.2°C 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)
- CT head (as indicated)
- Flat Plate Abdomen (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 CO2 retention)

Intake and output

- If oral intake less than 1200 mL/24 hours
- Push fluids or IV / D Clysis

Name of prescriber and designation (print) Signature Date (yyyy-MM-dd)
Online Palliative Resources

Online Resources:

- Prov Pall/EOL Care webpage: [https://myhealth.alberta.ca/palliative-care](https://myhealth.alberta.ca/palliative-care)
- EZ Website: [www.palliative.org](http://www.palliative.org)
  - [99 Common Questions Handbook (pdf, free)](http://www.palliative.org/99questions)
  - [Alberta Hospice Pall Care Manual (pdf, free)](http://www.palliative.org/manual)
  - [Palliative Care Tips](http://www.palliative.org/tips)
  - [A Caregiver’s Guide](http://www.palliative.org/guide)
- [Pallium Canada ($)]: Pocketbook, eBook, app

Further Educational Opportunities ([www.palliative.org](http://www.palliative.org)):
- [LEAP (Learning Essential Approaches to Pall Care)](http://www.palliative.org/leap)
- Annual Edm Palliative Care Conference (Oct)
QUESTIONS?