Objectives

- Describe pain syndromes that are typically encountered in oncology nursing
- Discuss pharmacological and non-pharmacological strategies for cancer pain management
- Describe special issues in pain management in the last days of life

Cancer Pain: Overview

- 50% of patients in all stages of cancer have pain
- 70-90% of patients with advanced disease have moderate to severe pain
- Inadequate pain control
  - Decreases quality of life
  - Increases suffering
  - Increases cost of care
  - Increases morbidity and admissions
  - May impact mortality

Morbidity and Mortality

- There is increasing evidence that cancer survival is linked to good pain and symptom control
- NCCN guidelines recommend screening for pain at each visit
**Types of Pain**

- **Acute Pain**
  - Less than 3 months’ duration
- **Chronic Pain**
  - More than 3 months’ duration
- **Cancer Pain**
  - “Active” cancer
  - Chronic cancer-related pain in the survivor
  - End-of-Life pain

**Sources of Cancer Pain**

- **From the Cancer**
  - Abdominal and back pain from pancreas cancer
  - Upper arm pain from pathological humerus fracture

- **From the Cancer Treatment**
  - Chemotherapy-induced painful peripheral neuropathy
  - Post-mastectomy pain syndrome

- Or, **Unrelated** to the cancer or treatment
  - Chronic low back pain
  - Osteoarthritis

**Pain Etiology Based on Physiology**

- **Nociceptive / Somatic pain**
- **Nociceptive / Visceral pain**
- **Neuropathic pain**

- *Nociceptive* = normal processing of noxious stimuli (pain signals) from the periphery
- *Neuropathic* = abnormal processing of pain signals due to damage or dysfunction in the peripheral or central nervous system


**Why is it Important to Determine the Source of Cancer Pain?**

- The treatment depends on the pain etiology and mechanism
Somatic Pain

- Quality
  - Aching, throbbing
- Responds to
  - Opioids, NSAIDs*, acetaminophen*
- Oncological treatments
- Examples:
  - Bone pain due to metastases
  - Tumor pressure on psoas muscle causing pain w/ hip flexion

Visceral Pain

- Quality
  - Cramping, colic, squeezing
  - Oftentimes referred to another site
- Responds to
  - Opioids
  - Oncological therapies
- Interventions: Celiac plexus block
- Stents: Biliary or nephrostomy stents
- Examples
  - Malignant bowel obstruction
  - Ureteral obstruction
  - Pancreas tumor

Neuropathic Pain

- Abnormal processing of pain signals due to damage or dysfunction in the peripheral or central nervous system
- Quality
  - Burning, electrical shocks
  - Dysesthesias (painful tingling), allodynia (painfully sensitive skin)
- Responds to
  - Anticonvulsants, antidepressants, interventional blocks, opioids
- Examples
  - Surgical neuropathy: post-mastectomy/thoracotomy
  - Brachial plexus neuropathies: lung or breast cancer
  - Post-radiation plexopathies (breast, lymphoma)
  - Chemotherapy-induced peripheral neuropathy (CIPN)

Basic Pain Assessment

The “Golden Six” Questions

- Location
  - “Point to where it hurts”
- Quality
  - Aching & dull, sharp & stabbing, burning
  - Miserable, unbearable, punishing, “like torture”
- Quantity (Intensity)
  - Mild, moderate, severe
- Duration
  - Frequency, timing, pattern
  - Worse in the evenings
- Aggravating and alleviating factors
  - Worse with walking, standing, eating, becoming upset
  - Better with rest, activity, distraction, laughter
- Associated symptoms
  - Nausea, dizziness, insomnia
Assessing the "Quantity" (Intensity) of Pain

- **Numerical Scale**
  - “Rate your pain on a scale of zero to ten, with ‘zero’ being ‘no pain,’ and ‘ten’ being the ‘worst pain imaginable.”

- **Descriptive Scale**
  - “None,” “Mild,” “Moderate,” “Severe”

Other Methods to Assess Pain Intensity

- **Multilingual Pain Assessment Tools**
    - Spanish:
      - Por favor indique el número que mejor describa su dolor (Mar grados al máximo el mán menor su dolor).<br>      - Por favor indique el número que mejor describe su dolor (Mar grados al máximo el mán menor su dolor).<br>      - Pain score on the number chart. Anódale uno o más.

- **Faces Pain Scale-Revised**

Additional Pain History

- **Pain medication history**
  - Medications previously tried
  - Review reports of an “allergy” to opioid
    - Often this is actually an expected side effect of opioids, such as nausea or constipation
    - May be issues related to post-operative or in-patient setting, rather than opioids, such as hallucinations
  - **What is the “Meaning” of the pain?**
    - “If the pain is worse, it means the cancer is worse.”
    - “I’m afraid of dying.”
  - **Cultural factors**
    - “Isn’t morphine just for people who are dying?”

Pain Assessment Involves More Than Just a Number!

- **Pain intensity ratings are very useful, but are a unidimensional construct**
  - Complainants of “pain” may represent complex psychosocial constructs which no opioid will touch!
  - Dame Cicely Saunders’ concept of “Total Pain”
  - Anxiety may appear as pain, and pain may appear as anxiety
  - Keep your eyes and ears open, listen beyond the words that that are used
  - When all else fails, don’t forget that simply listening and “being there” is, in and of itself, therapeutic
  - **Empathic presence** goes a long ways towards healing and hope, and relief of suffering
Multimodal Approach to Cancer Pain

- **Drugs**
  - Opioid analgesics
  - Non-opioid analgesics (acetaminophen, NSAIDs)
  - Co-analgesics / Adjuvant Agents (anticonvulsants, antidepressants)

- **Oncologic therapies**
  - Chemotherapy, biologicals
  - Radiation therapy
  - Surgery

- **Interventional blocks and procedures**
  - Celiac plexus block, saddle block, superior hypogastric block
  - Bile duct, duodenal, rectal or ureteral stents

- **Physical modalities**
  - Physical therapy, occupational therapy
  - Manual lymphatic drainage

- **Complementary and Alternative Modalities (CAM)**
  - Acupuncture*, massage*, aromatherapy, Reiki
  - Mindfulness and relaxation strategies, meditation * Avoid if thrombocytopenia

Treatment of Cancer Pain

- **First, set realistic expectations!**
  - The goal is not “zero pain”
  - Rather, the goal is “tolerable” pain and
  - The lowest doses of meds needed to reach that goal
  - With the fewest analgesic side effects

- **Second, Ask: What kind of pain am I treating?**
  - Somatic or visceral or neuropathic?
  - Existential pain?

- **Third, always consider the psycho/social/spiritual aspects contributing to the pain experience**

An Approach to Analgesics for Cancer Pain

- **“By the mouth”**
  - AKA: “If the gut works, use it!”

- **“By the clock”**
  - Around the clock dosing for constant/steady pain
  - Avoid peaks and valleys / roller coaster

- **“By the ladder”**
  - World Health Organization Cancer Pain Ladder

- **“With attention to detail”**
  - Individual focus
World Health Organization Pain Ladder

Opioids (Narcotics)

- The best drugs available for cancer pain management
- (Also the most feared)

Opioids for Cancer Pain

- "Pure" Opioids: No upper dose ceiling
  - Morphine
    - the "gold standard" for comparison
  - Oxycodone
  - Fentanyl
  - Oxymorphone
  - Methadone
- Combination products: limited maximum dose
  - Hydrocodone + acetaminophen (Vicodin®)
  - Hydrocodone + ibuprofen (Vicoprofen®)
  - Oxycodone + acetaminophen (Percocet®)

Opioids: What NOT to Use

- Meperidine (Demerol®)
  - Short half-life
  - Toxic metabolite, normeperidine, has a longer half-life than meperidine; accumulates in renal dysfunction, may cause seizures
- Propoxyphene (Darvon®)
  - Toxic metabolite, norpropoxyphene
  - Less potent than acetaminophen and aspirin
- Mixed agonists-antagonists
  - Pentazocine (Talwin®), butorphanol (Stadol®), nalbuphine (Nubain)
  - Major psychomimetic effects, especially in elders and renal impairment
  - Low maximal efficacy, ceiling effect
  - Potential to reverse mu-receptor analgesia and cause withdrawal
- Partial agonists
  - Buprenorphine
  - Potential to reverse mu-receptor analgesia and cause withdrawal

**Opioid Pharmacokinetics**

<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>Intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset of Action</strong></td>
<td>30-60 minutes</td>
<td>3-5 min fentanyl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-10 min morphine</td>
</tr>
<tr>
<td><strong>Peak Effect</strong></td>
<td>60-90 minutes</td>
<td>15-30 minutes</td>
</tr>
<tr>
<td><strong>Duration of Action</strong></td>
<td>3-6 hours</td>
<td>3-4 hours morphine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 hours fentanyl</td>
</tr>
<tr>
<td><strong>Half-Life</strong></td>
<td>2-4 hours</td>
<td>--</td>
</tr>
<tr>
<td><strong>Steady State</strong></td>
<td>4-5 half lives (~15 hrs)</td>
<td>5 half lives (~12 hours)</td>
</tr>
</tbody>
</table>


**Opioid Dose Calculations**

- Opioid dose escalation for poorly controlled pain, (once steady-state has been achieved):
  - For moderate to severe pain, titrate up by: **30-50%**
  - For severe pain, titrate up by: **50-100%**
  - For frail, elderly, renal or hepatic impairment, not at steady-state, titrate up by: **20%**

- To determine the dose for breakthrough pain (BTP, immediate release) medicine, calculate **10-20% of** the total opioid dose taken in the last 24 hours
  - Give that dose q3-4 hours oral or q15 min IV


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**Cancer Pain Management: Severe Pain**

**The Opioid-Naïve Patient**

**Oral**
- Morphine 5-15 mg po
- Reassess in 60 minutes
  - Pain better: continue at same dose
  - Pain same: repeat dose
  - Pain worse: titrate by 50-100% (10-30 mg po)
- Reassess in 60 minutes

**Intravenous**
- Morphine 2-5 mg IV
- Reassess in 15 minutes
  - Pain better: continue at same dose
  - Pain same: repeat dose
  - Pain worse: titrate by 50-100% (4-10 mg IV)
- Reassess in 15 minutes

**Note:** This example uses morphine, but any opioid can be utilized.


**The Opioid-Tolerant Patient**

**Oral**
- Administer 10-20% of total opioid dose taken in the last 24 hrs
- Assess in 60 minutes
  - Pain better: continue at the same dose
  - Pain same: repeat same dose
  - Pain worse: titrate by 50-100%
- Reassess in 60 minutes

**Intravenous**
- Administer 10-20% of total opioid dose taken in the last 24 hrs
- Assess in 15 minutes
  - Pain better: continue at the same dose
  - Pain same: repeat same dose
  - Pain worse: titrate by 50-100%
- Reassess in 15 minutes

How is “Opioid Tolerant” Defined?

- Patient is chronically receiving opioid analgesics on a daily basis, for one week or longer, in the following doses or more:
  - Morphine 60 mg/day
  - Oxycodone 30 mg/day
  - Fentanyl patch 25 mcg/hr
  - Oxymorphone 25 mg/day
  - Hydromorphone 8 mg/day
  - Or equivalent dose of another opioid


Opioids: Adverse Effects

**ADE that reduce over time:**
- Nausea
- Pruritus
- Sedation
- Dry mouth
- Lightheadedness/dizziness
- Cognitive changes
- Delirium
- Respiratory depression
- Urinary retention
- Mood change: euphoria

**Do not improve over time:**
- Constipation
- Sleep disordered breathing
- Obstructive sleep apnea
- Central sleep apnea
- Some cognitive effects
- Driving Safety
- Urinary retention
- Mood changes: dysphoria
- Endocrine effects
- Hypogonadism
  - Hypotestosterone
  - Cessation of menses
- Sexual dysfunction

Opioid Therapy Bowel Program

- Preventative Bowel Program – Everyday Use
  - Osmotic laxative + Stimulant
    - MiraLax 17 gm daily to BID
    - Senna 8.6 mg or bisacodyl 5 mg 1-2 BID
  - Fluids, daily walking, prunes

- “Rescue” Plan
  - Magnesium citrate ½ - 1 bottle q12-24 hrs x 2
  - Bisacodyl 10 mg supp pr (avoid if neutropenic or thrombocytopenic)

Other Opioid Adverse Drug Effects

- Myoclonus
  - Brief, involuntary jerking arising from CNS
  - Most common with higher doses of morphine
    - Due to metabolites M-3-G and M-6-G
    - Especially in renal compromise and older adults
- Opioid-induced hyperalgesia
  - Rare phenomenon in which the opioid causes paradoxical worsening of pain
  - Treatment: Dose reduce or rotate to another opioid
    - Ketamine infusions

Cancer Pain Management

Co-Analgesics / Adjuvant Medications

- For neuropathic pain, CIPN, (? bone pain?)
  - Antidepressants
    - SNRIs: Duloxetine (Cymbalta®), venlafaxine (Effexor®)
    - TCAs: nortriptyline, amitriptyline
  - Anticonvulsants
    - Gabapentin (Neurontin®), pregabalin (Lyrica®)
  - Topical agents
    - Lidocaine 5% patch (Lidoderm®) - post-herpetic neuralgia
    - Capsaicin

CIPN = Chemotherapy-induced peripheral neuropathy. SNRI = Serotonin-norepinephrine reuptake inhibitor. TCA = tricyclic antidepressants. Not recommended due to multiple drug interactions with chemotherapy.

Cancer Pain Management

Non-Opioid Analgesics

- Nonsteroidal anti-inflammatory agents (NSAIDs) for nociceptive pain, bone pain
  - Naproxen, ibuprofen
  - Avoid if h/o gastrointestinal bleeding or ulcers, renal impairment, on anticoagulation therapy, thrombocytopenia.
- Not recommended with many chemotherapy agents
  - Acetaminophen for nociceptive pain
    - Limit to 2-3 grams/day
    - 500 mg tablet = 4-6 tab/day
    - Avoid if elevated LFT, hepatic disease, taking opioid combination products (e.g. Percocet®)

Cancer Pain Management

Palliative Anticancer Therapies

- Radiation therapy
  - 75% of patients with bone metastasis obtain some relief from palliative radiation, half become pain free
- Chemotherapy: Reduces tumor burden which reduces pain
- Surgery/Procedures
  - Orthopedic procedures to stabilize areas high risk for fracture or ORIF
  - Colon or rectal stents/colostomy for bowel obstruction
  - Common bile duct stents for obstruction/jaundice
- Bisphosphonates: Reduces pain from bony metastasis
  - Pamidronate, zolendronic acid (Zometa®), alendronate (Fosamax®)
- Octreotide
  - Reduce pain related to malignant bowel obstruction
  - Helpful in carcinoid syndrome

Cancer Pain Management

Nonpharmacological Strategies for Pain Management

Interventional Techniques

- Nerve blocks
  - Temporary or Neurolytic
  - Celiac plexus block for pancreatic cancer
  - Endoscopic vs. percutaneous approach
  - Superior hypogastric plexus block
  - Cervical, bladder, prostate, rectum
  - Saddle block
  - Rectal, vaginal, perineal, scrotum, penis
- Vertebroplasty/kyphoplasty
  - Injection of polymethyl methacrylate cement / with balloon inflation to decompress the vertebra
  - For metastatic compression fractures
  - Lesioning of nerves, roots, plexus, spinal cord
  - Rarely done for exceptional cases only
  - Pain may start to return in 6 months
  - May cause worsening pain “anesthesia dolorosa”
Nonpharmacological Strategies for Pain Management

Physical Measures

- Hot or cold packs
  - 10-15 minutes QID
- Massage
- Physical Therapy
- Manual Lymphatic Drainage (MLD) for lymphedema
- Positioning
  - Hospital bed
- Canes, walkers, braces

Cognitive/Behavioral Therapies

- Relaxation/guided imagery
- Distraction
- Humor
- Expressive arts/music
- Cognitive reframing
- Support groups
- Spiritual support, prayer, meditation
- Counseling

Integrative Therapies

- Acupuncture/acupressure
- Reiki
- Aromatherapy

Don’t Miss This Pain Syndrome!
Spinal Cord Compression/ Cauda Equina Syndrome

- Second most common neurological complication of cancer (after brain mets)
  - Vertebral body metastasis causes pressure on the spinal cord/nerve roots
  - Usually occurs in known metastatic disease, but may be presenting sign of cancer
- Most commonly seen in cancers with bony metastasis
  - Breast, prostate and lung cancer (15-20%) 
- Pain is the first sign!
  - Progressive, severe, focal back pain is the initial symptom in 80% of cases
- Pain onset is an average of 7 weeks before other neurological deficits
- Thoracic spine is most common
- If untreated, virtually 100% of patients will become paraplegic!

Signs and Symptoms of Spinal Cord Compression

- Saddle anesthesia
  - Numbness in perineum and lower buttocks
- Bowel or bladder changes
  - Fecal incontinence from lax anal sphincter
  - Urinary overflow incontinence, high post-void residual
- New weakness in upper or lower extremities
  - Stumbling gait, clumsiness, “heaviness” in legs
- Pain worse with recumbency
  - Must sleep in a semi-recumbent position
- Pain in a band-like fashion
- Thoracic spine is most common site
- SCC is a medical emergency. If suspected, instruct patient to go to ED, report to oncologist immediately
- MRI of spine is the gold standard for diagnosis
- Treatment: high dose steroids, spine radiation, surgery

Pain Management at End of Life

- Patients fear pain at end of life more than than they fear death
- Although death is inevitable, a miserable painful death is not
- Fear of inflicting harm or hastening death may prevent providers from adequately treating uncontrolled pain
  - However, in reality, inadequate pain control at the end of life may actually hasten death!
  - Tip: What may appear to be “pain” may actually be end of life delirium
  - Very common at end of life in cancer deaths
  - Treated with antipsychotics, not opioids!

Pain Management Tips at End of Life

- Simplify medication regimen
  - If patient unable to swallow
    - Crush tablets and add a few drops of vanilla flavor (.3 cc), administer sublingual/oral
    - Consider alternate routes (IV, Subcutaneous, rectal)
    - Avoid transdermal fentanyl if severely cachectic
  - If liver and renal dysfunction, drug clearance impaired; may need to reduce dose or extend frequency
    - Preferred drugs: oxycodone, hydrocodone, methadone
  - Assess for psychosocial /existential distress which may be worsening pain
  - Provide support family and other caregivers

Palliative Sedation at End of Life

- “The intentional induction of sedation for the purpose of relieving severe, refractory symptoms including pain, agitation and delirium in patients who are dying.”
- Not typically required for good EOL pain and sx mngt
- This is not euthanasia or assisted suicide!
- Agents used include
  - midazolam (Versed), lorazepam (Ativan),
  - thiopental (Pentothal), propofol
  - pentobarbital (Nembutal), phenobarbital
- Opioids for pain or dyspnea should be continued

Case Study: Worsening Pain - 1

- You are a nurse working in a medical oncology office caring for a 56 yo woman with metastatic breast cancer.
- Her husband has called in several times in the last week reporting her pain is worse.
- Pain meds were increased last week from oxycodone SR (OxyContin®) 10 mg BID to 20 mg BID
- Today he calls sounding desperate, says her pain is severe, and reports it now takes at least 15 tablets per day of oxycodone 5 mg immediate release, to “even start to touch her pain.”
- You consult with the oncologist who has you instruct her to increase the oxycodone SR 70 mg TID

What do you think of this order?

Case Study: Worsening Pain - 2

- Do The Math!
- Current use:
  - Oxycodone SR 20 mg BID = 40 mg/day
  - Oxycodone 5 mg/tab x 15 tab/day = 75 mg/day
  - 40+75 = 115 mg/day oxycodone
- Oxycodone SR 20 mg TID = 60 mg/day
- What is a better order?

Case Study: Worsening Pain - 3

- Current use = oxycodone 115 mg/day
- For ongoing, severe pain, increase dose by 50-100%
- = Oxycodone 172-230 mg/day
- Long acting: OxyContin 60-80 mg TID
  - = 180-240 mg/day
- Short acting: Oxycodone 10-15 mg tab 1-2 q3h prn
  - [10-20% of 24 hour total dose]

Palliative Sedation at EOL

- Prior to initiating, discuss plan with pt (if able), family, and staff
  - Document informed consent discussion, any plans for artificial nutrition/hydration
  - Confirm DNR/DNI orders are documented in the chart
  - (Ethics consult if required at your institution)
- Assure a peaceful, quiet setting, with a minimum of intrusions
  - Limit or discontinue vital sign checks, turn off alarms
  - Discontinue meds or treatments that are not contributing to comfort
- Offer chaplain or social work support to family
- Family and Staff Education is key to success
- Reassure family / loved ones that palliative sedation is not euthanasia or assisted suicide!
  - Research shows that patients do not die any earlier with palliative sedation
- Seek emotional support if you need it

Case Study: Worsening Pain - 4

- She was seen one week ago by the oncologist to review scans and labs.
- At that visit she was told the tumor was growing despite the chemotherapy.
  - "You failed the last treatment available."
  - "There's nothing more we can do."
  - Patient refused Hospice Care
    - "We're not ready to give up yet."
- How might these statements impact her pain perception?

Case Study: Pain Crisis - 5

- The patient enrolls in Hospice a few days later.
- Her pain has been well controlled on OxyContin 100 mg TID, and oxycodone 15 mg for BTP x 3-5/day.
- Today her husband calls reporting she is in the worst pain he has ever seen, it is terrible. She is vomiting everything and cannot keep the pills down. He frantically asks what he can do to help her pain, “or I’ll have to call 911”
- What are your options right now to help her?

Case Study: Pain Crisis - 6

- Alternate routes of administration immediately available:
  - Sublingual
    - Crush oxycodone 15 mg tabs, give SL
    - Do not crush OxyContin
  - Rectal administration
    - Both OxyContin and oxycodone
  - Hospice “Comfort Kit”
    - Morphine oral solution 10 mg/ml
  - Re-dose every 30 minutes until comfortable

Conclusion

- Pain is commonly associated with cancer, especially at end of life
- Cancer pain can be controlled, usually with oral medications
- Opioids are the primary therapy for cancer pain management
- There are multiple strategies available to treat cancer pain
- The nurse has an important role in assessing and managing cancer pain
- Always remember the importance of assessing for existential distress as part of the “Total Pain” experience
Recommended Reading & Resources

- Primer of Palliative Care, 5th ed. Quill et al. 2010. American Academy of Hospice and Palliative Medicine. AAHPM.org. $25
- Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 6th ed. American Pain Society. ampainsoc.org. $15
- National Comprehensive Cancer Network; NCCN.org
- Guidelines on: Adult Cancer Pain | Palliative Care | Survivorship
- National Cancer Institute (cancer.gov); Patient Ed Booklet: “Pain Control”
- PartnersAgainstPain.org

Additional Reading

Barriers to Pain Relief

- Professionals
  - Inadequate training in pain assessment and management, especially at end-of-life
  - Concern for medication side effects
  - Fear of addicting the patient
  - Concern that opioids will hasten death
  - Concerns of regulatory control

Barriers to Pain Relief

- Health Care System
  - Regulatory control
    - DEA oversight
    - FDA/REMS: Risk Evaluation Mitigation Strategy
  - Lack of availability of drugs in many pharmacies
    - “We don’t sell OxyContin here”
  - Cost of drug
    - Insurance reimbursement/copay
Rank the Out-of-Pocket Cost of Common Long-Acting Opioids

- **Lowest Cost**
  - Methadone 5 mg TID, #90: $14
  - Morphine SR (MS Contin®) [generic] 30 mg BID, #60: $30

- **Moderate Cost**
  - Fentanyl patch (Duragesic®) 25 mcg/hr #10: $154

- **High Cost**
  - Oxycodone SR (OxyContin®) [brand name] 20 mg BID, #60: $397
  - Morphine ER (Avinza®) [brand name] 30 mg BID: $407

- **Very Expensive**
  - Oxymorphone SR (Opana®) 10 mg BID, #60: > $500
  - Hydromorphone ER (Exalgo®) 12 mg qd #30: > $500

SCCA Pharmacy out-of-pocket cost 4/2013

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Barriers to Pain Relief: Patient/Family

- Fear of addiction
- Reluctance to report pain
  - Want to be a “good” patient and not distract the oncologist
- Concern for adverse effects of pain medications
  - Constipation, sedation, cognitive changes
- Fear of becoming “immune” to opioids if used too early in the disease trajectory

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Addiction...Know Your Definitions!

- **Tolerance**: a *physiological* response; increased dose needed for same effect. Presents initially as decreased *duration* of analgesia.
  - Consider progression of disease as the cause rather than tolerance
- **Physiological dependence**
  - Abstinence syndrome (withdrawal symptoms) occur if the drug is abruptly discontinued, or reversal agent used (naloxone)
- **Addiction = psychological dependence**
  - CRAVING the drug
  - COMPULSIVE use
  - Impaired CONTROL over drug use
  - CONTINUED use despite harm
  - Use of drug for reasons other than pain control

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Chemotherapy-induced peripheral neuropathy: CIPN

- **Platinum compounds - up to 92% incidence**
  - Cisplatin, carboplatin, oxaliplatin
  - Ovarian, breast, GI, lung, testicular
- **Taxanes – up to 78% incidence**
  - Paclitaxel (Taxol®); Protein-bound paclitaxel (Abraxane®); Docetaxel (Taxotere®)
  - Breast, lung, stomach, head/neck, prostate
- **Vinca alkaloids - up to 57% incidence**
  - Vincristine, vinblastine, vinorelbine
  - Breast, head/neck, leukemia, lymphoma
- **Other classes – up to 81% incidence**
  - Bortezomib (Velcade®), thalidomide
  - Multiple myeloma
- **NOTE**: CIPN may be painful or non-painful

Risk Factors for Developing CIPN

- **Host Factors**
  - Preexisting painful neuropathy
  - Nutritional deficits
  - Older age
  - HIV infection

- **Drug Factors**
  - Higher individual doses of neurotoxic agents
  - Higher cumulative doses of neurotoxic agents
  - Multiple neurotoxic agents

“Coasting”

- An interesting phenomenon in which neuropathy may not start until treatment is completed, and may continue to worsen for a period of time (weeks to months)


CIPN Descriptions

- CIPN includes both painful and non-painful conditions
- Stocking-glove distribution
  - Length dependent
  - May involve predominantly hands or feet
- Non-painful
  - Numbness, non-painful tingling
- Painful sensations:
  - Paresthesias (painful tingling), burning, shooting


CIPN Distress

- CIPN is distressing to patients, even if not painful
  - Negatively impact on quality of life
  - Insensate digits or feet make it difficult to perform instrumental activities of daily living such as buttoning a shirt, typing on a keyboard, walking, or driving
  - Patient education:
    - Protect numb fingers, especially when handling hot or frozen foods or washing dishes
    - Check feet regularly (similar to diabetic foot exam)
    - Driving safety

CIPN Prevention and Treatment: Evidence

- Very little!
- Prevention
  - Rodent: acetyl-L-carnitine, olesoxime, minocycline show promise
  - Human: glutathione, glutamine, Vit E: "might work"
- Now discounted: [IV Ca/Mg before and after oxaliplatin infusion]
- Treatment:
  - RCTs show no benefit from gabapentin, lamotrigine, nortriptyline, amifostine
  - Conflicting evidence for acetyl-L-carnitine
- Recently published RCT showed improved in pain and QOL with tx of CIPN
  - Duloxetine
- Other RCTs in progress are showing promise for tx of CIPN
  - Pregabalin
  - Topical baclofen/amitriptyline/ketamine

CIPN: Chemotherapy-induced peripheral neuropathy.

Smith EML. Effect of duloxetine on pain, function, QOL, for CIPN. JAMA. 2013;309(13)1359-67.

Chronic Pain from Radiation Therapy

- Post-radiation syndromes are less common now due to improved radiation tx
  - Brachial or lumbosacral plexopathy
    - Neuropathic pain in dermatomal patterns of the arm or leg after radiation to the axilla or pelvis
    - Breast, lung, GI or GYN cancers, Hodgkin’s disease
    - Peak onset 2-4 years post-treatment (range 6 month-20 years)
    - Risk: younger age, concurrent cytotoxic chemotherapy
  - Lymphedema
    - Radiation to the head/neck, arm, breast, leg, or pelvis
    - May be painful, or simply uncomfortable
  - Proctitis or cystitis
    - Burning pain in the bladder or rectum, after pelvic radiation for prostate, rectal, cervical or endometrial cancer
  - Radiation enteritis
    - Pelvic radiation, causing chronic diarrhea and painful defecation from rectal excoriation, mucosal ulceration, and GI adhesions

Lepc, 2008. Management of Chronic Pain in Cancer Survivors, Cancer J., 14(6), 401-409

Post-surgical Pain Syndromes

- Post-amputation pain
  - Phantom limb pain
  - Stump pain
- Post-thoracotomy pain
- Post-mastectomy pain
- Post-radical neck dissection pain
- Lymphedema


Osteoporosis in the Cancer Patient

- Increases risk of painful events
  - Vertebral body compression fractures
  - Femoral neck fractures
- Common in cancer survivors due to:
  - Chemotherapy-induced ovarian failure
  - Surgical menopause
  - Aromatase inhibitors: letrozole (Femara®)
  - Androgen-deprivation therapy: prostate cancer
  - High dose steroids: hemopoietic cell transplant (HCT), lymphoma
- DEXA screening

Osteoporosis Treatment

- Bisphosphonates
  - pamidronate (Aredia®), zoledronic acid (Zometa®), or alendronate (Fosamax®)
- Small risk of osteonecrosis of the jaw or atypical fractures
- Benefit outweighs hazards in higher risk patients such as breast or prostate cancer survivors
- Weight bearing exercise
- Calcium/ Vitamin D


Avascular Necrosis

- Chronic painful degenerative condition
- Femoral head and knees most common
- Risk Factors:
  - HCT (especially allogeneic)
  - Childhood ALL
  - Long term high-dose steroid use
- Theorized Mechanism:
  - Disruption in blood supply to bone
  - Long term exposure to high dose steroids causes fat embolism in microvascular structures


Avascular Necrosis: Management

- Joint replacement is the only definitive treatment
- Cortical bone drilling to promote bone growth
- Off-load the joint with cane/crutches
- Water aerobics/swimming
- Opioids-focus on stable dose
- AVN seriously impacts patient QOL
  - Support needed


AI-Induced Myalgias & Arthralgias

- Common ADE of Aromatase Inhibitor (AI) therapy
  - Used in breast cancer to extend disease-free survival, taken for 5-10 years
  - Letrozole (Femara®), exemestane (Aromasin®), anastrozole (Arimidex®)
- Incidence of myalgias & arthralgias 35-50%
  - Onset symptoms at 1.6 months, peaks at 6 months
  - 60% report moderate to severe intensity
  - Symmetrical pain in hands, wrists, knees, neck, shoulder, feet, back
  - Trigger finger, carpal tunnel
  - Morning stiffness common

**AI-Induced Myalgias & Arthralgias**

- Adherence to therapy is an issue with AI's
  - 2 studies show 13-22% discontinuation rate
  - However, analysis of pharmacy records in 12,000 pts revealed **only 50-68% adherent to AI therapy at 3 years**

- Treatment:
  - NSAIDs, acetaminophen, short course low dose prednisolone
  - SSRI, pregabalin, Vit D, diuretics, bisphosphonates
  - Exercise, acupuncture, massage, PT, TENS
  - Most symptoms resolve with completion of AI therapy
  - Switch to another drug in the AI class
    - Switch to tamoxifen after a minimum of 2 years on AI


**Dyspareunia**

- Sexual dysfunction is common in survivors
  - Anorgasmia, low libido, erectile dysfunction
  - Dyspareunia (painful intercourse)

- Common after tx for breast and GYN cancers
  - Vaginal atrophy/dryness from menopause from surgery or chemotherapy
  - Pelvic radiation decreases blood flow to the vaginal wall or causes pelvic fibrosis
  - 81% of ovarian cancer survivors report vaginal dryness, which is a significant problem for 25%

- Management of dyspareunia
  - Vaginal moisturizers and lubricants, work with partner to find intimacy strategies that work, vaginal dilators for stricture


**Chronic Graft vs. Host Disease cGVHD**

- Post-hematopoietic cell transplant
  - 80% transplants are stem cell rather than bone marrow
  - Leukemia, lymphoma, multiple myeloma

- Chronic GVHD: >100 days post-transplant

- Higher risk
  - Allogeneic transplant (donated from other person) vs. autologous
  - Stem cell transplant > bone marrow tx (NEJM; 2012; 16:1487)
  - Older age
  - Histocompatibility disparities, gender mismatch
  - Severe acute GVHD

- 30-80% transplant recipients who have survived >6 months have cGVHD

- Typically affects skin, liver, oral mucosa, GI, lungs, eyes


**Chronic GVHD Pain Syndromes**

- Skin:
  - Scleroderma-like, painful joint contractures, skin atrophy, ulcerations
  - Trunk, buttocks, hips, thighs
  - Contributes to generalized muscle wasting

- Mucous membranes
  - Oral and vaginal ulcerations
  - Vaginal estrogen

- Ocular pain, photophobia

- Treatment is immunosuppression
  - Prednisone plus cyclosporine or tacrolimus