Module: Pain

Learning Objectives

Attitudes

- Reflect on pain perception, assessment and treatment
- Recognize that pain management requires a multidisciplinary, patient-centered approach
- Understand that pain can be a manifestation of physical illness as well as existential and spiritual distress
- Understand that treatment of pain needs to be customized to the individual patient
- Understand that opioids can be used to treat pain effectively and its use is not synonymous with addiction

Knowledge

- Identify how treatment options vary based on pain severity
- Describe indications, pharmacology and side effects of NSAID use for mild cancer pain
- Describe indications, pharmacology and side effects of opioids including: morphine, oxycodone, hydromorphone, fentanyl and methadone for moderate-severe cancer pain
- Describe different routes of opioid administration, including oral, intravenous, and transdermal
- Identify major side effects of opioids
- Discuss indications for opioid switching
- Describe opioid potency ratios
- Define and distinguish between opioid tolerance, physical dependence and psychological dependence (addiction)
- Recognize Total Pain and implement treatment tools.
- Describe indications, pharmacology and side effects of adjuvant therapies including SNRIs and antiepitleptic drugs (AEDs)
- Describe indications for interventional pain management therapies I.e. neurolytic blocks
- Describe indications for external radiation therapy
- Describe scenarios for palliative consultation
- Describe therapeutic pain control options after palliative surgery

Skills

- Ability to perform a nuanced pain assessment
- Develop a treatment plan for patients, with use of short and long acting opioids
- Prescribe opioids, including knowing starting doses and dose escalation timelines
- Understand the factors involved in opioid switching and make transitions between opioids using equianalgesic ratios
- Demonstrate when to consult specialty services for pain management, i.e. radiation oncology, interventional radiology, palliative medicine, etc.

Module Content
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Module: Pain

Pain:

Symptom management is a cornerstone of Palliative Care, with pain being one of the most common and distressing symptoms. It is paramount for the provider to distinguish between physical pain and other causes of suffering for patients receiving palliative care. For patients with serious illness, existential distress and other spiritual, social and emotional pain sources may manifest as physical pain. This is important to remember in patients who present with hard to control or hard to understand pain such as rapidly escalating opioid needs or pain "all over" the body.

Pain Assessment:

Step 1: determine the location and quality of pain using the PQRST pneumonic:

P – provoking/relieving factors – elucidate inciting and ameliorating events, evaluate the efficacy of their home pain management regimen.

Q – quality:

Somatic pain: dull/aching, well-localized – fractures, bone metastasis, muscle strains

Visceral pain: dull or sharp/well-localized or referred – visceral metastasis, gastritis, peritonitis

Neuropathic pain: burning/sharp, radiating, numbness – chemotherapy side effect, herpes zoster, diabetic neuropathy, nerve impingement due to mass effect

Many patients may have coexistent pain qualities.

R – radiation, if pain radiates and location

S – severity: usually reported as a Visual Analogue Scale of 0-10 (0/10 = no pain, 10/10 = worst possible pain)

T – timing – whether episodic or constant

Step 2: assess impact on quality of life.) and set goals for pain relief. Specific tools: PEG or SOAPP-SF

Treatment:

Treatment guidelines for pain management in palliative care settings differ from those used for acute and chronic pain as set by the CDC (Centers for Disease Control). In fact, the 2022 specifically exclude patients with cancer and those receiving palliative or end of life care.

The revised WHO (World Health Organization) analgesic ladder can be used for guidance, with pharmaceutical options detailed below along with interventional techniques like nerve blocks when appropriate.

Mild pain:

Non-Opioids

- NSAIDs (nonsteroidal anti-inflammatory drugs):
  - Non-selective COX inhibitors (target COX-1 and 2) include ibuprofen, naproxen, sulindac, meloxicam (COX2>1 for the last two)
  - Selective COX 2 inhibitors like Celecoxib, have lower gastro-intestinal (GI) side effects but may have increased risk of cardiovascular (CV) events
  - Topical NSAIDs like diclofenac may be more desirable when appropriate due to lower systemic absorption
  - Long term use must be in conjunction with GI prophylaxis (for i.e. Pepcid)
  - Avoid in patients with known history of GI bleeding, kidney dysfunction or cardiovascular disease

- Aspirin
  - use with caution in elderly patients and those with GI bleed risk, currently rarely used for symptom management

- Acetaminophen
  Cox-3, mechanism of action is not fully understood

4g per 24 hours, <3g for elderly patients or liver dysfunction

Special Note: may need to avoid anti-pyrectics in patients with neutropenia as they may mask fever

Moderate pain:

Single agents:

Short acting/immediate release

- Oxycodone 5 mg (tablet or liquid) q 3-4 hours
  - Can consider starting at 2.5 mg for elderly patients
  - Onset: 10-15 minutes
  - Duration: 3-6 hours
  - *NOTE: avoid use in moderate to severe renal or hepatic dysfunction*

- Morphine 15 mg (tablet or liquid) q8 hours
    - Can consider 7.5 mg for elderly/opioid naïve patients
    - Onset: PO 15 - 30 minutes
    - Duration: 4 hours
    - *NOTE: avoid use in moderate to severe renal or hepatic dysfunction*

Combination products

- Acetaminophen/aspirin + oxycodone (tablet) q3-4 hours
- Acetaminophen/aspirin + hydrocodone (tablet) q3-4 hours

Notes:

Recommend against use of "weak opioids" (i.e. codeine, hydrocodone, tramadol) since they depend on individual metabolization to active metabolite, i.e., codeine to morphine. Risk of ineffective treatment (poor metabolizers) and opioid toxicity (ultra-metabolizers).

Combination products must be used with caution given recommended dose restrictions of acetaminophen (4g per 24 hours, <3g for elderly patients or liver dysfunction).

Severe pain:

Short acting/immediate release

- Morphine
    - Onset: PO 15 - 30 minutes, IV <5 min
    - Duration: 4 hours
    - Starting dose:
        - PO: 15 - 30 mg (tablet, solution)
        - IV: 2.5 - 5 mg
        - IM: 5 - 10 mg
    - *NOTE: avoid use in moderate to severe renal or hepatic dysfunction*

- Oxycodone
    - Onset: 10-15 minutes
    - Duration: 3-6 hours
    - Starting dose
        - PO: 5-10 mg (tablet, solution)
    - *NOTE: avoid use in moderate to severe renal or hepatic dysfunction*

- Hydromorphone
    - Onset: PO 15 - 30 minutes, IV 5 min
    - Duration: 3-4 hours
    - Starting dose:
        - PO: 2 - 4 mg (tablet, liquid)
        - IV: 0.2 – 1 mg

  - *NOTE: avoid use in moderate to severe hepatic dysfunction*

- Fentanyl
  - Onset: IV immediate
  - Duration: IV 30 minutes to 1 hour
  - Starting dose:
    - IV: 25 – 50 mcg
  - *NOTE: can be used in moderate to severe renal and hepatic dysfunction*

Long acting/Extended release

Consider adding a long-acting opioid if patient is requiring >4-5 PRN doses a day. Note that long-acting formulations are harder to titrate and should only be added once an estimate of the morphine equivalent daily dose (MEDD) for effective pain management is obtained.

Long-acting Morphine:

- MS Contin: duration: 8 - 12 hours
  - Starting dose: 15 mg (tablet) q12 hours (or ½ of their MEDD q12 hours)
  - Dose escalation: every 24-48 hours
- Kadian: duration: 12 - 24 hours
  - Starting dose: 30 mg (tablet) q24 hours
  - Dose escalation: every 24-48 hours
- *NOTES:*
  - *avoid use in moderate to severe renal or hepatic dysfunction*
  - *Use short acting formulation for breakthrough pain*
  - *These formulations must be swallowed whole, cannot be used in patients with dysphagia, or those with enteral access like nasogastric tubes*

Long acting Oxycodone

- OxyContin: duration: ≤ 12 hours
  - Starting dose: 10 mg (tablet) q12 hours
  - Dose escalation: every 24-48 hours
- Xtampza: duration: ≤ 12 hours
  - Starting dose: 9 mg (tablet) q12 hours
  - Dose escalation: every 24-48 hours
- *NOTES:*
  - *avoid use in moderate to severe renal or hepatic dysfunction*
  - *Use short acting formulation for breakthrough pain*
  - *Oxycontin cannot be used with feeding tubes, however Xtampza can be used*

Fentanyl

- Fentanyl patch (transdermal)
  - Onset: 6 hours

  - Duration: 72 - 96 hours
  - Starting dose: 12 mcg/hour q72 hours
  - Dose escalation: every 48-72 hours
- *Notes:*
  - *should not be used in opioid naive patients (at least 60 MEDD for >1 week)*
  - *Can be used in liver and renal dysfunction*
  - *Consider use in patients unable to swallow medications/with enteral access like nasogastric tubes.*
  - *May not be well absorbed in extremely cachectic patients or those with hypoalbuminemia (<3.5 g/dL) as most lipophilic opioid*

Methadone

  - Onset: 30 minutes to 1 hour
  - Duration: 4-8 hours
  - Starting dose:
    - PO: 2.5 mg (solution or tablet) q8-12 hours (in opioid naïve)
  - Dose escalation: every 3-5 days

NOTES:

  - *May help with neuropathic pain given antagonistic binding of NMDA receptors*
  - *Consider consulting palliative specialists if initiating methadone*
  - *One of the only long-acting PO formulation that is a solution – can be used with feeding tubes*
  - *Half-life up to 60 hours, much longer than duration of analgesia – higher risk of sedation and respiratory depression*
  - *QTc prolongation must be monitored - 450-500 is a relative contraindication, >500 absolute contraindication*
  - *Avoid use in severe hepatic impairment*

Opioid Switching:

When to consider switching to another opioid:

- Ineffective analgesia with initial opioid.
- Suspicion of hyperalgesia
- Concern for tolerance, i.e. escalating doses to achieve the same analgesic effect (especially if patient has been on the same opioid for >4 weeks)
- Cost, change of insurance formularies
- Change in medical status I.e. new onset renal impairment or sudden inability to take PO medications

What to consider when switching to another opioid:

- calculate the equianalgesic value to prevent over or under-dosing.
- Consider dose reduction of 25-50% given incomplete cross tolerance.

POTENCY RATIOS:

Opioid	Dose	Morphine Equivalent Daily Dose - MEDD ratio
Morphine PO **	30 mg	1:1
Morphine IV	10 mg	3:1
Oxycodone PO	20 mg	1.5:1
Hydromorphone IV	1.5 mg	20:1
Hydromorphone PO	7.5 mg	4:1
Fentanyl IV	100 mcg	300:1

**Morphine PO = MEDD

Fentanyl patch

24 hour MEDD	**Initial patch dose**
30 – 59 mg	12mcg/hr
60 – 134 mg	25 mcg/hr
135 – 224 mg	50 mcg/hr
225 – 314 mg	75 mcg/hr
315 – 405 mg	100 mcg/hr

Methadone

24 hour MEDD	**Oral morphine: methadone**
<30 mg	2:1
30 - 100 mg	4:1
100 – 300 mg	8:1
300 – 500 mg	12:1
500 – 1000 mg	15:1
1000 mg – 1200 mg	20:1
>1200 mg	Consider palliative consult

Side effect profile:

- GI:
  - Constipation – ensure robust bowel regiment is in place when administering opioids
  - Nausea – resolves after a few doses
- CNS :
  - Sedation, confusion – resolves after a few doses
  - Respiratory depression – tolerance develops rapidly; usually seen with new hepatic or renal dysfunction or rapid escalation of long-acting opioids like fentanyl patch or methadone
  - Delirium

  - Opioid Induced Neurotoxicity- range of symptoms including: hallucination, mycolonus, hyperalgesia, allodynia and seizure
    - Treatment: dose reduction, opioid rotation
- Cardiac:
  - Prolonged QTc with risk of torsades de pointes (ESPECIALLY with methadone)
- Urological:
  - Urinary retention
- Endocrinological:
  - Hypogonadism, sexual dysfunction

Tolerance and Addiction:

- Tolerance:
  - The need increase dose to get the same effect overtime; this occurs with usual use
- Physical Dependence:
  - Withdrawal symptoms if abruptly discontinued or an antagonist is administered; this occurs with usual use of long-term opioid therapy
- Chemical Coping:
  - The excessive or inappropriate use of opioids to cope with emotional distress
- Psychological Dependence (addiction):
  - Pre-occupation with acquisition and use of a drug regardless of the impact on themselves and despite harm

Adjuvant Therapies:

Antidepressants:

Serotonin-Norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs) have been shown to have benefit in treating neuropathic pain. SNRIs like duloxetine and venlafaxine are first line, given higher incidence of adverse effects with TCAs.

Please take note if patient is already on serotonergic agents since that may precipitate serotonin syndrome

- Duloxetine
  - Starting dose: 20-30 mg once daily
  - Dose escalation: increase to target dose of 60 mg/day after 1-2 weeks
  - *Note: Avoid use in hepatic impairment and severe renal impairment*

- Venlafaxine
  - Starting dose: 75 once daily
  - *Note: may take up to 6 weeks for full benefit*

AntiEpileptic Drugs:

- Gabapentin
    - Starting dose: 300mg once daily
    - Dose escalation: can get up to 1800 mg/day divided in three doses
    - *Note: Avoid use in renal impairment and for elderly patients especially if there is concern for altered mentation/falls*

- Pregabalin
    - Starting dose: 50 mg q8hours
    - Dose escalation: can get up to 100 mg q8 hours after 1-2 weeks
    - *Note: Dose reduction needed in renal impairment*

Corticosteroids

Corticosteroids can be considered in instances of acute pain flares, mass effect and edema. Avoid with NSAIDs

- It is important to consider the side effects of steroids and to limit use to 1-2 weeks.
- Added benefit of appetite stimulation
- Side effects include hyperglycemia, delirium
- Agents to consider:
    - Dexamethasone 4-8 mg PO once daily
    - Prednisone 20-40 mg PO once daily

Topical agents

- Lidocaine: can be used with localized pain, for e.g. rib fractures
    - Available as gel, ointment, spray, and patch
    - Patch can only stay on for 12 hours in a 24-hour period

- Diclofenac gel: details mentioned in Section "Treatment: Mild pain – Non opioids"
    - *Note: may have some systemic absorption – use with caution in patients with GI, renal or CV risk*

Non-pharmacological therapies:

External radiation therapy:

Effective in relieving pain caused by bone metastases, mass effect.

- Can take up to 2-4 weeks before optimum relief is seen
- May initially have worsening symptoms due to local inflammation
- Effect lasts about 2-3 weeks

Neurolytic Blocks:

Peripheral and autonomic nerve blocks can relieve pain in certain patients and should be considered if escalating doses of opioids are being needed to manage pain. Some common ones include:

- Celiac plexus blocks for patients with GI pathology, pancreatic cancer, etc.
- Coccygeal nerve block for patients with perianal pain

Transcutaneous Electrical Nerve Stimulation (TENS):

Most clinical trials have been inconclusive although there may be moderate evidence for use in neuropathic pain.

Behavioral therapy:

Chronic pain as well as terminal diagnoses can be associated with maladaptive thinking. Cognitive Behavioral Therapy can help reduce some of this catastrophizing thinking. It has been shown to reduce pain intensity in chronic pain patients.

Total Pain:

- Also known as existential distress and often coexists with spiritual distress
- Overall, no universally agreed upon, concrete definition exists
- Important to assess at each visit, feelings of pain may be related to loss of purpose
- Higher risk patients include those with limited socioeconomic support, low level of function and poorly controlled symptoms
- Treatment: manage possible co-morbid depression (adjuvants may be particularly useful), explore positive reframing, psychological or Chaplin support as available/applicable

Postoperative pain control after Palliative Surgery:

- Patients with prior surgeries or exposure to narcotics, as well as patients with alcohol use disorder likely will experience higher than average pain scores. It is important to realize that these patients may require higher than normal doses of narcotic pain medications, and it is important to include non-narcotic pain regimens with these patients as well.

IV Narcotics:

- Peripheral IV Injection
- Patient controlled analgesia (PCA); can be both on-demand as well as basal dose
    - Fentanyl
    - Morphine

- Dilaudid

Infusionals:

- Pure infusional epidural
- Patient controlled epidural analgesia (PCEA)
- Peripheral IV lidocaine
- Peripheral IV ketamine
- Local infusion pain management pump

Injections:

- TAP block (transversus abdominus plane) for analgesia of anterior abdominal wall
- Local anesthesia (lidocaine-shorter acting, Marcaine-longer acting)

Non-Narcotics:

- Tylenol (IV or PO)
- NSAIDS (Ibuprofen or Toradol)
- Gabapentin
- Tramadol (less CNS side effects than narcotics)

Adjunctive Therapies:

Effective in addition to above therapies.

- Heat packs
- Ice packs
- Back support brace (after abdominal surgery)

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Pre/Post Test

Questions

1) NSAIDs should be avoided in patients with _____ risk.

2) The CDC (Centers for Disease Control) guidelines for pain management include patients with cancer and those receiving palliative or end-of-life care. (True/False)

3) What is the risk associated with using "weak opioids" like codeine?

_____

4) Which opioid is absolutely contraindicated in renal dysfunction/failure?

_____

5) Fentanyl patch should not be used in opioid naïve patients. (True/False)

6) Describe three scenarios where opioid switching should be considered
   a. _____
   b. _____
   c. _____

7) 30 mg of oral morphine is equianalgesic to
   a. _____ mg of oral hydromorphone (Dilaudid)
   b. _____ mg of IV fentanyl

8) Which opioid side effect do patients rapidly develop tolerance to?

_____

9) Which cardiac side effect can be seen with methadone use?

_____

10) In the following scenarios, which adjuvant therapies may be appropriate to consider
    a. Patient with breast cancer, pain from bone metastases: _____
    b. Patient with chemotherapy induced peripheral neuropathy: _____
    c. Patient with severe abdominal pain in the setting of pancreatic cancer: _____

11) Which of the following infusional pain medications has the fastest onset of action?

a. Morphine

b. Fentanyl

c. Ketamine

d. Dilaudid

Case Vignettes:

JF a 74-year-old male with widly metastatic colon cancer on the palliative care unit currently receiving Morphine 3 mg/per hour continuous IV infusion; this dose has steadily increased over the past 24 hrs. He has been growing progressively agitated and moans in pain even with the slightest physical stimulation. You believe he has opioid induced neurotoxicity, what do you do?

A) Start Haldol

B) Opioid rotation with dose reduction

C) Increase Morphine

D) Start Ativan

DB is a 62 year old female with recurrent breast cancer who has been told recently that there are no further treatment options. You are seeing her in your outpatient Palliative Care Clinic. She is quite tearful and withdrawn. You ask her how you can help, she insists that she has pain everywhere and the pain medication is not helping.

Her daughter raises a concern that the patient is frequently crying and not wanting to engage with her family as she had previously done. The patient routinely expresses that there is no point to her life that she feels she is a burden on her family. You believe she may be experiencing total pain, what is the next best step?

A) Start Zyprexa

B) increase her opioid dose by 25%

C) Reframing negative thoughts ie allowing family to care for her as she once cared for them

D) Recommend SNF placement

Answers

1. Cardiovascular; gastrointestinal bleeding; renal dysfunction
2. False
3. Ineffective treatment (poor metabolizers), opioid toxicity (ultra-metabolizers)
4. Morphine
5. True
6. Ineffective analgesia with initial opioid; suspicion of hyperalgesia; developing tolerance; cost, change of insurance formularies; change in medical status e.g. new onset renal impairment or sudden inability to take PO medications
7. a: 7.5 mg (ratio 4:1 morphine:dilaudid); b: 100 mcg
8. Nausea; sedation; respiratory depression
9. QTc prolongation
10. a: external radiation therapy; b: duloxetine; venlafaxine; gabapentin; pregabalin c: celiac plexus neurolytic block
11. Fentanyl

Vignette 1: B

Vignette 2: C

Module: Pain

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