KNOW CANCER-RELATED PAIN
Learning Objectives

• After completing this module, participants will be able to:
  – Discuss definitions, prevalence, and causes of cancer pain
  – Understand the patient burden caused by cancer pain
  – Explain the pathophysiological mechanisms of cancer pain
  – Describe the mechanisms, benefits, and adverse effects of various pharmacological treatments for cancer pain
  – Select appropriate pharmacological and non-pharmacological strategies for the management of cancer pain
Table of Contents

• Definitions of cancer and cancer-related pain
• What causes cancer-related pain?
• How prevalent is cancer-related pain?
• What is the patient burden of cancer-related pain?
• How is cancer-related pain assessed and managed?
Definitions

• **Nociceptive pain**
  – Pain arising from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors
  – In cancer, it probably involves dynamic interactions and crosstalk between the cancer and the primary afferent nociceptor

• **Neuropathic cancer pain**
  – Always in combination with nociceptive pain so is mixed pain
  – Can be related to the cancer itself or to the acute or chronic effects of cancer treatment

• **Associated cancer pain**
  – Related to antineoplastic treatment
Under-reporting of Cancer-Related Pain

- Reasons are complex and poorly understood
  - Appear to be partly due to a number of beliefs held by patients, families, and healthcare professionals

- Reasons include
  - Belief that pain is inevitable in cancer
  - Belief that “good” patients do not complain about pain
  - Concern that talking about pain may distract physician from treating the cancer
  - Fear of addiction to medication
  - Concerns about tolerance (i.e., risk of uncontrolled pain later in illness)
  - Concerns about side effects
  - Concern that pain means disease progression
  - Fear of injections

Under-treatment of Cancer-Related Pain

• Barriers to treatment for cancer pain include
  – Infrequent assessment\(^1\)
  – Clinicians believe “real” pain must be substantiated by “objective” tests\(^1\)
  – Limited access to opioids due to abuse concerns\(^2\)

Prevalence of Cancer pain

- Prevalence of pain among cancer patients\(^1\)
  - 33 to 50% in patients undergoing cancer treatment
  - >70% in patients with advanced disease
- Varies by diagnosis and disease stage\(^2\)

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Patient Burden Due to Cancer Related Pain

• Cancer pain has a significant negative effect on patient quality of life\textsuperscript{1,2}
• Higher levels of pain are associated with poorer quality of life\textsuperscript{2}
  – Decreased social activities
  – Decreased physical functioning
  – Impaired cognitive functioning
• Increased psychological distress is associated with higher levels of pain\textsuperscript{3}
• More than one third of cancer patients with pain rate their pain as \textbf{moderate or severe}\textsuperscript{4}

Increasing cancer pain may be associated with advanced disease with a limited prognosis\textsuperscript{5}

The First Step: Make the Diagnosis

- What is causing the pain?
  - The cancer?
  - The cancer treatment?
  - An unrelated cause?
Causes of Cancer-Related Pain

• Cancer related pain may be
  – Related directly to the neoplasm
    • Occurs in roughly 75% of patients
  – Caused by antineoplastic treatment
    • Occurs in roughly 25% of patients with cancer

Pathophysiologica...
Nociception: Neural Process of Encoding Noxious Stimuli

Consequences of encoding may be autonomic (e.g., elevated blood pressure) or behavioral (motor withdrawal reflex or more complex nocifensive behavior). Pain perception is not necessarily implied.

Nociceptive Pain

- Usually aching or throbbing and well-localized
- Usually time-limited
  - Resolves when damaged tissue heals
  - Can be chronic
- Generally responds to conventional analgesics
# Nociceptive Cancer Pain Syndromes

<table>
<thead>
<tr>
<th>Origin of Pain</th>
<th>Pain Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral</td>
<td>• Hepatic distension syndrome</td>
</tr>
<tr>
<td></td>
<td>• Midline retroperitoneal syndrome</td>
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<tr>
<td></td>
<td>• Chronic intestinal obstruction</td>
</tr>
<tr>
<td></td>
<td>• Peritoneal carcinomatosis</td>
</tr>
<tr>
<td></td>
<td>• Malignant perineal pain</td>
</tr>
<tr>
<td></td>
<td>• Adrenal pain syndrome</td>
</tr>
<tr>
<td></td>
<td>• Ureteric obstruction</td>
</tr>
<tr>
<td>Somatic</td>
<td>• Tumor-related bone pain</td>
</tr>
<tr>
<td></td>
<td>• Tumor-related soft tissue pain</td>
</tr>
<tr>
<td></td>
<td>• Paraneoplastic pain syndromes (e.g., muscle cramps)</td>
</tr>
</tbody>
</table>

What Is Neuropathic Pain?

**Neuropathic Pain**

*Pain caused by a lesion or disease of the somatosensory nervous system*

- **Peripheral Neuropathic Pain**
  *Pain caused by a lesion or disease of the peripheral somatosensory nervous system*

- **Central Neuropathic Pain**
  *Pain caused by a lesion or disease of the central somatosensory nervous system*

Neuropathic Pain

- Pain often described as tingling, shock-like, and burning
  - Commonly associated with numbness
- Almost always a chronic condition
- Responds poorly to conventional analgesics

Common Descriptors of Neuropathic Pain

- Burning
- Tingling
- Pins and needles
- Electric shock-like
- Numbness

Numbness is a cardinal sign of nerve damage

## Nociceptive vs. Neuropathic Pain

<table>
<thead>
<tr>
<th>Nociceptive</th>
<th>Neuropathic</th>
</tr>
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<td></td>
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</table>

Mixed Nociceptive and Neuropathic Pain in Cancer

Sensitization
Peripheral and central sensitization

Axonal damage
Degeneration and regeneration

Mechanisms of Neuropathic Pain

Nerve lesion/disease

Brain

Central sensitization

Loss of inhibitory control

Descending modulation

Peripheral sensitization

Ectopic discharge

Nociceptive afferent fiber

Spinal cord

Clinical Example of Nociceptive Cancer-Related Pain

• Bone metastases
  – Pain may be due to
    • Direct invasion
    • Secondary pathologic fracture
    • Damage to adjacent structures

Clinical Example of Nociceptive Cancer Pain

• Epidural spinal cord compression
  – Can cause pain and potentially irreversible loss of neurologic function
  – Diagnosed through radiographic evidence of indentation of the thecal sac
  – Ischemia may be the cause of the nociceptive pain
Clinical Examples of Neuropathic Cancer Pain

• Malignant painful radiculopathy
• Plexopathies
• Metastatic spine compression
• Painful peripheral neuropathies
• Paraneoplastic sensory neuropathy

Treatment-Related Cancer Pain Syndromes

- Painful peripheral neuropathy
- Raynaud’s syndrome
- Bony complications of long-term steroids

- Radiation-induced brachial plexopathy
- Chronic radiation myelopathy
- Chronic radiation enteritis and proctitis
- Burning perineum syndrome
- Osteoradionecrosis

- Post-mastectomy pain syndrome
- Post-radical neck dissection pain
- Post-thoracotomy pain syndrome or frozen shoulder
- Post-surgery pelvic floor pain
- Stump pain
- Phantom limb pain

What are the most common types of cancer-related pain you see in your practice?
Pain Assessment is an Integral Part of Cancer Patient Care

- Disease status
- Cause of Pain
- Other Factors
- Impact of pain
- Comorbid conditions
- Pathogenesis
- Pain syndrome
- Quality of life
- Psychosocial factors

Importance of Pain Assessment

Pain is a significant predictor of morbidity and mortality

- Screen for red flags needing immediate investigation, referral, or treatment
- Identify and treat underlying cause
- Recognize type of pain
- Determine baseline pain intensity

How do you assess cancer-related pain in your practice?
Brief Pain Inventory (BPI)

Determine Pain Intensity

### Simple Descriptive Pain Intensity Scale

<table>
<thead>
<tr>
<th>No pain</th>
<th>Mild pain</th>
<th>Moderate pain</th>
<th>Severe pain</th>
<th>Very severe pain</th>
<th>Worst pain</th>
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</table>

### 0–10 Numeric Pain Intensity Scale

<table>
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<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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</table>

### Faces Pain Scale – Revised

![Faces Pain Scale – Revised](image)

Locate the Pain

Body maps are useful for the precise location of pain symptoms and sensory signs*

*In cases of referred pain, the location of the pain and of the injury or nerve lesion/dysfunction may not be correlated
DN4

- Completed by physician in office
- Differentials neuropathic from nociceptive pain
- 2 pain questions (7 items)
- 2 skin sensitivity tests (3 items)
- Score ≥4 is an indicator for neuropathic pain
- Validated

DN4 = Douleur neuropathique en 4 questions
painDETECT

- Patient-based, easy-to-use screening questionnaire
- Developed to distinguish between neuropathic pain and non-neuropathic pain*
- Validated: high sensitivity, specificity, and positive predictive accuracy
- Seven questions about quality of pain and three about severity of pain
- Questions about location, radiation and time course

*Validation was in patients with low back pain
LANSS Scale

- Completed by physician in office
- Differentiates neuropathic from nociceptive pain
- 5 pain questions and 2 skin sensitivity tests
- Identifies contribution of neuropathic mechanisms to pain
- Validated

LANSS = Leeds Assessment of Neuropathic Symptoms and Signs
The “Total Pain” Concept

- Social pain
- Psychological pain
- Spiritual pain
- Physical pain

TOTAL PAIN

Overall Goals in Pain Management

- Involve the patient in the decision-making process
- Agree on realistic treatment goals **before starting** a treatment plan

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Goals in Cancer Pain Management

- Goals are improved comfort, function, and safety
- Increase quality of life
  - Decrease pain
  - Increase physical functioning
  - Increase social functioning
  - Restore normal sleep patterns
  - Increase psychological well-being
  - Return to work
  - Work quality and hours
- Comprehensive pain management is needed
- Prevention of expected analgesic side effects is important
- Optimize patient and family education and physical and cognitive integrative interventions

Non-pharmacological Therapy for Cancer-related Pain

Psychotherapy

Physiotherapy

Social services/support

Non-pharmacological therapies should be used in conjunction with pharmacotherapies to manage the overall condition of the patient.
Discussion Question

WHAT NON-PHARMACOLOGICAL APPROACHES TO MANAGING CANCER-RELATED PAIN DO YOU INCORPORATE INTO YOUR PRACTICE?

ARE THERE NON-PHARMACOLOGICAL MODALITIES YOUR PATIENTS REGULARLY ASK ABOUT?
Pharmacological Management of Cancer Pain

Step 1
- Nonopioid
  +/- Adjuvant

Step 2
- Opioid for mild to moderate pain
  +/- Nonopioid
  +/- Adjuvant

Step 3
- Opioid for moderate to severe pain
  +/- Nonopioid
  +/- Adjuvant

Non-Opioid Analgesics

- Acetaminophen/paracetamol
- NSAIDs
- Coxibs
- Metamizole

Coxib = cyclooxygenase inhibitor; NSAID = non-steroidal anti-inflammatory drug
Acetaminophen

• Action at molecular level is unclear
• Potential mechanisms include:
  – Inhibition of COX enzymes (COX-2 and/or COX-3)
  – Interaction with opioid pathway
  – Activation of serotoninergic bulbospinal pathway
  – Involvement of nitric oxide pathway
  – Increase in cannabinoid-vanilloid tone

COX = cyclooxygenase
Acetaminophen/Paracetamol Dosage

- Maximum dosage 3 to 4 g/day (depending on country)
- Dosage adjustment required for hepatic and renal insufficiencies

NSAIDS for Cancer Pain

• Weigh risks against benefits

• Side effects include\(^1\)
  – Gastrointestinal risks
  – Cardiovascular risks
  – Renal risks

• For patients with cancer pain, NSAIDs are conventionally used for\(^2\)
  – Mild pain
  – Moderate pain

• NSAIDs can be considered for bone pain\(^2\)

NSAID = non-steroidal anti-inflammatory drug
What Are NSAIDs?

**NSAID** = **Non-Steroidal Anti-Inflammatory Drug**

- Analgesic effect via inhibition of prostaglandin production
- Broad class incorporating many different medications

- Diclofenac
- Ibuprofen
- Naproxen
- Celecoxib
- Etoricoxib
- Parecoxib

Coxib = cyclooxygenase-2-specific inhibitor
How Do nsNSAIDs/coxibs Work?

Coxib = cyclooxygenase-2-specific inhibitor; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific NSAID

Adverse Effects of nsNSAIDs/Coxibs

All NSAIDs
- Gastroenteropathy - gastritis, bleeding, ulceration, perforation
- Cardiovascular thrombotic events
- Renovascular effects
  - Decreased renal blood flow
  - Fluid retention/edema
  - Hypertension
- Allergic phenomenon

Cox-1-mediated NSAIDs (nsNSAIDs)
- Decreased platelet aggregation

Coxib = cyclooxygenase-2-specific inhibitor; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific NSAID
nsNSAIDs/Coxibs and Cardiovascular Risk

Composite includes non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death compared with placebo; chart based on network meta-analysis involving 30 trials and over 100,000 patients.

Coxib = cyclooxygenase-2 inhibitor; CV = cardiovascular; nsNSAID = non-specific non-steroidal anti-inflammatory drug

Risk Factors for Gastrointestinal Complications Associated with nsNSAIDs/Coxibs

Opioids for Cancer Pain

Opioid-based pharmacotherapy is the mainstay of symptomatic treatment of cancer pain

- Are safe for the management of cancer pain
- Provide a good balance between efficacy (pain relief) and side effects
- Misuse, addiction, and diversion are not relevant concerns in patients with cancer pain

Use of Opioids for Cancer Pain

- Skilled use of opioids is crucial to relief of cancer pain
- Mild to moderate/uncontrolled pain with acetaminophen or NSAID: add a step 2 or 3* opioid given orally
- Immediate-release and slow-release oral formulations of morphine, oxycodone, and hydromorphone can be used for dose titration
- Transdermal fentanyl and buprenorphine are alternatives to oral opioids
- Breakthrough pain should be treated with additional doses of immediate-release oral opioids

*Refers to the World Health Organization pain ladder for cancer
NSAID = non-steroidal anti-inflammatory drug
How Opioids Affect Pain

Reduce pain by:

- Altering limbic system activity
- Activating descending pathways
- Working at the periphery

Opioids and Pain Management

<table>
<thead>
<tr>
<th>Opioid Receptor</th>
<th>Responses</th>
</tr>
</thead>
</table>
| Mu              | • Supraspinal analgesia  
• Respiratory depression  
• Sedation  
• Miosis  
• Euphoria  
• Cardiovascular effects  
• Pruritus, nausea/vomiting  
• Decreased gastrointestinal motility  
• Dependence  
• Tolerance |
| Delta           | • Analgesia  
• Euphoria  
• Dysphoria  
• Psychotomimetic effects |
| Kappa           | • Spinal analgesia  
• Dysphoria  
• Psychotomimetic effects  
• Miosis  
• Respiratory depression  
• Sedation |
Adverse Effects of Opioids

- Nausea
- Vomiting
- Constipation
- Respiratory depression
- Cognitive impairment
- Sedation
- Lightheadedness
- Dizziness
- Orthostatic hypotension
- Fainting

Other
- Itching
- Miosis
- Sweating
- Urinary retention

CNS = central nervous system
Opioids Used for Cancer Pain

1. Non-opioid +/- Adjuvant
2. Opioid for moderate pain +/- Non-opioid +/- Adjuvant
3. Opioid for moderate to severe pain +/- Non-opioid +/- Adjuvant

- Morphine
- Oxycodone
- Hydroxymorphone
- Methadone
- Tapentadol
- Fentanyl
- Buprenorphine
- Tramadol
- Tilidine/naloxone
- Codeine

Myths about Opioids

- Opioids are associated with addiction in cancer pain
- Tolerance limits the use of opioids in patients with cancer
- Opioids are dangerous because of respiratory depression in patients with cancer

Adjuvant Therapies in Cancer Pain

• Can be used with other drugs at any level of the WHO pain ladder

• Examples
  – Antidepressants
  – Anticonvulsants
  – Muscle relaxants
  – Bisphosphonates
  – Calcium channel blockers
How Antidepressants Modulate Pain

Inhibiting reuptake of serotonin and norepinephrine enhances descending modulation

Ascending input

Descending modulation

Glial cell activation

Brain

Perception

Nerve lesion

Ectopic discharge

Transmission

Nociceptive afferent fiber

Spinal cord

# Adverse Effects of Antidepressants

<table>
<thead>
<tr>
<th>System</th>
<th>TCAs</th>
<th>SNRIs</th>
</tr>
</thead>
</table>
| Digestive system | • Constipation  
• Dry mouth  
• Urinary retention | • Constipation  
• Diarrhea  
• Dry mouth  
• Nausea  
• Reduced appetite |
| CNS             | • Cognitive disorders  
• Dizziness  
• Drowsiness  
• Sedation | • Dizziness  
• Somnolence |
| Cardiovascular  | • Orthostatic hypotension  
• Palpitations | • Hypertension |
| Other           | • Blurred vision  
• Falls  
• Gait disturbance  
• Sweating  
• Impotence  
• Reduced libido | • Elevated liver enzymes  
• Elevated plasma glucose  
• Sweating  
• Impotence  
• Reduced libido |

CNS = central nervous system; TCA = tricyclic antidepressant; SNRI = serotonin-norepinephrine reuptake inhibitor
Anticonvulsant Therapy for Cancer Pain

- Sodium channel blockers
- $\alpha_2\delta$ ligands
α₂δ Ligands Bind to α₂δ Subunit of Voltage-Gated Calcium Channels

Bind here

Lipid bilayer

Extracellular

Cytoplasmic

Note: gabapentin and pregabalin are α₂δ ligands
Arikkath J, Campbell KP. Curr Opin Neurobio 2003;13(3):298-307;
### Adverse Effects of $\alpha_2\delta$ Ligands

<table>
<thead>
<tr>
<th>System</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive system</td>
<td>• Dry mouth</td>
</tr>
<tr>
<td>CNS</td>
<td>• Dizziness</td>
</tr>
<tr>
<td></td>
<td>• Somnolence</td>
</tr>
<tr>
<td>Other</td>
<td>• Asthenia</td>
</tr>
<tr>
<td></td>
<td>• Headache</td>
</tr>
<tr>
<td></td>
<td>• Peripheral edema</td>
</tr>
<tr>
<td></td>
<td>• Weight gain</td>
</tr>
</tbody>
</table>

$\alpha_2\delta$ ligands include gabapentin and pregabalin

CNS = central nervous system

Invasive Therapies for Cancer Pain

- Recommended only for selected patients when pharmacological and non-pharmacological therapy fails
- Available entities:
  - Injection therapy
  - Neurolytic therapy
  - Intrathecal administration of medication
  - Neuromodulation

Intrathecal Pump
Intrathecal Pump
What Is Breakthrough Pain?

In cancer patients, breakthrough pain typically refers to a transitory flare of pain in the setting of otherwise stable chronic pain managed with opioids.

Management of Cancer Pain

Cancer pain can be managed through a variety of approaches

Management of Breakthrough Pain

- Medications for breakthrough pain can be
  - An immediate release oral or parenteral opioid
  - An opioid + non-opioid combination
  - A rapid-onset, transmucosal fentanyl formulation

Portenoy RK. Lancet. 2011;377(9784):2236-47
Management of Metastatic Bone Pain

- Entities include
  - Disease modifying treatments
  - Radiotherapy
  - Bisphosphates
  - Symptomatic treatments
    - NSAIDS/coxibs
    - Steroids
    - Opioids

Coxib = cyclooxygenase inhibitor; NSAID = non-steroidal anti-inflammatory drug
## Selected Cancer Pain Management Guidelines

<table>
<thead>
<tr>
<th>Organization</th>
<th>Country of Origin</th>
<th>Year</th>
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<tbody>
<tr>
<td>World Health Organization&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>1996</td>
</tr>
<tr>
<td>French National Federation of Cancer Centres&lt;sup&gt;2&lt;/sup&gt;</td>
<td>France</td>
<td>2002</td>
</tr>
<tr>
<td>Scottish Intercollegiate Guidelines Network (SIGN)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Scotland</td>
<td>2008</td>
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<tr>
<td>RAND Corporation&lt;sup&gt;4&lt;/sup&gt;</td>
<td>USA</td>
<td>2008</td>
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<tr>
<td>Cancer Care Ontario's Cancer-related Pain Management Guideline Panel&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Canada</td>
<td>2012</td>
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<tr>
<td>European Society for Medical Oncology&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Europe</td>
<td>2012</td>
</tr>
<tr>
<td>European Association of Palliative Care&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Europe</td>
<td>2012</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network</td>
<td>USA</td>
<td>2014</td>
</tr>
</tbody>
</table>

Palliative Care

• Palliative care should be integrated **early** in the cancer management strategy
• Care should be managed by a specialized, multidisciplinary team of health care providers
• Emphasis should be placed on the QoL of patient and his or her family

**Early palliative care leads to better patient and caregiver outcomes, improvement in symptoms, quality of life, and patient satisfaction and reduces caregiver burden**

QoL = quality of life
Key Messages

• Cancer pain is a common condition
• Cancer pain severely adversely affects quality of life
• Cancer pain is a significant burden to the patient and his or her family
• Careful assessment is a prerequisite for the effective management of cancer pain
• Management of cancer pain requires a multidisciplinary approach
• Most cancer pain can be managed safely and effectively using combination therapies with opioids
• There is no need for a cancer patient to suffer unnecessarily
References


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