Objectives

- List pharmacologic and nonpharmacologic interventions for pain management in cancer patients
- Identify different types of pain and appropriate interventions
- Identify criteria for eligibility for medical cannabis for cancer patients

Overview and Impact

- 10 million cancer patients and survivors, residual symptoms of both disease and treatment represent a significant and under-recognized public health burden.
- Cancer is increasingly becoming a "chronic" illness, amplifying the issue of symptom burden—chronic, lifelong
- Historically, symptom management is focused on "after the fact", rather than prevention

Overview and Impact

- Severe symptoms make patients delay or terminate treatment or make them ineligible for treatment
- Consumers have higher expectations for better symptom control
- NCI: recommends more symptom research

Supportive Care in the Oncology Patient

Maslow’s Hierarchy

- Physical symptoms
- Psychological 
  & Social Issues
- Information
- Security

Meaning of pain

- Worsening disease
- Previous experiences: witnesses others in pain
- Decreasing functional capacity
- Punishment
- Fear of loss of control, loss of independence
  - Depression
  - Increased suicidality with uncontrolled pain
- Relief of pain often ‘cures’ perceived psychiatric disorders
Undertreatment of Pain: Clinician Factors

- Lack of training beyond the basics
- Lack of communication --- time
- Provider and patient discrepancy in judgement of severity of pain (especially when patient reports pain > 7)
- Fear of respiratory depression
- Fear of causing addiction
- Patients may minimize pain reports due to fear of not being treated for their cancer.

Types of Cancer Pain

- **Nociceptive Pain**: Primary activation of visceral or somatic nociceptors by a primary or metastatic tumor, typically impinging on adjacent tissues or obstructing blood vessels
- **Visceral Pain**: Mechanical invasion or stretching of hollow visera or distortion of the capsule of solid organs: eg. liver
- **Neuropathic Pain**: Entrapment and injury of nerves directly from tumor or damage to nerves by proteolytic enzymes made by tumor cells. Also malignant involvement of the CNS, such as leptomeningeal carcinomatosis.

Causes of Cancer Pain

- Release of chemicals by tumors that excite or sensitize peripheral nociceptive primary afferents: prostaglandins, endothelins, TNF
- Ischemia and necrosis that activate pain receptors
- Rapid weight loss, muscle hypercatabolism, immobilization, increased muscle tension cause muscular pain
- Inflammation caused by tumor-induced mediators, such as cytokines

Watch the Literature: Role of Cytokines in Pain

- Cytokines are soluble proteins or glycoproteins that act as mediators of cell-to-cell communications and are integral to the function of immune cells.
- Cytokines are aberrantly produced by cancer cells, macrophages, and other phagocytic cells.
- In addition to causing inflammatory pain, cytokines are also suspected to contribute to cachexia, anorexia, enhanced energy expenditure (hypermetabolic state), asthenia, in cancer.

Treatment Related Pain

- Joint and muscle pain due to chemo and hormone therapy
- Mucositis/esophagitis from chemo, radiation, immunosuppresion
- Chemo-induced neuropathy
- Surgical interventions that give rise to nerve damage and chronic post-op pain
- Opioids—paradoxical effect

When Opioids Hurt

- Opioid-induced hyperalgesia: sensitization of pronociceptive mechanisms. Patients receiving opioids to relieve pain may paradoxically experience worse pain as the dose of opioid is increased, by increasing sensitivity to pain while escalating physical dependence. Usually seen with chronic opioid treatment
- Neurotoxicity: due to accumulation of toxic metabolites. Risk with renal insufficiency, dehydration.
  - Delirium
  - Myoclonus
  - Seizure
- Tolerance: desensitization of anti-nociceptive mechanisms
Cancer-induced Bone Pain
- Mechanical distortion of the periosteum (the membrane covering the surfaces of bones) which has nociceptive nerve endings, making it very sensitive. Injury or infiltration of these nerves that innervate the bone marrow cause the achy pain patients report.
- Alterations in bone turnover, disruption of the normal osteoclast and osteoblast activity
- Loss of mechanical strength of bone leading to osteolysis, pathological fractures
- Boney mets can cause muscle spasms

Treatment of Bone Pain
- Usually described as continuous, achy with sharp exacerbations—incident pain typically with movement: “It doesn’t hurt unless I move.”
- Considered a subset of nociceptive and somatic pain, often with neuropathic component.
- Frequent failure in pain management is to rely only on opioids for pain control.
- Usually requires combination therapy: opioids with adjuvants: anti-inflammatories and neuropathic meds such as anticonvulsants.

Adjuvant Therapy for Bone Pain
- NSAIDS: ibuprofen, naprosyn
- COX-2 selective NSAIDs for pts on anticoagulation or have impaired clotting: Celoxib
- Toradol IV or po in limited prognosis
- Steroids, especially in spinal cord compression
  Decadron drug of choice due to minimal mineralocorticoid effects (salt and water retention, extracellular fluid volume expansion, hypertension, potassium depletion, and metabolic alkalosis) Long T1/2: 36-54 hours allows for daily administration. If an acute course is discontinued within 2 wks, adrenal suppression unlikely
- Radiation therapy
- Bisphosphonates—$$$, usually infused monthly
- Radionuclide therapy (strontium) -indicated for longer prognosis (> 6 mo), multiple boney mets

Neuropathic Pain
- Complex pain state in either the periphery or CNS which occurs when nerve fibers are damaged, dysfunctional, or injured and send incorrect signals to the pain center.
- In the periphery, neuropathic pain occurs due to “peripheral sensitization” simultaneously causing a lower threshold for nerve firing (“burning” pain) and spontaneous nerve firing (paresthesias): wind up
- In the CNS, sensitization to firing from C pain fibers and disinhibition can occur at the spinal cord level resulting in allodynia and hyperalgesia
  - Allodynia: nonpainful stimuli causes pain
  - Hyperesthesia: increased sensitivity/exagerrated response to painful stimuli

Wind-Up Phenomenon
- NMDA receptors are formed at the back part of the spinal cord (Dorsal Horn) when other pain receptors have been bombarded with pain stimuli for an extended period of time.
- NMDA receptors use a very fast neurotransmitter and they cause a marked increase in the amount of pain transmitted to the brain.
- NMDA receptors also prevent opioids from working to their full effectiveness.
- NMDA receptors are thought to be responsible for “Wind-up” seen in neuropathic pain. Nerve fibers that transmit painful impulses to the brain become "trained" to deliver pain signals better. Just like muscles get better at sports with training, the nerves become more effective at sending pain signals to the brain. The intensity of the signals increases over and above what is needed to get your attention. To make matters even worse, the brain becomes more sensitive to the pain. (emedicinehealth, 2007)

Neuropathic Cancer Pain Syndromes
- Caused by direct infiltration of the tumor including cranial nerve neuralgias, neuropathies, radiculopathies, plexopathies (cervical, brachial and lumbosacral), as well as central pain from spinal cord compression.
- Chemo-induced neuropathic pain
- Surgeries can cause neuropathic pain: mastectomy, neck dissections, thoracotomy, amputations with phantom limb pain and stump pain.
Neuropathic Pain: Descriptors

- Burning
- Numb
- Tingling/“pins and needles”
- Sharp/shooting/stabbing
- Radiating
- Electrical shocks
- Throbbing/pulsating
- “like walking on marbles”

Neuropathic Pain: Nonpharmacologic Treatment

- Radiation therapy: for nerve compression,
- Surgical decompression: spinal cord compromise.
- Acupuncture (no studies for cancer related neuropathic pain but some evidence for the use of acupuncture in diabetic neuropathy.)
- Interventional Pain techniques

Interventional Pain Management

- Epidurals, Intrathecalcs: Delivery directly to CNS
  - Use opioids, local anesthetics, clonidine, baclofen, etc
  - Reduces or can eliminate opioid requirements
  - More rapid control of symptoms
  - Implanted pain pumps: think progression in relation to cost
- Vertebroplasty: tumor-related compression fractures
- Neurolytic blocks
  - Celiac plexus: for upper abdominal visceral pain
  - Hypogastric plexus: pelvic visceral pain: bladder, cervical/ovarian, rectal, prostate

Neuropathic Pain Treatment

- Corticosteroids: Decadron
- Antidepressants
  - TCAs: strong evidence for their use (nortryptiline and amitriptyline) but anticholinergic adverse effects can limit their use.
  - SNRIs: increasingly used, (venlafaxine and duloxetine) shown to be of some benefit in studies of patients with diabetic neuropathy.
  - Helpful if patient is also depressed.
- Opioids: Mainstay but better pain control if used with adjuvants. Studies have demonstrated that between gabapentin, morphine, and gabapentin/morphine combination achieved the best analgesic response; both medications were at lower doses than when used exclusively.
- Methadone
- Topical Agents: Lidoderm, capsaisin (depletes substance P, a pain neurotransmitter)
- Anesthetics
  - Lidocaine (IV, bridge until more effective longer term measures)
  - Ketamine: NMDA receptor antagonist with analgesic, dissociative, sedative and amnesic properties. has been shown in multiple studies to improve pain control as an adjunct and helpful in situations of neurotoxicity and “wind up phenomenon.”

Neuropathic Pain Treatment: Anticonvulsants

- Binds to the calcium channels on nociceptive neurons.
- Gabapentinoids, compared to other anticonvulsants, tend to not have as many drug interactions or adverse effects.
- Renal excretion so careful dosing in patients with renal dysfunction.
- Gabapentin (Neurontin)
  - Initiate at 100 mg q 8 hrs, increase q 2-3 day
  - Titrated upward to effective dose, usually 900-3600 mg per day
  - Subclinical side effects: drowsiness
  - Has not been found to be effective in CIPN in studies
- Pregabalin (Lyrica)
  - Similar to gabapentin in action but typically better side effect profile and quicker titration
  - Initial dose: 50-75 mg 2x daily; titrate to max of 300 mg per day after 1 week
- Carbamazepine (Tegretol): trigeminal neuralgia
- Valproic Acid (Depakote)

Chemo-induced PN

- Many of the best agents for solid tumor treatment have neurotoxicity as dose-limiting side effects:
  - Taxanes (paclitaxel)
  - Vinca alkaloids (vincristine)
  - Platinum-complex agents (oxaliplatin)
  - Proteosome-inhibitors (bortezomib)
- Less common: 5-FU
Why does it matter?

- Development of CIPN can be dose-limiting, thus promoting evolution of drug resistance
- CIPN is a frequent cause of chemo dose reduction or termination of otherwise successful treatment
- 20% of patients develop a neuropathic pain syndrome that is difficult to treat, can be chronic, and range from annoying to debilitating in it’s effects.

CIPN Presentation

- Typically simultaneous onset in hands and feet: stocking/glove presentation
- Different from diabetic neuropathy which affects the longest nerves first: feet to legs to hands
- Affects fine motor coordination, sensation of pin pricks, cold hypersensitivity (not heat): hurts to pick up a cold pop can.

Mechanism of CIPN

- Research has found atypical mitochondria (swollen) in the sensory axons—not motor—making them unable to manufacture ATP (the energy currency every cell in our body uses)
- What happens if axonal mitochondria don’t make enough energy (ATP)?
  - Energy deficiency may lead to depolarization and spontaneous discharge of A-fibers and C-fibers
  - Severe energy deficiency may lead to degeneration, especially in regions of high metabolic demand.

Future Research

- Knowing the mechanism opens the door to developing potential treatments to prevent and manage neuropathy.
- Focus medical treatment on medicines that affect the mitochondria:
  - Olesoxime
  - Topiramate
  - Acetyl-L-carnitine: commonly available nutritional supplement.

Methadone

- Mechanism of action: stimulates opiate receptors and inhibits NMDA receptors
- Methadone is effective for neuropathic pain due to NMDA receptor antagonist activity
- Available: oral, SL, (pills, liquids, concentrated solutions) and IV
- Inexpensive

Methadone

- Pharmacokinetics:
  - Lipophilic, (Other opioids are hydrophilic)
  - Unique effect on neurotransmitters: inhibits re-uptake of serotonin and norepinephrine
  - Rapid distribution: fast acting
  - good GI absorption, including oral mucosa
  - Initial duration of action for pain relief 6-12 hours
  - BUT long and variable elimination half-life: 8-59 hours, resulting in drug accumulation during initial titration period of 3-5 days
**Methadone Pharmacokinetics: Tricky to dose, titrate**

- Biphasic elimination: due to lipophilic nature
  - Phase 1: 8-12 hours corresponds to analgesic duration of action
  - Phase 2: 30-60 hours—sufficient to prevent withdrawal

**Drawbacks to Methadone**

- Liquid/tablets taste bitter
- Association with heroin addiction/treatment
- Physicians, nurses, pharmacists are unfamiliar with methadone
- Needs close follow up with a knowledgeable provider, takes time
- Risk for QTc Prolongation and Torsade de Pointes (form of VT in patients with a long QT interval)
  - Primarily in doses > 200 mg per day and IV
  - Do not use in QTc > 500, avoid in patients with bradycardia, ventricular arrhythmias
  - Get baseline EKG, and serial EKGs with dose increases.

**Drug Interactions**

<table>
<thead>
<tr>
<th>Decrease Methadone Levels</th>
<th>Increase Methadone Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline (Elavil)</td>
<td>Cimetidine (Tagamet)</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>Flucconazole (Diffucan)</td>
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<td>Estrogens (Premarin)</td>
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<tr>
<td>Fosphenytoin (Cerebyx)</td>
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<tr>
<td>HIV Antivirals</td>
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<td>Phenytoin (Dilantin)</td>
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<tr>
<td>Rifampin</td>
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<tr>
<td>Risperdone (Risperdal)</td>
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<tr>
<td>Verapamil (Calan, Isoptin)</td>
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</tbody>
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**Monthly Cost Comparison**

<table>
<thead>
<tr>
<th>AWP (Average Wholesale Price) 2005</th>
<th>cost per month</th>
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</thead>
<tbody>
<tr>
<td>MS Contin</td>
<td>$440</td>
</tr>
<tr>
<td>Oxycontin</td>
<td>$890</td>
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<tr>
<td>Fentanyl patch</td>
<td>$1060</td>
</tr>
<tr>
<td>Dilaudid</td>
<td>$330</td>
</tr>
<tr>
<td>Methadone</td>
<td>$12 - $25</td>
</tr>
</tbody>
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**Medical Cannabis**

- Indications:
  - Cancer associated with severe/chronic pain, nausea or severe vomiting, or cachexia or severe wasting.
  - Terminal illness: “To qualify for the program, you must suffer from cancer or a terminal illness with a probable life expectancy of under one year, if your illness or its treatment produces one or more of the following: severe or chronic pain; nausea or severe vomiting; or Cachexia or severe wasting.”
  - Intractable pain: “a pain state in which the cause of the pain cannot be removed or otherwise treated with the consent of the patient and in which, in the generally accepted course of medical practice, no relief or cure of the cause of the pain is possible, or none has been found after reasonable efforts.”