Cancer Pain Management: An Update

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Winnipeg Regional Health Authority
Topics

Pain-what is it?
Assessment of cancer pain
Types of pain in the terminally ill
Treatments and complications
Patient education
<table>
<thead>
<tr>
<th></th>
<th>Canada</th>
<th>Manitoba</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Cases (1997)</td>
<td>134,100</td>
<td>5,400</td>
</tr>
<tr>
<td>Deaths (1997)</td>
<td>65,300</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60,700</td>
<td>2,550</td>
</tr>
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</table>
## Symptom Prevalence

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence</th>
</tr>
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<tbody>
<tr>
<td>Pain</td>
<td>80 - 90%</td>
</tr>
<tr>
<td>Fatigue/Asthenia</td>
<td>75 - 90%</td>
</tr>
<tr>
<td>Constipation</td>
<td>70%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>60%</td>
</tr>
<tr>
<td>Nausea</td>
<td>50 - 60%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30%</td>
</tr>
<tr>
<td>Delirium</td>
<td>30 - 90%</td>
</tr>
<tr>
<td>Depression/suffering</td>
<td>40 - 60%</td>
</tr>
</tbody>
</table>
Opioid Receptors

Classically, opioids active on CNS receptors

mu (μ) kappa (κ) delta (δ) receptors

Now found on:

- peripheral neurons
- immune cells
- inflamed tissue
- respiratory tissue
- GI tract
A cancer is not only a physical disease, it is a state of mind.

M. Baden, New York Times, 1979
# Pain Assessment

<table>
<thead>
<tr>
<th>Temporal features</th>
<th>Medication(s) taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location/Radiation</td>
<td><em>Dose</em></td>
</tr>
<tr>
<td>Severity/Quality</td>
<td><em>Route</em></td>
</tr>
<tr>
<td>Aggravating and alleviating factors</td>
<td><em>Frequency</em></td>
</tr>
<tr>
<td>Previous history</td>
<td><em>Duration</em></td>
</tr>
<tr>
<td>(chronic pain, family)</td>
<td><em>Efficacy</em></td>
</tr>
<tr>
<td>Meaning</td>
<td><em>Side effects</em></td>
</tr>
</tbody>
</table>
Pain Assessment

History
Physical exam
Imaging
  X ray, CT scan, MRI, bone scan
Blood testing
  Ca++, renal function, infection
Cancer Pain

**Nociceptive**

Somatic:

- intermittent to constant
- sharp, knife-like, localized
- e.g. soft tissue infiltration
Cancer Pain

**Nociceptive**

*Visceral*: constant/intermittent
crampy/squeezing
poorly localized, referred
e.g. intra-abdominal mets
Cancer Pain

**Nociceptive**

*Bony*: constant, dull ache localized, may have neuropathic features

e.g. vertebral metastases pathologic fractures
Cancer Pain

**Neuropathic**

Destruction/infiltration of nerves

a) *dysesthetic:*

- burning/tingling
- constant, radiates

  e.g. post-herpetic neuralgia
Cancer Pain

**Neuropathic**

Destruction/infiltration of nerves

b) *neuralgic*:

- shooting/stabbing
- shock-like/lancinating
- paroxysmal

- e.g. trigeminal neuralgia
Cancer Pain

**Breakthrough**

“Incidental” pain
Severe transitory increase in pain on baseline of moderate intensity or less
Caused by movement, positioning, BM, cough, wound dressing, etc
Often ass’d with bony metastases

Portenoy R, Sem Onc, 24:S16-7-S16-12;1997
Mild pain (0-3)
Moderate pain (4-6)
Severe pain (7-10)

**WHO pain ladder**

By the mouth
By the clock
By the ladder

Acetaminophen
Codeine
Morphine
## Opioid Choice in Canada

<table>
<thead>
<tr>
<th>Opioid</th>
<th>PO</th>
<th>IV</th>
<th>PR</th>
<th>LA</th>
<th>TD</th>
<th>TM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Methadone</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
## Analgesic Equivalence

<table>
<thead>
<tr>
<th>Opioid</th>
<th>PO</th>
<th>IV/SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2 mg</td>
<td>1 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>5 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Methadone</td>
<td>1 mg</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td></td>
<td>50 mcg</td>
</tr>
<tr>
<td>Sufentanil</td>
<td></td>
<td>5 mcg</td>
</tr>
<tr>
<td>Codeine</td>
<td>100 mg</td>
<td>50 mg</td>
</tr>
</tbody>
</table>
Opioids

**Infrequent dosing**

- **Toxicity**
- **Analgesia**
- **Pain**

**Effect**

**Time**

Arrows indicate the timing of the effects.
Opioids

Adequate dosing

Toxicity

Analgesia

Pain

Effect

Time
Opioid Side Effects

- Constipation
- Nausea/vomiting
- Urinary retention
- Itch/rash
- Dry mouth
- Respiratory depression
- Drug interactions
<table>
<thead>
<tr>
<th><strong>Opioid</strong></th>
<th><strong>Active Metabolites</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine/</td>
<td>Morphine-6-glucuronide</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Morphine-3-glucuronide</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Norormorphine</td>
</tr>
<tr>
<td></td>
<td>Noroxycodone</td>
</tr>
<tr>
<td>Methadone</td>
<td>Oxymorphone</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>None known</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Opioid-Induced Neurotoxicity (OIN)

Neuropsychiatric syndrome
Cognitive dysfunction
Delirium
Hallucinations
Myoclonus/seizures
Hyperalgesia/allodynia
OIN: Treatment

- Opioid rotation
- Reduce opioid dose
- Hydration
- Circadian modulation
- Psychostimulants
- Other Rx
Opioid Rotation

Metabolites cause OIN
Change to another opioid analgesic
25 - 50% dose reduction
Morphine/hydromorphone/oxycodone
Second line agents
  fentanyl/sufentanil
  methadone
# Pain Management

<table>
<thead>
<tr>
<th>Nociceptive</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>soft tissue</td>
<td>opioids</td>
</tr>
<tr>
<td>visceral</td>
<td>opioids</td>
</tr>
<tr>
<td></td>
<td>steroids</td>
</tr>
<tr>
<td></td>
<td>surgery</td>
</tr>
<tr>
<td></td>
<td>radiation tx</td>
</tr>
</tbody>
</table>
# Bone Metastases

Frequency of Bone Metastases Associated With Common Malignancies

<table>
<thead>
<tr>
<th>Primary tumor</th>
<th>Bone mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast carcinoma</td>
<td>50%–85%</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>60%–85%</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td>64%</td>
</tr>
<tr>
<td>Bladder carcinoma</td>
<td>42%</td>
</tr>
<tr>
<td>Thyroid, kidney carcinoma</td>
<td>28%–60%</td>
</tr>
</tbody>
</table>

Bone Pain

**Pharmacologic treatment**

Opioids

NSAIDs/steroids/Cox-2 inhibitors

Bisphosphonates

- pamidronate (Aredia®)
- clodronate (Bonefos®)
- zoledronate (Zometa®)
Adjuvants

**NSAIDs**

Anti-inflammatory, anti-PEG

S/E: gastritis/ulcer, renal failure

↑ K⁺, platelet dysf’n

Ibuprofen, naproxen

Don’t use both steroids & NSAIDs!
Adjuvants

**Cox-2 Inhibitors**

- **Celecoxib** (Celebrex®)
- **Rofecoxib** (Vioxx®)
- **Meloxicam** (Mobicox®)
- **Valdecoxib**

- Anti-inflammatory
- Anti-prostaglandin
- S/E: less gastritis
- no platelet dysf’n
- renal failure still a problem
- OD dosing
- expensive
Bisphosphonates: Mechanism of Action

Actions of the bisphosphonates

- Physico-chemical
- Cellular

Clodronate

- Binding to the Ca-Ph crystals
- Fusion

Hemopoietic stem cell

Pre-osteoclast

Osteoclast

Collagen

Inhibition of dissolution of the mineral phase

Mineral
Bone Pain

**Radiation treatment**

- Single tx (800 cGy)
- Multiple fx (200 cGy x 3-5)
- Effective immediately
- Maximal effect 4 - 6 wks
- 60-80% pts get relief
- Strontium-89
Bone Pain

Surgical options

- Pathologic # (splint, cast, ORIF)
- Intramedullary support
- Spinal cord decompression
- Vertebral reconstruction
Neuropathic Pain

**Pharmacologic treatment**

- Opioids
- Steroids
- Anticonvulsants
- TCAs (dysesthetic)
- NMDA receptor antagonists
- Anaesthetics
Adjuvants

**Steroids**

- ↓ inflammation
- ↓ edema
- ↓ spontaneous nerve depolarization

Multipurpose
Adjuvants

**Anticonvulsants**
- Gabapentin (Neurontin®)
- Lamotrigine (Lamictal®)
- Carbamazepine (Tegretol®)
- Valproic acid (Depakene®)
Adjuvants

**Antidepressants**

- Amitriptyline (Elavil®)
- Nortriptyline (Aventyl®)
- Desipramine (Norpramin®)

SSRIs: results disappointing
Adjuvants

**NMDA Receptor Antagonists**
(N-methyl-D-aspartate)
Ketamine
Dextromethorphan
Methadone
Neuropathic Pain

**Non-pharmacologic**
- Radiation tx
- Anaesthetic tx
  - nerve block
  - epidural block
Breakthrough Pain

**Pharmacologic**
50-100% q4h dose
oral or parenteral
can be q 1 - 2 h prn
May cause severe sedation, toxicity
Delay in effect 15 - 30 min
Incident Pain

_Ideal agent:_

Potent, pure opioid μ agonist
Rapid onset
Early peak effect
Short duration
Easily administered
SL/TM routes advantageous
## Incident Pain Protocol Using Fentanyl

<table>
<thead>
<tr>
<th>Protocol Step</th>
<th>Medication</th>
<th>Sublingual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fentanyl</td>
<td>12.5 μg</td>
</tr>
<tr>
<td>2</td>
<td>Fentanyl</td>
<td>25 μg</td>
</tr>
<tr>
<td>3</td>
<td>Fentanyl</td>
<td>50 μg</td>
</tr>
<tr>
<td>4</td>
<td>Fentanyl</td>
<td>100 μg</td>
</tr>
</tbody>
</table>

Each step repeated 1 - 2 x q 15 min
Alternative Therapies

- Acupuncture
- Cognitive/behavioral therapy
- Meditation/relaxation
- Guided imagery
- Herbal preparations
- Magnets
- Therapeutic massage
Barriers to Pain Control

- Inadequate assessment
- Lack of patient education
- Improper dosing
- Side effects of analgesics
- Patient concerns re: opioid analgesics
- Patient compliance
Tolerance

Reduced potency of analgesic effects of opioids following repeated administration, i.e., increasing doses are necessary to produce pain relief

Related to opioid receptor regulation

Less common in pts with cancer pain

Often reason pts “save” opioids until terminal phase

Dependence

Physical dependence: normal response to chronic opioid administration

Evident with opioid withdrawal: yawning, sweating, tremor, fever, ↑ HR, insomnia, muscle/abdominal cramps, dilated pupils

Avoided by ↓ dose 20-30%/day
Addiction

Psychological dependence

“A pattern of drug use characterized by a craving for opioids...manifest...[by] compulsive drug-seeking behavior leading to...overwhelming involvement in use and procurement of the drugs.”

Hanks & Cherny, Oxford Textbook of Palliative Medicine, 2nd ed., 1998, Chapter 9.2.3
Key Education Points

- Current, accurate information
- Use available resources
- Involve family & caregivers
- Know pt knowledge base
- Address pt priorities first
- Small doses of useful info (e.g., S/E)
- Individualize to pt (social, education level)
Summary

Cancer pain common but undertreated
Assessment essential
Tailor treatment to pain type
Adjuvants Rx useful
Anticipate side effects
Patient education important
Help is available