

## Pain Management in Patients with Cancer

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## Disclosure

- Relevant Financial Conflicts of Interest
  - **CE Presenter, Victoria Jensen:**
    - None
  - **CE Mentors, Stacy Prelewicz and Joanne Kuznicki:**
    - None
- Off-Label Uses of Medications
  - Intrathecal administration of hydromorphone, bupivacaine, and fentanyl



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## Learning Objectives for Technicians

1. Classify pain in patients with cancer.
2. Describe goals of pain management in patients with cancer.
3. Examine alternative formulations for pain management in patients with cancer.



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## Learning Objectives for Pharmacists

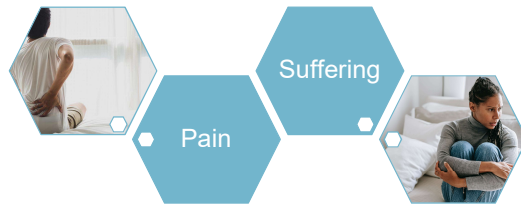
1. Apply guideline-directed therapy when utilizing opioids.
2. Select an appropriate non-opioid analgesic regimen for neuropathic pain, skeletal pain, and other pain syndromes.
3. Evaluate the utility of interventional procedures in patients with cancer.
4. Design an appropriate monitoring plan to evaluate the efficacy and safety of a pain regimen in a patient with cancer.



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## Classifying Pain in Cancer

Technician Objective 1



## Describing Pain

Pain definition (IASP 2020):

“An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.”

Raja SN et al. Pain. 2020;161(8):1978-82.

IASP: International Association for the Study of Pain



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## Describing Pain

### Onset

Acute

Chronic

### Etiology

Caused by cancer

Secondary to cancer

Secondary to cancer treatment

Caused by a concurrent disease

### Transmission

Nociceptive

Neuropathic

von Gunten CF. J Pediatr Hematol Oncol. 2011;33:S12-S18.



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## Describing Pain

Location, referral pattern, radiation of pain

Intensity

Interference with activities

Timing

- Onset, duration, course, persistent, intermittent

Quality

- Aching, stabbing, throbbing, or pressure related to somatic pain in skin, muscle, and bone
- Gnawing, cramping, aching, or sharp pain related to visceral pain in organs or viscera
- Burning, tingling, shooting, or electric-shocking pain related with neuropathic pain

Aggravating and alleviating factors



National Comprehensive Cancer Network (NCCN). Adult Cancer Pain. (Version 6.2021).

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## Pain Etiology



Mucositis



Bone pain



CIPN



Post-Surgical pain



Nerve compression

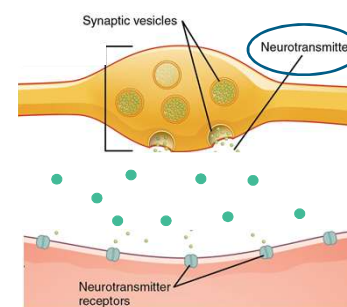


Abdominal pain

CIPN: Chemotherapy-Induced Peripheral Neuropathy



## Pain Pathways



von Gunten CF. *J Pediatr Hematol Oncol.* 2011;33:S12-S18.  
Falk S, et al. *British Journal of Pain.* 2014;8(4):154-162.



## Pain Pathways

Prostaglandins



Substance P

Serotonin

Histamine

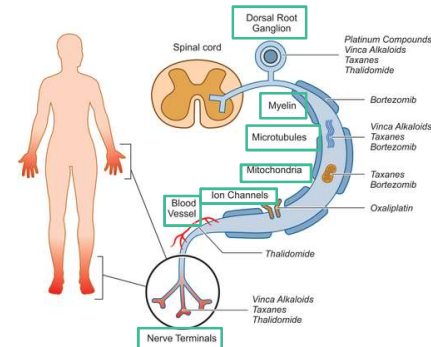
Acetylcholine

Bradykinin

von Gunten CF. *J Pediatr Hematol Oncol.* 2011;33:S12-S18.  
Falk S, et al. *British Journal of Pain.* 2014;8(4):154-162.



## CIPN Mechanism



Park SB, et al. *Ca Cancer J Clin.* 2013;63:419-437.



## Pain Etiology: Cancer Treatment

### Chemotherapy-Induced Peripheral Neuropathy

- Immunomodulatory agents
- Platinum agents
- Taxanes
- Vincristine
- Bortezomib
- Brentuximab vedotin
- Enfortumab vedotin

### Musculoskeletal

- Aromatase inhibitors
- Immunotherapy



Park SB, et al. *Ca Cancer J Clin*. 2013;63:419-437.

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## Pain Management Goals

*Technician Objective 2*



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## 5 A's of Outcomes

Analgesia

Activities

Adverse effects

Aberrant drug taking

Affect



National Comprehensive Cancer Network (NCCN). *Adult Cancer Pain*. (Version 6.2021).  
World Health Organization. *Who Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents*. 2018.

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## Guideline-Directed Opioid Use

*Pharmacist Objective 1*

ASCO

NCCN

WHO

ASCO: American Society of Clinical Oncology Practice  
NCCN: National Comprehensive Cancer Network  
WHO: World Health Organization

## Guideline-Directed Opioid Use Key Points

- Risks vs. benefits
- Education
- Monitor
- Taper
- Accessibility
- Route
- Precautions
- Adjuvants
- Formulation

American Society of Clinical Oncology (ASCO). Management of Chronic Pain in Survivors of Adult Cancers. 2016.  
National Comprehensive Cancer Network (NCCN). Adult Cancer Pain. (Version 6.2021).  
World Health Organization. WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents. 2018.



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## Calculating Oral Morphine Equivalence (OME)

Drug	Parenteral (mg)	Oral (mg)
<b>Morphine</b>	<b>10</b>	<b>30</b>
Fentanyl TD	N/A	12 mcg/hr
Hydrocodone	N/A	30
Hydromorphone	2.5	7.5
Oxycodone	N/A	20
Tramadol	N/A	300 - 600

Practical Pain Management (PPM). Remedy Health Media. 2021.



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## Patient Case

- AJ is a 58yom with stage III rectal adenocarcinoma who is here for cycle 12 of FOLFOX treatment. He reports having some tingling and numbness in his fingers following cycle 1 that has increased in severity over the past month. In the last week he has found it difficult to button his shirts before going to work. With spring around the corner, he is concerned he will not be able to golf this season with his brother.



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## Knowledge-based Question

Technician Objective 1: Classify pain in patients with cancer.

1. Which option best describes AJ's pain?
  - a. Acute, nociceptive
  - b. Acute, neuropathic
  - c. Chronic, nociceptive
  - d. Chronic, neuropathic



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## Knowledge-based Question

Technician Objective 2: Describe goals of pain management in patients with cancer.

2. Select the most appropriate goal for treatment of AJ's cancer-treatment associate pain.
  - a. Aim for a pain score goal of 0
  - b. Improve pain management to allow patient to golf
  - c. Increase sedation to allow patient to relax pain-free
  - d. Experience no adverse effects with pain regimen medications



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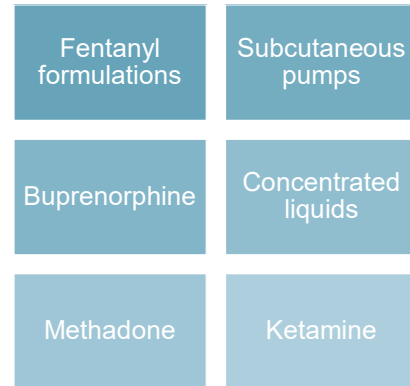
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## Alternative Formulations

Technician Objective 3



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## Fentanyl Formulations

Type	Brand Name	REMS	Cost (AWP unit price)	Absorption	Time to Peak	T <sub>1/2</sub>
Patch	Duragesic®		\$14*	-	20-72 h	20-27 h
Lozenge	Actiq®	X	\$19*	25% buccal 75% GI tract	20-40 min	
Sublingual tab	Abstral®	X	\$57	50% (part buccal, part GI)	30-60 min	3-14 h (dose dependent)
Sublingual spray	Subsys	X	\$37	50% buccal, part GI)	90 min	
Buccal tab	Fentora	X	\$73*	50% buccal 50% GI tract	47 min	3-4 h (100-200 mcg), 11-12 h (400-800 mcg)
Nasal spray	Lazanda	X	\$1122	76%	15-21 min	15-25 h

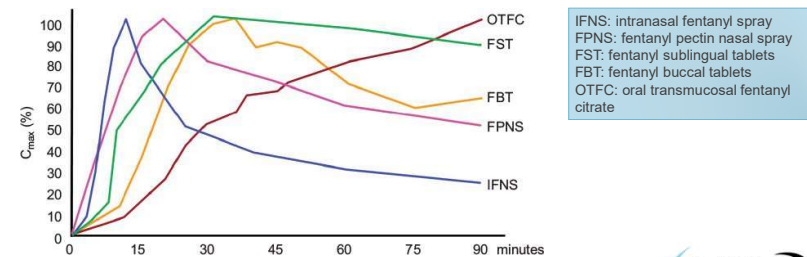
\*Generic available



Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, Waltham, MA: UpToDate, Inc.; July 30, 2021.  
Micromedex (Columbia Basin College Library ed.) [Electronic version] Greenwood Village, CO: Truven Health Analytics.

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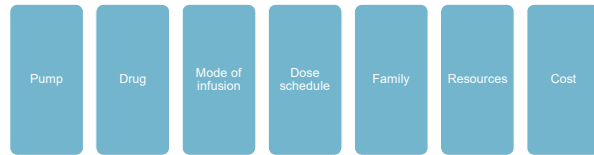
## Fentanyl Formulations



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## Subcutaneous Pumps

- Indicated in dysphagia
- Utilize doses consistent with IV administration
- Requires multiple injection sites to optimize tissue absorption
- Consider selection of:



Mercadante S. Drugs. 2017;77:629-635

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## Other Alternative Formulations

- Buprenorphine patch, film, and tablet
  - Partial mu-receptor agonist
  - X waiver not required for pain
- Concentrated liquids (20 mg/mL)
  - Oral morphine and oxycodone
  - Convert based on existing opioid requirement
- Methadone
  - REMS program, urine drug screen and pain contract
  - Starting dose 2.5 – 5 mg every 8 to every 12 hours
- Ketamine IV
  - Noncompetitive NMDA receptor antagonist
  - Refractory pain in acute on chronic setting
  - Requires Acute Pain Service consult

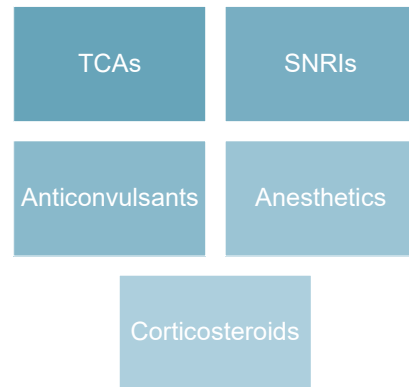


Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, Waltham, MA: UpToDate, Inc.; July 30, 2021.  
Micromedex (Columbia Basin College Library ed.) [Electronic version] Greenwood Village, CO: Truven Health Analytics.

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## Non-Opioid Analgesic Regimens

Pharmacist Objective 2



TCAs: Tricyclic Antidepressants  
SNRIs: Serotonin and Norepinephrine Reuptake Inhibitors

## Acetaminophen and NSAIDs

- Risk vs. benefit between patient and clinician
- Considerations:
  - Masking fevers
  - Acetaminophen: liver metastases
  - NSAIDs: celecoxib, diclofenac gel, thrombocytopenia, GI malignancies



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## Non-opioid Analgesics

Class	Drug	Starting Dose
Anticonvulsants	Gabapentin	100-300 mg daily
	Pregabalin	50 mg once daily or BID
SNRI	Duloxetine	20-30 mg
TCAs	Desipramine	10-25 mg daily
	Nortriptyline	
Anesthetic	Lidocaine	4-5% patch once daily
Corticosteroids*	Dexamethasone	Multiple variations
Topical NSAID	Diclofenac gel	4 g to each affected area up to 4 times daily

\*Dexamethasone is most commonly used due to less mineralocorticoid effect



Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, Waltham, MA: UpToDate, Inc.; July 30, 2021.  
Micromedex (Columbia Basin College Library ed.) [Electronic version] Greenwood Village, CO: Truven Health Analytics.

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## Treatment of Different Cancer Pains

Oral mucositis	• Opioids, local anesthetics, oral care protocols
Bone pain	• Opioids, NSAIDs, acetaminophen, steroids • Bisphosphonates, denosumab
Painful lesions	• Opioids, radiation, hormones, chemotherapy
Spinal cord compression	• Corticosteroids, opioids, surgery
Liver capsular pain	• Corticosteroids, topical lidocaine



National Comprehensive Cancer Network (NCCN). Adult Cancer Pain. (Version 6.2021).

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## CIPN Treatment: Target Doses

Gabapentin • 1800-2700 mg/day

Pregabalin • 150-300 mg BID

Duloxetine • 60 mg daily

Desipramine • 75 mg daily

Nortriptyline • 100 mg daily



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## Knowledge-based Question

Pharmacist Objective 2: Select an appropriate non-opioid analgesic regimen for neuropathic pain, skeletal pain, and other pain syndromes.

3. True or False: Gabapentin would be preferred over opioids for treatment of peripheral neuropathy in AJ.



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## Application-based Question

Technician Objective 3: Examine alternative formulations for pain management in patients with cancer.

- Working as a discharge technician, you receive a prescription for a new start Duragesic® (fentanyl patch). What benefits and concerns do you anticipate for this patient with cancer-related pain?



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## Interventional Procedures

Pharmacist Objective 3

Intrathecal pain pump

Plexus block

Kyphoplasty  
or  
vertebroplasty

## Intrathecal Pain Pumps

Morphine

Hydromorphone

Fentanyl

Ziconotide

Bupivacaine

Decreased systemic side effects

- Constipation
- Respiratory depression
- Sedation

Safety

- Pocket fill
- Granuloma

Operations

- Initial placement
- Reservoir refills



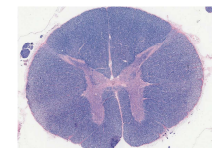
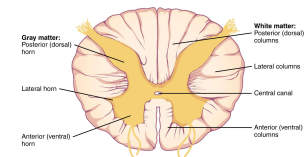
USHP

Deer TR, et al. *Neuromodulation: Technology at the Neural Interface*. 2017;20(2):96-132.  
Deer TR, et al. *Pain Medicine*. 2019;20(4):784-798.

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## Intrathecal Pain Pumps

- Serum levels correlate with side effects
- Pump settings
  - Flow rate
  - Basal
  - Bolus
- Lipophilicity
- Baricity



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Deer TR, et al. *Neuromodulation: Technology at the Neural Interface*. 2017;20(2):96-132.  
Deer TR, et al. *Pain Medicine*. 2019;20(4):784-798.

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## Intrathecal Pain Pumps: Ziconitide

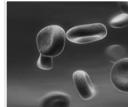




- Mechanism: bind to N-type  $Ca^{+2}$  channels, blocking  $Ca^{+2}$  permeability and disrupting influx into presynaptic terminals → inhibiting neurotransmitter release
- Narrow therapeutic window
- Contraindicated in history of psychosis
- No risk for tolerance or withdrawal
- Side effects: **hallucinations**, dizziness, nausea, confusion, nystagmus, ↑CK

Deer TR, et al. *Neuromodulation: Technology at the Neural Interface*. 2017;20(2):96-132.  
Deer TR, et al. *Pain Medicine*. 2019;20(4):704-708.



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## Intrathecal Pain Pump Placement Interactions

Anticoagulants, Antiplatelets	NSAIDs	Herbals	CNS Acting Agents	VEGF and BTK inhibitors
 <ul style="list-style-type: none"> <li>• Warfarin</li> <li>• Enoxaparin</li> <li>• Dabigatran</li> <li>• Rivaroxaban</li> <li>• Heparin</li> <li>• Clopidogrel</li> </ul>	 <ul style="list-style-type: none"> <li>• Aspirin</li> <li>• Ibuprofen</li> <li>• Ketorolac</li> <li>• Naproxen</li> </ul>	 <ul style="list-style-type: none"> <li>• Ginseng</li> <li>• Ginkgo</li> <li>• Garlic</li> <li>• Fish oil</li> </ul>	 <ul style="list-style-type: none"> <li>• Benzodiazepines</li> <li>• Antidepressants</li> <li>• Anticonvulsants</li> <li>• Muscle relaxants</li> <li>• Alcohol consumption</li> </ul>	 <ul style="list-style-type: none"> <li>• Bevacizumab</li> <li>• Sorafenib</li> <li>• Sunitinib</li> <li>• Ibrutinib</li> <li>• Acalabrutinib</li> </ul>

NSAID: Non-steroidal anti-inflammatory drugs  
VEGF: vascular endothelial growth factor  
BTK: Bruton's tyrosine kinase

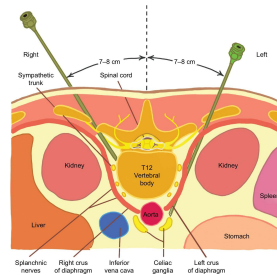
Deer TR, et al. *Neuromodulation: Technology at the Neural Interface*. 2017;20(2):96-132.



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## Plexus Blocks

- Ultrasound-guided
- Rapid pain relief
- Early intervention of visceral pain with neurolytic block in patients (n=109) with abdominal or pelvic pain
  - ↓ pain at weeks 2 and months 1-5
  - ↓ opioid use and related adverse effects



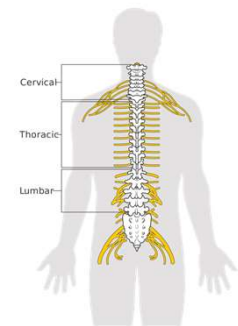
Candido et al. *Curr Pain Headache Rep*. 2017;21:12.



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## Kyphoplasty or Vertebroplasty

- Minimally invasive procedure
- Cement mixture injection
- Indicated in metastatic spinal cord compression
- Imaging required to identify isolated vs. diffuse involvement



Berenson J, et al. *Lancet Oncol*. 2011;12(3):225-35.  
Buchbinder R, et al. *NEJM*. 2009;361(8):357-68.  
Kyriakou C, et al. *Blood Cancer Journal*. 2019;9(3):1-0.



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## Kyphoplasty or Vertebroplasty



### 2009 Sham Trial

- Excluded spinal cancer
- Vertebroplasty (n=38) vs. sham procedure (n=40) found no significant difference in pain score reduction at week 1 or at 1, 3, or 6 month follow-up

### CAFE Trial (Cancer Patient Fracture Evaluation)

- Early intervention of kyphoplasty (n=70) superior to non-surgical treatment (n=64) of pain associated with vertebral compression fractures in cancer patients based on Roland-Morris disability questionnaire (RDQ)
- Increase QOL and rapid pain relief sustained at 1-year

Berenson J, et al. *Lancet Oncol*. 2011;12(3):225-35.  
Buchbinder R, et al. *NEJM*. 2009;361(6):557-68.  
Kyriakou C, et al. *Blood Cancer Journal*. 2019;9(3):1-0.



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## Application-based Question



Pharmacist Learning Objective 3: Evaluate the utility of interventional procedures in patients with cancer.



5. Match the following with their appropriate indication in patients with cancer.

#### Interventions:

- Kyphoplasty
- Intrathecal pain pump
- Plexus block

#### Indications:

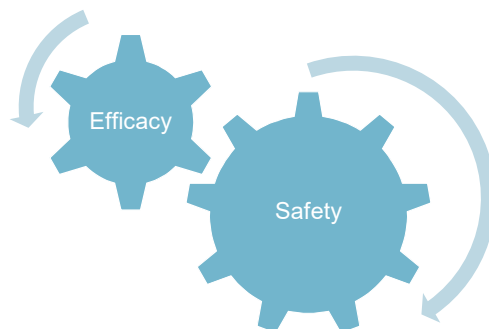
- Post-surgical pain
- Systemic pain requiring ↑↑↑ PO opioids
- Pain with spinal compression



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## Monitoring Plan

Pharmacist Objective 4



## Safety: Drug Interactions

### CYP3A4 Substrates

- Buprenorphine, fentanyl, hydrocodone, oxycodone, tramadol

### CYP2D6 Substrates

- Hydrocodone, oxycodone, tramadol

Methadone: substrate of **CYP2B6**, **3A4**, 2C19, 2D6, 2C9

None: morphine, hydromorphone, oxymorphone



National Comprehensive Cancer Network (NCCN). Adult Cancer Pain. (Version 6.2021).

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## Safety: Drug Interactions

- Azole antifungals, clarithromycin, erythromycin, imatinib **INCREASE** concentrations of:
  - Buprenorphine, fentanyl, hydrocodone, methadone, oxycodone
- Methadone and buprenorphine increase risk for **QTc prolongation** with:
  - BRAF inhibitors (i.e. dabrafenib), ceritinib, crizotinib, dasatinib, ibrutinib, lapatinib, lenvatinib, nilotinib, olanzapine
- Enzalutamide and apalutamide **DECREASE** concentrations of:
  - **Fentanyl**, oxycodone, buprenorphine, hydrocodone, methadone,



National Comprehensive Cancer Network (NCCN). Adult Cancer Pain. (Version 6.2021).

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## Safety: Side Effect Management

Constipation

Nausea

Pruritus

Delirium

Sedation

Respiratory depression



National Comprehensive Cancer Network (NCCN). Adult Cancer Pain. (Version 6.2021).

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## Naloxone

### Who

- $\geq 50$  OME\*/day
- Intrathecal pumps
- Concomitant CNS-acting medications

### Other Considerations

- Environment
- Cost

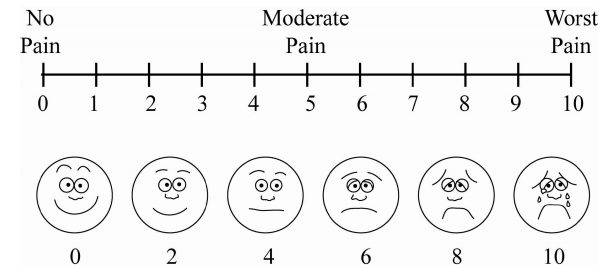
\*OME: Oral Morphine Equivalent



Centers for Disease Control and Prevention. CDC Guideline for Prescribing Opioids for Chronic Pain. 2016.

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## Efficacy: Pain Intensity Rating



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## Efficacy

Opioid choice    Lowest opioid dose    Steady state    Breakthrough pain

**USHP**

National Comprehensive Cancer Network (NCCN). Adult Cancer Pain. (Version 6.2021).

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## Other Considerations

*For Pharmacists and Technicians*

Palliative Care Consultation    Regulatory Compliance

Hospice    Financial Considerations

## Application-based Question

Pharmacist Learning Objective 4: Design an appropriate monitoring plan to evaluate the efficacy and safety of a pain regimen in a patient with cancer.

6. LJ is a 54 yof with cervical cancer and refractory pain here today for an appointment to evaluate intrathecal pump placement. The anesthesiologist wants to use ziconotide, bupivacaine, and hydromorphone and asks you to perform a medication review. She receives bevacizumab, cisplatin, and paclitaxel for cancer treatment and takes ginseng daily for nausea.

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## Wrapping Up

5 A's of outcomes    Monitor safety and efficacy

Alternative formulations    Interventional procedures

Guideline-directed therapy    Pain syndrome-specific therapy

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