Larry Clark Memorial Lecture
“Dealing with Challenging Symptom Management Issues”

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Oregon Hospice & Palliative Care Association
Professional Practices Exchange 2017

Requested Topics for Today’s Presentation

1. “Switching” to formulary medications
2. Symptom management issues
3. Transitioning between analgesics
4. Medical marijuana use in hospice
5. Administering naloxone in hospice care today

Advice from NHPCO Regarding Medicare Part D

1. Make sure to explain to the patient and family that Medicare requires the hospice provider to provide a medication list to Medicare which must be reviewed and updated weekly.
2. Explain to patients and families that they will not be able to pick up medications not included in the hospice plan.
3. Medicare Part D will only pay for those medications if the hospice provider validates the medication with the pharmacy and provides information that it is related to the terminal illness or related conditions and can be covered by Part D.
4. Discuss the possibility that there could be drugs that are the patient’s liability. If the patient wants to continue taking drugs that have been determined by the hospice to be medically unnecessary and are not included in the hospice plan of care.
More CMS Medication Audits?

• Is your hospice prepared?
• CMS suggests that “most medications a hospice patient takes should be covered by hospice”…
• Hospice formulary management is key!

CMS & Medicare Part D

• 2017: “Hospices” continue to bill Medicare Part D for medication related to either the terminal and or secondary diagnosis!
• Clarification: Hospices don’t bill Medicare Part D, Pharmacies do!
• CMS Goal: Hospice pays for all medications used during hospice care ????

CMS & Hospice Formulary Management

CMS:
• Hospices have the right to elect a medication formulary.
• Hospices do not have to pay for non-formulary medications.
• Medicare Part D is not to pay for medications used to palliate symptoms associated with the primary or secondary diagnosis…
Which medications should be minimized in end of life care?

Symptom Management Facts

• Good symptom control is an essential component of care at the end of life.\(^1\)
• Patients suffering with treatable symptoms in hospice care\(^2\)
  • Pain 76%
  • Anxiety and agitation 43%
  • Depression 51%
  • Lack of appetite 63%
  • Nausea and vomiting 24%

Eliminate Other Causes of Symptoms\(^2\)

• Does the patient have an infection?
• Is pain under control?
• Is the patient having any psychosocial or emotional issues?
• When was the last bowel movement?
• Does the patient have a fever?
• Does the patient have any breathing difficulty?
• Is the patient’s bladder full?
• Has the patient received any new medication?
• Is anything physically interfering with the patient’s comfort?
Pain Management

- Greater use of valid pain assessment scales constitutes an area for improvement in hospice care.\(^1\)
  - 70% of patients assessed with a valid pain scale saw improvement in pain.\(^2\)
- Many dying patients experience serious pain, despite the availability of effective medications.\(^1\)
- In the study Symptom Burden at the End of Life, 76% of patients presented with pain present upon admission assessment.\(^3\)

Keep Families Aware of the Benefits of Pain Management

- Improving patient quality of life
- Minimize side effects
- Enhance patient comfort and physical function
- Regulate sleep routine

Wong Baker FACES* Pain Rating Scale

Ask: What pain management intervention will work the best for this patient?\(^3\)
Selecting the Right Opioid

- It's complicated!
- Age
- Renal Function
- Hepatic Function
- Environment of Care
- Diagnosis & Type of Pain
- Past Medical History

Opioid Adverse Reactions

- Nausea
- Vomiting
- Constipation
- Delirium
- Respiratory depression
- Tolerance
- Abdominal bloating/discomfort

Methadone Mary’s Greatest Concern

Will there be a national shortage of opioids before the end of 2017?

Why?
Equianalgesic Dosing

- Is your hospice staff competent?
- Conversion from one opioid to another will be more necessary than ever before the end of 2017...

### Transitioning Analgesics

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>Parental</th>
<th>Oral</th>
<th>Oral Duration of Action (Hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
<td>3-4</td>
</tr>
<tr>
<td>Codeine</td>
<td>150</td>
<td>250</td>
<td>3-6</td>
</tr>
<tr>
<td>Fentanyl (transdermal)</td>
<td>0.1</td>
<td>N/A</td>
<td>72 (transdermal)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>N/A</td>
<td>30</td>
<td>4-6</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
<td>4-5</td>
</tr>
<tr>
<td>Oxydolone</td>
<td>10</td>
<td>20</td>
<td>3-4</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
<td>10</td>
<td>4-6</td>
</tr>
<tr>
<td>Tramadol</td>
<td>100</td>
<td>320</td>
<td>4-6</td>
</tr>
</tbody>
</table>

### EOL Care & Medical Marijuana Use

- Anything a patient “takes”, licit or illicit, should be listed on the hospice medication profile as part of the medical record!
- Alcohol
- Marijuana
- Medications
- Supplements
- Vitamins
- Nutritional products
Marijuana Legalization Status

Barriers to Use of Medical Marijuana

1. Method of Delivery and Patient Individual Condition
   - Multiple methods of delivery (inhalation, suppository, oral) and different patient conditions, which can alter drug absorption, cause variability in the effect of medical cannabis.

2. Insufficient Quality Control
   - High risk of contaminated products and lack of standardized doses.

3. Inadequate Monitoring and Prevention
   - Lack of surveillance, training, and education available to prevent addiction and relies solely on the physician-patient relationship.

4. Insufficient Research Available
   - Due to barriers 1-3 it is difficult to conduct research with specific set variables (i.e., dosage, quality, patient's conditions).

Marijuana + Opioids?

- Studies indicate:
  - Cannabinoids produce antiinflammatory and antinociceptive effects at peripheral, spinal, and supraspinal sites.
  - Cannabinoid receptors modulate nociceptive thresholds and may play a role in the etiology of chronic pain states.
  - Cannabinoids and opioids can potentiate each other's effects.
  - Some authors suggest the use of cannabinoids to reduce need for opioids.
Pharmacologic Parameters of Oral and Inhaled Marijuana

<table>
<thead>
<tr>
<th>Pharmacologic Parameter</th>
<th>Oral</th>
<th>Inhaled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability, %</td>
<td>6-20</td>
<td>10-40</td>
</tr>
<tr>
<td>Time to peak concentration</td>
<td>1-6 hours</td>
<td>2-10 minutes</td>
</tr>
<tr>
<td>Maximal duration</td>
<td>2-3 hours</td>
<td>Close-dependent; maximal psychotropic effects, 20 minutes; with rapid decline lasting 45-60 minutes</td>
</tr>
<tr>
<td>Distribution</td>
<td>90% plasma; protein-bound 10% red blood cells 1% in brain</td>
<td>90% plasma; protein-bound 10% red blood cells 1% in brain</td>
</tr>
<tr>
<td></td>
<td>crosses placenta and found in breast milk</td>
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</tr>
</tbody>
</table>


Marijuana to Treat CINV in Cancer Patients

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Patient Population</th>
<th>Therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT/crossover</td>
<td>High-dose methotrexate N=15</td>
<td>Smoked or oral THC vs. placebo</td>
<td>Reduced nausea and vomiting by 52%</td>
</tr>
<tr>
<td>RCT/crossover</td>
<td>Doxorubicin-cyclophosphamide N=15</td>
<td>Smoked or oral THC vs. placebo</td>
<td>Reduced nausea and vomiting by 52%</td>
</tr>
<tr>
<td>Review of 6 unpublished studies, including 4 RCTs</td>
<td>Chemotherapy not specified N=26 for THC vs. placebo</td>
<td>Smoked or oral THC vs. placebo</td>
<td>80-93% reduction in CINV; marijuana shown to be as effective as phenothiazine</td>
</tr>
</tbody>
</table>

CINV: chemotherapy-induced nausea and vomiting; RCT: randomized controlled trial; THC: β-9-tetrahydrocannabinol


Dosing Marijuana

- 10 mg oral THC = 60 mg of codeine
- Low dose = <7 mg
- Medium dose = 7-18 mg
- High dose = >18 mg
- Cannabis has biphasic effects
- Small doses are helpful for: nausea, appetite, pain, sleep, mood, and anxiety
- Larger doses can have the opposite effect: increased anxiety, pain, and depression

Drug Interactions

- Additive CNS depressant effects with other psychotropics
- Cannabinoids inhibit numerous CYP450 enzymes, although generally not at typical therapeutic concentrations.
- Caution is advised when substrates for CYP2C19, 2D6 (e.g., venlafaxine) and 3A4 (e.g., albuterol, celecoxib, fenbufen, suflaxifen) are used concurrently with nabiximols.
- The metabolism of nabiximols is marginally inhibited by CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole, ritonavir) and may be induced by CYP3A4 inducers (e.g., carbamazepine, rifampin).
- Drugs that elevate heart rate: anticholinergics, caffeine, stimulants (AVOID combination)

Undesirable Effects of Cannabinoids

<table>
<thead>
<tr>
<th>Possible Consequences of Medications + Marijuana</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana may:</td>
</tr>
<tr>
<td>- Increase bleeding risk when taken with other anticoagulants/NSAIDS</td>
</tr>
<tr>
<td>- Warfarin (Coumadin®)</td>
</tr>
<tr>
<td>- Rivaroxaban (Xarelto®)</td>
</tr>
<tr>
<td>- Heparin</td>
</tr>
<tr>
<td>- Clopidogrel (Plavix®)</td>
</tr>
<tr>
<td>- Ibuprofen, Naproxen (NSAIDS)</td>
</tr>
<tr>
<td>- Affect blood sugar levels</td>
</tr>
<tr>
<td>- Monitor closely in patients with diabetes mellitus/insulin resistance/medications accordingly</td>
</tr>
<tr>
<td>Affect blood pressure</td>
</tr>
<tr>
<td>- Monitor closely in patients with hypertension/lowering medications</td>
</tr>
<tr>
<td>- Increase drowsiness when in combination with other benzodiazepines, narcotics and alcohol</td>
</tr>
</tbody>
</table>
| Research is minimal therefore combining cannabis and other medications should be closely monitored
Medication Induced Constipation

Opioid Induced Constipation\(^5\) (OIC)

• There is no uniform way to diagnose OIC.
• The clinical presentation of OIC does not differ from that of functional constipation except that the constipation occurs with opioid treatment.
• The most common symptoms used as inclusion criteria in these trials are less than three bowel movements (BMs)/week, straining, hard stools and sensation of incomplete evacuation.
• “The hand that writes the opioid Rx also writes the laxative/stool softener Rx!”

Anxiety & Agitation

Agitation- Extreme emotional disturbance; perturbation\(^\text{*}\)
- Anger
- Despair
- Combativeness
- Irritability
- Grimacing
- Pacing
- Insomnia

Anxiety- State of uneasiness and apprehension\(^*\)
- Nervousness
- Terrified
- Tension
- Fear
- Anguish
- No eye contact
Anxiety & Agitation

Benzodiazepines
- First line for anxiety
- AVoID diazepam (Valium®)
- Alprazolam (Xanax®)
- Clonazepam (Klonipin®)
- Lorazepam (Ativan®): preferred
  - "clean"

Antipsychotics
- First line for agitation
- Haloperidol (Haldol®)
- Chlorpromazine Suspension 50 mg/ml (compounded)
- Olanzapine (Zyprexa®)
- Quetiapine (Seroquel®)
- Risperidone (Risperdal®)

Treating Depression in Hospice

- The medical literature suggests that the incidence of major depression in terminally ill patients ranges from 25% to 77%.
- Early treatment is more effective than late treatment.
- Clinicians often wait to address depression until the last weeks of life. At this point, it is usually too late to successfully treat.

Depression

Psychostimulants
- Methylphenidate
  - Drug of choice for treating depression in patients with a prognosis of <3 months
  - Rapid onset
  - Response in days
  - Can be titrated to effect, start 2.5 mg QD

Tricyclic Antidepressants
- Nortriptyline (Pamelor®)
- Desipramine (Norpramin®)
- Use first line when there is a comorbidity of neuropathic pain
Depression

**SSRIs**
- Fluoxetine (Prozac®)
- Citalopram (Celexa®)
- Sertraline (Zoloft®)
- If a response is acceptable in weeks to months
- 70% of patients show response
- Should start on low doses and titrate

**Other medications**
- Trazodone (Desyrel®)
- Mirtazapine (Remeron®)
- "Portmaneau Medication"

Lack of appetite

- **Antidepressant**
  - Mirtazapine – preferred
  - 7.5 to 15 mg po Q HS
- **Corticosteroids**
  - Prednisone
  - 10 mg po QD am
  - Dexamethasone
  - 2 mg po QD am
- **Hormones**
  - Megestrol Acetate – VERY non preferred!!

Pathophysiology of nausea/vomiting

- **Chemoreceptor Trigger Zone (CTZ)**
- **Cortex**
- **Vestibular Apparatus**
- **GI Tract**

**Neurotransmitters**
- Serotonin
- Dopamine
- Acetylcholine
- Histamine

**EPEC Project 1999**
Informa=on	adapted	from:
Pallia)ve	Care	Pocket	Consultant	2001
Twycross	et	al.	1997
Source	component	images	modified	from:
dreams)me.com
brainhq.com

Vomiting Center
ACh
m
H
1
μ-opioid
5HT
2
Gut Wall
Chemoreceptor  Trigger
Zone
Cerebral Cortex
Vestibular nuclei

Gastric irritants
Abdominal Radiotherapy
Intestinal distension
Cytotoxic Chemotherapy
Opioids, Digoxin
Hypercalcemia/
Uremia
Clonidine
Fear/
Anxiety
Movement/
Vertigo
Raised Intracranial pressure
Gastric atony
Retroperistalsis
Thoracic & abdominal muscle contractions

AChm = anticholinergics
5HT = serotonin type 2, 3, & undefined
D2 = dopamine type 2
H1 = histamine type 1
GABA = gamma-aminobutyric acid
ά = alpha adrenergic type 2

Olanzapine Pharmacology
• Combination Dopamine and Serotonin 5HT2 and 5HT3 antagonist
• Classified as an atypical antipsychotic
• Can be used off label for the treatment and prevention of refractory chemotherapy induced nausea and vomiting
• As an antipsychotic, maintains the possible side effects of weight gain, hyperglycemia, confusion/sedation, and extrapyramidal effects
Management of nausea / vomiting

- Dopamine antagonists
- Antihistamines
- Anticholinergics
- Prokinetic agents

- Anxiolytics
- Antacids
- Cytoprotective agents
- Serotonin antagonists
- Other medications

"Portmanteau" drugs

- Drug therapies that can be utilized for their multiple therapeutic effects and side effects
- Olanzapine (Zyprexa)
  - N/V
  - Antipsychotic
  - Agitation
- Mirtazapine (Remeron)
  - N/V
  - Antidepressant
  - Insomnia
  - Appetite stimulant
- Haloperidol (Haldol)
  - N/V
  - Antipsychotic

Oregon & OTC Naloxone

- "During the 2016 Legislative Session, House Bill (HB) 4124 passed into law and was signed by Oregon Governor Kate Brown on April 4, 2016. The law is intended to increase access to the life-saving opiate overdose reversal drug, naloxone (Narcan®). The law permits pharmacists to prescribe unit-of-use naloxone and the necessary supplies for administration to a person or organization that conducts training, and to an individual who has completed an OHA approved training."
Washington & Naloxone

• The State of Washington permits pharmacists to dispense naloxone through a collaborative practice agreement.
• Under this agreement, pharmacists are required to document all patients to whom they dispense naloxone, attach a training checklist with the patient’s initials, acknowledging that they were trained in the appropriate administration techniques.

Intranasal Naloxone

• Prescribing:
  • Naloxone 2 mg/2 ml prefilled syringe, 2 syringes  
• Instructions for use:  
  • Spray one-half of syringe into each nostril upon signs of opioid overdose; Call 911. May repeat x1.  
• Storage Conditions:  
  • Store naloxone in the original package at room temperature.  
  • Avoid light exposure.
Intramuscular Naloxone

- Prescribing:
  - Naloxone 0.4mg/ml single dose vial, 2 vials
  - Naloxone 0.4 mg/0.4 ml No. 1 twin pack
- Instructions for use:
  - Inject 3 ml IM upon signs of opioid overdose. Call 911. May repeat x2.
- Storage Conditions:
  - Store naloxone in the original package at room temperature.
  - Avoid light exposure.

Thank You & Feel Free to Contact Me!
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Delta Care Rx
Mary.Mihalyo@Deltacarerx.com
References


