Goals of treatment in managing cancer-related pain
Deciding on the Best Course of Treatment for the Patient

Collaborative Care

Patient as the ultimate manager of his/her illness

Family

Patient

General practitioner ± other health care professional(s)

Pain Is Characterized by Changes in Pain Response to Painful Stimuli

- **Hyperalgesia** (increased response to a stimulus that is normally painful)
- **Allodynia** (pain due to stimulus that does not normally provoke pain)

Non-Pharmacological Management of Cancer-Related Pain

• Non-pharmacological treatments can be used to improve
  – Pain control
  – Coping
  – Adaptation
  – Self-efficacy

• Non-pharmacological approaches include
  – Cognitive behavioral therapy
  – Mind-body approaches

CBT for Cancer-Related Pain

• Focuses on
  – Maintaining quality of life through improved self-efficacy
  – Developing a sense of control over the illness and its consequences
  – Learning self-regulation skills to improve emotional functioning

• Modifies thinking patterns (dichotomous thinking, catastrophization, overgeneralization)

• Dysfunctional cognitive patterns typically arise from limited information and do not entirely reflect reality

• Gives patients a reality-based alternative version/interpretation of events
  – Elicits a more adaptive emotional response, improved coping

CBT = cognitive behavioral therapy
Mind-Body Approaches to Cancer-Related Pain

• Usually an adjunct to pharmacological therapy
• Relaxation therapy
  – Can transiently reduce pain intensity\(^2\)
  – May be associated with relaxation-induced panic\(^3\)
• Imagery creates a positive cognitive and emotional state that can ameliorate pain through\(^4\)
  – Recall of pleasant sights, smells, sounds, or tastes,
  – Somatic sensations (touch, movements, positions)

# Non-pharmacological Interventions for Cancer-related Pain

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological</td>
<td>• Hypnosis&lt;br&gt;• Relaxation&lt;br&gt;• CBT</td>
</tr>
<tr>
<td>Physical</td>
<td>• Acupuncture&lt;br&gt;• Transcutaneous electrical nerve stimulation&lt;br&gt;• Healing touch and massage&lt;br&gt;• Occupational therapy</td>
</tr>
<tr>
<td>Clinical process</td>
<td>• Pain assessment&lt;br&gt;• Physician advice and communication&lt;br&gt;• Education</td>
</tr>
</tbody>
</table>

- Non-pharmacological interventions are commonly used in clinical practice
- It is challenging to design studies to obtain reliable evidence of efficacy

CBT = cognitive behavioral therapy
Bennett MI, Closs SJ. *Pain Clinical Updates* 2010; 18:1-6.
Psychological Therapies for Cancer-related Pain

- Individual and group counseling
- Biofeedback
- Relaxation techniques
- Self-hypnosis
- Visual imaging
- Learning or conditioning techniques
- Behavioral techniques
- Cognitive techniques
- Psychotherapy

Non-Pharmacological Management of Cancer-related Pain

• Can improve
  – Pain control
  – Coping
  – Adaptation
  – Self-efficacy

• Approaches include
  – Cognitive behavioral therapy
  – Mind-body approaches
NCCN Guideline: Non-pharmacological Treatment of Cancer Pain

**Recommended**
- Integrative interventions (cognitive and spiritual)
- Interventional strategies (nerve blocks, vertebroplasty, kyphoplasty, regional infusion of analgesics, RF ablation)

**Not recommended**
- Do not use interventional strategies in patients that are unwilling, suffer from infections or coagulopathy, or have very short life expectancies

**Insufficient evidence**

NCCN = National Comprehensive Cancer Network
Pharmacologic therapy for cancer-related pain
Overview of Treatment Principles in the Management of Cancer-related Pain

- Pain control is an essential part of oncologic management\(^1\)
- A multidisciplinary team may be needed\(^1\)
- Psychosocial support must be available\(^1\)
- Analgesics for cancer pain should be given\(^2\)
  - By the mouth
  - By the clock
  - By the ladder
  - For the individual
  - With attention to detail

Overview of Treatment Principles for Cancer-related Pain: Breakthrough Pain

• Give medication for continuous pain on a regular schedule\(^1\)
  – Give added doses for breakthrough pain

• Allow rescue doses of 10-20% of the 24 h oral dose every hour as needed\(^1\)
  – Ongoing need for rescue doses may indicate a need to increase regularly scheduled dose

• Opioids used as rescue medications should have\(^2\)
  – Rapid onset of analgesic effect
  – Short duration analgesic effect

Management of Breakthrough Cancer Pain

• Offer short-acting drugs as needed during regular opioid treatment\textsuperscript{1,2}
  • Immediate release opioid
  • Opioid + non-opioid combination product
  • Rapid-onset, transmucosal fentanyl formulation

• Rapid-onset, transmucosal fentanyl formulations\textsuperscript{2}
  – Indicated for cancer-related breakthrough pain
  – Allow rapid absorption through mucosa
  – Address mismatch between time course of typical breakthrough pain and slower onset of an oral drug

Bone Pain in Cancer

• Bone metastases are a frequent complication of cancer
• Metastatic bone disease is one of the most common causes of cancer pain
• Some patients have pain in the bones and others have pain due to complications, such as neurological impairment secondary to nerve compression in spine or the base of skull
• Pain can be unrelated to tumor size

TENS = transcutaneous electrical nerve stimulation
Management of Cancer Bone Pain

- Non-pharmacological
  - Cutaneous stimulation, TENS, massage therapy, exercise
- Chiropractic or Osteopathic
  - Manipulation techniques
- Psychotherapeutic
  - Relaxation techniques, mindfulness-based stress reduction, hypnosis, psychotherapy
- Pharmacological
  - Calcitonin, bisphosphonates, corticosteroids, cannabinoids, analgesics
- Radiotherapy and Radionuclides
- Hormonal
- Interventional

TENS = transcutaneous electrical nerve stimulation
Radiotherapy for Bone Pain

- Relieves pain
- Prevents impending pathological fractures
- Promotes healing of pathological fractures
- Successful in pain relief in 60-70% of patients
  - Takes up to 3 weeks for full effect
- Single fraction treatments have same response rate as multiple fractions

## Medications for Bone Pain: Mechanisms of Action

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanisms of Action</th>
</tr>
</thead>
</table>
| Bisphosphonates¹,² | • Decrease bone resorption  
                          • Increase mineralization by inhibiting osteoclast activity  
                          • Possible antitumor activity                                    |
| Denosumab³       | • Antibody targeting the receptor activator of nuclear factor kappa B ligand (RANKL)  
                          • Prevents osteoclast formation                                        |

---

## Medications for Bone Pain: Adverse Effects

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Adverse Effects</th>
</tr>
</thead>
</table>
| Bisphosphonates | • Osteonecrosis of the jaw  
                 | • Hypocalcemia  
                 | • Proteinuria and renal insufficiency  
                 | • Acute phase response  
                 | • Ocular toxicity  
                 | • Bone, joint, or muscle pain  
                 | • Atrial fibrillation and stroke                                                |
| Denosumab       | • Osteonecrosis of the jaw  
                 | • Hypocalcemia  
                 | • Renal effects  
                 | • Neutralizing antibodies  
                 | • Infections                                                                |

Overview of Medication Classes for Cancer-related Pain
How Opioids Affect Pain

Modify perception, modulate transmission and affect transduction by:

• Altering limbic system activity; modify sensory and affective pain aspects
• Activating descending pathways that modulate transmission in spinal cord
• Affecting transduction of pain stimuli to nerve impulses

# Opioids and Pain Management

<table>
<thead>
<tr>
<th>Opioid Receptor</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mu</strong></td>
<td>Supraspinal analgesia, respiratory depression, sedation, miosis, euphoria, cardiovascular effects, pruritis, nausea/vomiting, decreased gastrointestinal motility, dependence, tolerance</td>
</tr>
<tr>
<td><strong>Delta</strong></td>
<td>Analgesia, euphoria, dysphoria, psychotomimetic effects</td>
</tr>
<tr>
<td><strong>Kappa</strong></td>
<td>Spinal analgesia, dysphoria, psychotomimetic effects, miosis, respiratory depression, sedation</td>
</tr>
</tbody>
</table>

Opioids Modulate Control of “ON” and “OFF” Cells

- Opioid stimulation of mu-receptors on “ON” cells
  - Reduced “ON” cell activity
  - Reduced facilitation of pain transmission at dorsal horn
  - Less pain

- Opioid stimulation of mu-receptors on GABA-ergic interneurons innervating “OFF” cells
  - Reduced GABA-ergic interneuron activity
  - Reduced inhibition of “OFF” cells
  - Increased “OFF” cell inhibition of pain transmission at dorsal horn
  - Less pain

GABA = γ-aminobutyric acid
Opioids Can Induce Hyperalgesia

- **Primary hyperalgesia**
  - Sensitization of primary neurons $\rightarrow$ decrease threshold to noxious stimuli within site of injury
  - May include response to innocuous stimuli
  - Increase pain from suprathreshold stimuli
  - Spontaneous pain

- **Secondary hyperalgesia**
  - Sensitization of primary neurons in surrounding uninjured areas
  - May involve peripheral and central sensitization

Opioids Can Induce Allodynia

- Pain evoked by innocuous stimuli
- Central sensitization → pain produced by Aβ fibers
- Possibly mediated by spinal NMDA receptors

NMDA = N-methyl-D-aspartate
## Adverse Effects of Opioids

<table>
<thead>
<tr>
<th>System</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, constipation</td>
</tr>
<tr>
<td>CNS</td>
<td>Cognitive impairment, sedation, lightheadedness, dizziness</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Orthostatic hypotension, fainting</td>
</tr>
<tr>
<td>Other</td>
<td>Urticaria, miosis, sweating, urinary retention</td>
</tr>
</tbody>
</table>

CNS = central nervous system

What Are NSAIDs (nsNSAIDs/Coxibs)?

NSAID = Non-Steroidal Anti-Inflammatory Drug

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

**Examples of nsNSAIDs:**
- Diclofenac
- Ibuprofen
- Naproxen

**Examples of Coxibs:**
- Celecoxib
- Etoricoxib
- Parecoxib

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

How Do nsNSAIDs/Coxibs Work?

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

COX-2 Is Expressed in the CNS

• PGs in the CNS are important in central sensitization and hyperalgesia\(^1\)
• Peripheral inflammation $\rightarrow$ central induction of COX-2
  – Occurs even with complete sensory nerve block\(^3\)
  – Humoral signal (IL-6?) may play a role in signal transduction across blood-brain barrier\(^3\)
  – IL-1beta plays an important role centrally\(^3\)
  – Elevation of PGs in CSF lead to hyperalgesia\(^3\)
  – Inhibition of IL-1beta synthesis or receptors reduce CSF levels of COX-2, PGs and hyperalgesia\(^3\)
  – Central inhibition of COX-2 has similar effects\(^3,4\)

CNS = central nervous system; CSF = cerebrospinal fluid; IL = interleukin; PG = prostaglandin
COX-2 Results in Sensitization to Pain

• **Peripheral Sensitization**
  
  – COX-2 is expressed following tissue injury
  
  – PGs produced increase nociceptor sensitivity to pain

• **Central Sensitization**
  
  – Peripheral inflammation → induction of COX-2 in CNS
  
  – Occurs even with complete sensory nerve block, possibly due to a humoral signal
  
  – PGs produced by COX-2 in CNS → further sensitization to pain

• **Result:** hyperalgesia and allodynia

CNS = central nervous system; PG = prostaglandin
COX-2 Is Involved in Central Sensitization

- Central induction of COX-2 → increased PG production
- PGE2 stimulation of EP receptors in dorsal horn will:
  - Activate PKC → phosphorylation and further enhancement of NMDA channel opening
  - Directly activate certain dorsal horn neurons by opening EP2 receptor-linked ion channels
  - Reduce inhibitory transmission of glycinergic inter-neurons
  - Increase depolarization and excitability of dorsal horn neurons

EP = E-prostanoid; NMDA = N-methyl-D-aspartate; PG = prostaglandin; PGE2 = prostaglandin E2; PKC = protein kinase C
COX-2 Inhibition Minimizes Sensitization

- Signal for COX-2 induction likely to persist with peripheral inflammation
- To minimize sensitization, COX-2 should be inhibited both centrally and in the periphery as early as possible
  - Continue until peripheral inflammation resolved

Ideal COX-2 inhibitor should be able to act peripherally as well as centrally and should readily cross the blood-brain barrier

Adverse Effects of NSAIDs/Coxibs

All NSAIDs
- Gastroenteropathy (e.g., gastritis, bleeding, ulceration, perforation)
- Cardiovascular thrombotic events
- Renovascular effects
  - Decreased renal blood flow
  - Fluid retention/edema
  - Hypertension
- Hypersensitivity

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

Coxib = COX-2-specific inhibitor; NSAID = non-steroidal anti-inflammatory drug; NSAID = non-specific non-steroidal anti-inflammatory drug
CV Risk of nsNSAIDs/Coxibs in Acute Pain*  

Risk of Death/Myocardial Infarction within First 7 Days of nsNSAID/Coxib Treatment in Patients with Previous Death/Myocardial Infarction

- Naproxen
- Diclofenac
- Ibuprofen
- Celecoxib
- Rofecoxib
- All nsNSAIDs/coxibs

*Coxib = COX-2-specific inhibitor; CV = cardiovascular; nsNSAID = non-specific non-steroidal anti-inflammatory drug
Gastrointestinal Risk of nsNSAIDs/Coxibs

Pooled Relative Risks and 95% CIs of Upper Gastrointestinal Complications

CI = confidence interval; Coxib = COX-2 inhibitor; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific non-steroidal anti-inflammatory drug

Risk Factors for Gastrointestinal Complications Associated with nsNSAIDs/Coxibs

ASA = acetylsalicylic acid; coxib = COX-2-specific inhibitor; GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific non-steroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor

GI Risk of nsNSAIDs/Coxibs in Acute Pain*

- During week 1 (53 cases, 22 controls): 11.7 (95% CI 6.5-21.0)
- After week 1 until discontinuation (353 cases, 268 controls): 5.6 (95% CI 4.6-7.0)
- First week after discontinuation (52 cases, 59 controls): 3.2 (95% CI 2.1-5.1)

CI = confidence interval; coxib = COX-2-specific inhibitor; GI = gastrointestinal; nsNSAID = non-specific non-steroidal anti-inflammatory drug

Effects of nsNSAIDs/Coxibs + ASA on Platelet Function

Baseline - 12 hours after NSAID - 24 hours after last NSAID, 22 hours after ASA 300 mg

Platelet Function Analyzer 100 Closure Time (seconds)

Placebo
Naproxen 550 mg
Ibuprofen 400 mg
Celecoxib 200 mg

n=24 healthy subjects

ASA = acetyl salicylic acid; coxib = COX-2-inhibitor; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific non-steroidal anti-inflammatory drug

Guidelines for ASA + NSAID Use

• Individuals taking low-dose ASA (75–162 mg/day) for vascular protection should avoid the concomitant use of nsNSAIDs
• If a patient taking low-dose ASA for vascular protection requires an anti-inflammatory drug, coxibs are preferred to nsNSAIDs

Both coxibs and nsNSAIDs increase cardiovascular risk and should be avoided if possible in patients at risk of ischemic vascular events

ASA = acetyl salicylic acid; coxib = COX-2-inhibitor; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific non-steroidal anti-inflammatory drug
Canadian Consensus on Prescribing NSAIDs

*In high-risk patients, a coxib and an nsNSAID + PPI show similar reductions of rebleeding rates, but these reductions may be incomplete.
†Most patients on ASA + naproxen would need an added PPI, but naproxen alone may be appropriate for some patients at very low gastrointestinal risk.

ASA = acetylsalicylic acid; coxib = COX-2-specific inhibitor; NSAID = non-steroidal anti-inflammatory drug; nsNSAID = non-specific NSAID; PPI = proton pump inhibitor.

### Guidelines for nsNSAIDs/Coxibs Use Based on Gastrointestinal Risk and ASA Use

<table>
<thead>
<tr>
<th></th>
<th>No Elevation in GI Risk</th>
<th>Elevated GI Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not on ASA</strong></td>
<td>nsNSAID alone</td>
<td>Coxib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nsNSAID + PPI</td>
</tr>
<tr>
<td><strong>On ASA</strong></td>
<td>Coxib + PPI</td>
<td>Coxib + PPI</td>
</tr>
<tr>
<td></td>
<td>nsNSAID + PPI</td>
<td>nsNSAID + PPI</td>
</tr>
</tbody>
</table>

Role of $\alpha_2\delta$-Linked Calcium Channels in Neuropathic Pain

Note: gabapentin and pregabalin are $\alpha_2\delta$ ligands
$\alpha_2\delta$ Ligands Bind to $\alpha_2\delta$ Subunit of Voltage-Gated Calcium Channels

Note: gabapentin and pregabalin are $\alpha_2\delta$ ligands
$\alpha_2\delta$ Ligands Reduce Calcium Influx in Depolarized Human Neocortex Synaptosomes

Fink K et al. Neuropharmacology 2002;42:229-36.
\( \alpha_2\delta \) Ligands Modulate Calcium Channel Trafficking

- \( \alpha_2\delta \) ligands reduce trafficking of voltage-gated calcium channel complexes to cell surface \textit{in vitro}
- \( \alpha_2\delta \) ligands prevent nerve-injury induced up-regulation of \( \alpha_2\delta \) in the dorsal horn

BCH = 2-(−)-endoamino-bicycloheptene-2-carboxylic acid; ER = endoplasmic reticulum; GBP = gabapentin
# Adverse Effects of $\alpha_2\delta$ Ligands

<table>
<thead>
<tr>
<th>System</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>CNS</td>
<td>Dizziness, somnolence</td>
</tr>
<tr>
<td>Other</td>
<td>Asthenia, headache, peripheral edema, weight gain</td>
</tr>
</tbody>
</table>

$\alpha_2\delta$ ligands include gabapentin and pregabalin

CNS = central nervous system

Antidepressants for Cancer Pain

• Antidepressants
  – Can be used to treat pain in opioid-treated populations with advanced medical illness
  – Predominantly used for neuropathic pain
  – May also be considered for other types of chronic pain

How Antidepressants Modulate Pain

Inhibiting reuptake of serotonin and norepinephrine enhances descending modulation.

# Suggested Mechanisms of Analgesic Action of Antidepressants

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Site of Action</th>
<th>TCA</th>
<th>SNRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reuptake inhibition</td>
<td>Serotonin Noradrenaline</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Receptor antagonism</td>
<td>α-adrenergic NMDA</td>
<td>+</td>
<td>(-) Milnacipran</td>
</tr>
<tr>
<td>Ion channel activation or blocking</td>
<td>Sodium channel blocker Calcium channel blocker Potassium channel activator</td>
<td>+</td>
<td>(-) Venlafaxine/(-) duloxetine ?</td>
</tr>
<tr>
<td>Increasing receptor function</td>
<td>GABA$_B$ receptor</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Opioid receptor binding/opioid-mediated effect</td>
<td>Mu- and delta-opioid receptor</td>
<td>(+)</td>
<td>(+) Venlafaxine</td>
</tr>
<tr>
<td>Decreasing inflammation</td>
<td>Decrease of PGE2 production decrease of TNFα production</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GABA = γ-aminobutyric acid; NDMA = N-methyl-D-aspartate; PGE = prostaglandin E; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; TNF = tumor necrosis factor

# Adverse Effects of Antidepressants

<table>
<thead>
<tr>
<th>System</th>
<th>TCAs</th>
<th>SNRIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive system</td>
<td>Constipation, dry mouth, urinary retention</td>
<td>Constipation, diarrhea, dry mouth, nausea, reduced appetite</td>
</tr>
<tr>
<td>CNS</td>
<td>Cognitive disorders, dizziness, drowsiness, sedation</td>
<td>Dizziness, somnolence</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Orthostatic hypotension, palpitations</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Other</td>
<td>Blurred vision, falls, gait disturbance, sweating</td>
<td>Elevated liver enzymes, elevated plasma glucose, sweating</td>
</tr>
</tbody>
</table>

CNS = central nervous system; TCA = tricyclic antidepressant; SNRI = serotonin-norepinephrine reuptake inhibitor
Acetaminophen

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

COX = cyclooxygenase
Invasive Modalities for Cancer Pain Management

- May provide pain relief to patients who do not respond adequately to traditional analgesic therapies
- Use of neurolytic substances has found a niche in treating pain related to abdominal and pelvic cancers
- Simple percutaneous injections of alcohol or phenol can provide relief in pancreatic, colon, or gynecologic cancer
- Percutaneous catheters for infusion of spinal analgesics can provide relief anywhere in the body
- Internal or external infusion pumps can be managed at home
Invasive Modalities for Cancer Pain Management

• Neurolytic blocks
• Spinal analgesics
• Regional local anesthetic infusions
• Other techniques
  – Spinal cord stimulation
  – Vertebroplasty
  – Lumbar epidural steroid
  – Intracerebroventricular opioids
  – Human chromaffin cell transplants
Invasive Therapies for Cancer-related Pain: Neurolytic Therapies

- Neurolytic techniques produce analgesia by destroying
  - Afferent neural pathways
  or
  - Sympathetic structures involved in pain transmission

- Achieving neural destruction
  - Surgery
  - Cold (cryotherapy)
  - Heat (radiofrequency thermal coagulation)
  - Injection of a material that damages the nerve

Invasive Therapies for Cancer-related Pain: Injection Therapies

- Soft tissue or joint injection of a dilute local anesthetic
  - Can reduce focal musculoskeletal pain
  - Should not be used in the presence of clinically significant coagulopathy or leukopenia

Invasive Therapies for Cancer-related Pain: Neurolytic Therapies

- Implanted catheters can be used for
  - Prolonged perineural or neuraxial infusion of analgesics
  - Electrical stimulation of peripheral nerves or spinal cord

- Both procedures avoid or limit side effects associated with systemic pharmacotherapy

- Disadvantages
  - Cost
  - Risk of infection
  - Mechanical failure

Co-Analgesics and Cancer Pain

• Drugs with a primary indication other than pain that have analgesic properties in some painful conditions
• Usually combined with a less than satisfactory opioid regimen in cancer pain
• Different types
  – Multipurpose
  – Neuropathic pain
  – Bone pain
  – Musculoskeletal pain
  – Bowel obstruction pain

## Types of Co-Analgesics for Management of Cancer Pain

<table>
<thead>
<tr>
<th>Type of Analgesic</th>
<th>Examples</th>
</tr>
</thead>
</table>
| **Multipurpose**                      | • Antidepressants  
• Corticosteroids  
• $\alpha_2$-adrenergic agonists  
• Neuroleptics                                           |
| **For neuropathic pain**              | • Anticonvulsants  
• Local anesthetics  
• N-methyl-D-aspartate receptor antagonists  
• Topic drugs (*e.g.*, lidocaine)                        |
| **For bone pain**                     | • Corticosteroids  
• Calcitonin  
• Bisphosphonates  
• Radiopharmaceuticals                                   |
| **For musculoskeletal pain**          | • Muscle relaxants  
• Tizanidine  
• Baclofen  
• Benzodiazepines                                       |
| **For bowel obstruction pain**        | • Octreotide  
• Anticholinergics  
• Corticosteroids                                         |
Summary: Co-Analgesics and Cancer Pain

- Consider optimizing opioid therapy before adding co-analgesic
- Consider burdens and potential benefits vs. other analgesic techniques
- Select most appropriate drug based on comprehensive patient assessment
- Prescribe based on knowledge of drug’s pharmacological characteristics, actions, approved indications, unapproved indications, likely side effects, potential serious adverse events, and drug-drug interactions
- Use the co-analgesic with the best risk:benefit ratio
- Avoid initiating several co-analgesics simultaneously
- Initiate treatment with low doses; titrate according to analgesic response and adverse effects
- Reassess efficacy and tolerability regularly
  - Taper/discontinue medications if no additional pain relief
- Consider combining multiple co-analgesics in selected patients
Drug Availability and Adherence
Prevalence of Non-adherence to Cancer Pain Therapy

Barriers to Optimal Management of Cancer Pain

- Institutional
  - Regulations regarding supply, prescription, and administration of opioids
- Healthcare professionals (HCPs)
  - Lack of knowledge in key areas of pain management
  - Lack of continuity of care among different HCPs
- Patients and their family/caregivers
  - Beliefs and perceptions about pain and pain medications

Patient Barriers to Adherence to Cancer Pain Therapy

- Fear of addiction
- Fear of tolerance
- Concern analgesics side effects are inevitable and unmanageable
- Fear of injections
- Fatalistic belief about cancer pain or belief that it is impossible to control
- Belief that “good” patients do not complain about pain
- Belief that healthcare professionals find it annoying to talk about pain and that this talk distracts from treating the cancer

Patients believe there is a trade-off between treating the pain and treating the cancer

Healthcare Provider Barriers to Effective Management of Cancer Pain

- Insufficient knowledge of pain management
- Insufficient assessment of pain
- Unwillingness to prescribe opioids
- Nurses unwilling to give opioids to patients
- Insufficient time to pay attention to patients’ pain needs
- Patients unwilling to report pain
- Patients refuse to take opioids
- Families unwilling to permit patients to take opioids
- Patients unable to pay for medications

Guidelines
WHO Pain Ladder for the Management of Cancer Pain

NCCN Guidelines for Management of Cancer Pain in Opioid-Naïve Patients*

*Opioid naïve includes patients who are not chronically receiving opioid analgesic on a daily basis and therefore have not developed significant tolerance. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.
NCCN Guidelines for Management of Cancer Pain in Opioid-Tolerant Patients

Monitor for acute and chronic adverse effects. (See Management of Opioid Adverse Effects, PAIN-F)

Opioid-Tolerant Patients

Initial Dose
- Pain ≥4 (moderate to severe)
- See Pain Intensity Rating (PAIN-A) or As indicated for uncontrolled pain (patient goals not met)
- Oral (peak effect 60 min)
- Intravenous bolus (peak effect 15 min) or PCA

Subsequent Dose
- Pain score unchanged or increased
- Increase dose by 50%-100%
- Repeat same dose
- Pain score decreased to 4-6
- Repeat same dose
- Pain score decreased to 0-3
- Continue at current effective dose as needed over initial 24 h

After 2-3 cycles, consider IV titration and/or see PAIN-6 for subsequent management and treatment

See Subsequent Pain Management, Mild Pain 0-3 (PAIN-6)

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NCCN = National Comprehensive Cancer Network
NCCN Guidelines for Subsequent Pain Management in Patients with Cancer*

PAIN INTENSITY

For **ALL** pain levels
- For persistent pain, initiate regular schedule of opioid with rescue dose as needed
- Continue management of constipation
- Provide psychosocial support
- Provide patient and family/caregiver education
- Optimize integrative interventions

Severe Pain 7-10
- See management for all pain levels above AND
- Reevaluate opioid titration
- Reevaluate working diagnosis with a comprehensive pain assessment
- Consider specific pain syndrome problems
- Consider pain specialty consultation
- Reevaluate adjuvant analgesics as indicated

Moderate Pain 4-6
- See management for all pain levels above AND
- Continue opioid titration
- Consider specific pain syndrome problems
- Consider pain specialty consultation
- Continue adjuvant analgesics titration

Mild Pain 0-3
- See management for all pain levels above AND
- Reassess and modify regimen to minimize adverse effects
- Adjuvant analgesics as needed

Opioid tolerant includes patients who are chronically receiving opioid analgesic on a daily basis. The FDA identifies tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

* NCCN = National Comprehensive Cancer Network
ESMO Clinical Practice Guidelines for Management of Cancer Pain

ESMO = European Society For Medical Oncology
EAPC Guidelines for the Use of Opioids for Cancer Pain

- For patients with mild to moderate pain or whose pain is not controlled by paracetamol or an NSAID, addition of a WHO step 2 opioid given orally may provide good pain relief
  - Alternatively, low doses of a step 3 opioid may be used
- There are no important differences between step 3 opioids given orally; any one may be used as the first choice for moderate to severe cancer pain
- Weak recommendation that 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

EAPC = European Association for Palliative Care; NSAID = non-steroidal anti-inflammatory drug; WHO = World Health Organization
EAPC Guidelines for the Use of Opioids for Cancer Pain

- Weak recommendation that methadone can be used as a step 3 opioid for moderate to severe cancer pain
- Weak recommendation that patients not achieving adequate pain relief on a step 3 opioid may benefit from switching to an alternative opioid
- Strong recommendation that breakthrough pain should be treated with additional doses of immediate-release oral opioids
- Appropriate titration of around-the-clock therapy should always precede the recourse to potent rescue opioid medications
- Weak recommendation to add NSAIDs to step 3 opioids to improve analgesia or reduce opioid dose required for pain relief
- Use of NSAIDs should be restricted due risks of serious adverse events
- Strong recommendation that amitriptyline or gabapentin should be considered for patients with neuropathic cancer pain that is only partially responsive to opioids

EAPC = European Association for Palliative Care; NSAID = non-steroidal anti-inflammatory drug
Literature Cited


Literature Cited (Continued 3)


