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Treating Pain in Cancer: A Science and an Art

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Disclosure

Ms. Baccari has nothing to disclose.

Learning Objectives

- Identify tools and resources for assessment of pain in patients with cancer
- Discuss current approaches to the treatment of pain, including modalities to ameliorate nociceptive and neuropathic pain syndromes
- Describe selected new investigational therapies
- Discuss the role of the advanced practitioner as a "palliative care generalist"

Assessing Pain

- Pain history
  - **P**lace: Where?
  - **A**mount: How much? How long?
  - **I**ntensifiers: Worse?
  - **N**ullifiers: Better?
  - **E**ffects: Medication effects (w/prior therapies), effect on QOL?
  - **D**escription: How does it feel?
- Medical history
  - Diagnosis, prognosis, other health problems
  - Psychosocial history
  - Physical exam
  - Diagnostic test results if appropriate

QOL = quality of life

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Pain Scales

http://www.wongbakerfaces.org/

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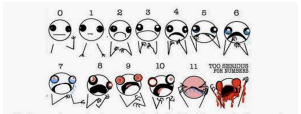

0.Hi. I am not experiencing any pain at all. I don't know why I'm even here
1: I am completely unsure whether I am experiencing pain or itching or maybe I just have a bad taste in my mouth.
2: I probably just need a Band Aid.
3: This is distressing. I don't want this to be happening to me at all.
4: My pain is not messing around.
5: Why is this happening to me??
6: Ow. Okay, my pain is super legit now.
7: I see Jesus coming for me and I'm scared.
8: I am experiencing a disturbing amount of pain. I might actually be dying. Please help.
9: I am almost definitely dying.
10: I am actively being mauled by a bear.
11: Blood is going to explode out of my face at any moment. Too Serious For Numbers: You probably have ebola. It appears that you may also be suffering from Stigmata and/or pinkeye.

Used with permission from http://hyperboleandahalf.blogspot.com

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Is All Pain the Same?

- Nociceptive pain
  - Visceral pain: Arises from viscera, mediated by stretch receptors
    - Poorly localized, deep, dull, cramping
  - Somatic pain: Arises from injury to body tissues
    - Well localized, variable in description
  - Inflammatory
    - NSAIDs (ibuprofen, ketorolac), COX2s, steroids (dexamethasone), acetaminophen, aspirin
  - Muscle spasms
    - Baclofen, tizanidine
- Neuropathic pain: Abnormal neural activity due to disease/injury or nervous system dysfunction
  - Shooting/burning/electric
  - Gabapentin, pregabalin, antiepileptics, TCAs, SNRIs, lidocaine patches

NSAID = nonsteroidal anti-inflammatory drug; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

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What's the Etiology?

Make sure you don't miss any **red flags**

- New back pain or bowel/bladder changes/incontinence?
  - Cord compression
- New headaches or confusion?
  - Brain mets, leptomeningeal disease
- Rib pain or pleuritic pain?
  - Pulmonary embolism, fracture
- New or OLD bony pain?
  - Fracture

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Pain Management

- Treat treatable causes
- Optimize analgesics
- Nonpharmacologic modalities
- Invasive procedures

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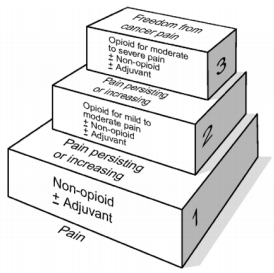
WHO Analgesic Ladder for Pain Related to Cancer



World Health Organization. Cancer Pain and Palliative Care, 1990. Available at http://www.who.int/cancer/palliative/painladder/en/

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Adjuvant Analgesics

- Anticonvulsants: Neuropathic pain
- NSAID/steroid: Inflammatory pain
- Bisphosphonates: Bony pain in cancer
- Muscle relaxants: Spasmodic muscle pain
- Antidepressants: Neuropathic pain
- Anticholinergics: Abdominal cramping pain
- Antibiotics: Infectious process (cellulitis/abscess/etc.)
- Radioisotopes: Diffuse bony pain (oncology)

Always think *Etiology*…

Use the right med for the right reason!

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Case #1: Professor T

- 72-year-old male with metastatic adenocarcinoma of unknown primary, presumed lung, metastases to brain (s/p SRS therapy) and bone (s/p XRT to sacrum a few months ago)
- Admitted to the intensive palliative care unit via ED with intractable right buttock/hip pain
- Home regimen: Oxycodone ER 80 mg po bid and oxycodone 20 mg po q3h PRN. Per patient's wife (a nurse), this pain has worsened over the past week and he is needing the PRN oxycodone almost every 3 hours.
- Received a few doses of IV hydromorphone in the ED with good but short-lived effect

s/p = status post; SRS = stereotactic radiosurgery; XRT = x-ray therapy; ED = emergency department; ER = extended release; PRN = as needed.

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Case #1: Professor T (cont)
What Do We Need to Know?

- Pain description: Sharp, sometimes feels like "pins and needles," starts in right buttock, some radiation along lateral right thigh
- Pertinent history of past illness: No bowel/bladder changes or incontinence; no history of fall or trauma
- Exam: Restless in bed, grimacing, tender at right buttock, bilateral LE strength equal and intact, sensation intact, no midline tenderness, forgetful and having trouble finding words

Which opioid has the best neuropathic pain coverage ?

A. Tramadol
B. Morphine
C. Hydromorphone
D. Methadone

Case #1: Professor T (cont)
Admission Plan

- Imaging
  - Plain films: No acute fracture
  - MRI: Patient required general anesthesia to tolerate!
    - No major change in known sacral metastases, some enlarging soft-tissue masses
- Short-term "band-aids"
  - NSAIDs (i.e., ibuprofen, ketorolac)
    - Caution: Bleeding risk, renal toxicity, < 5 days duration, cardiac risk
  - Steroids (i.e., dexamethasone)
    - Caution: Infection risk, delirium/agitation, hyperglycemia
  - IV opioids
    - They work…but not the best plan for home and are making him "goofy"

Case #1: Professor T (cont) Next Steps…

- Evaluation by radiation oncology
  - Can't radiate the pelvis any further
- Rotate home opioids to something new
  - Fentanyl transdermal patch
    - Pros: Easy to use, "clean" drug, easy to titrate
    - Cons: Need sufficient subcutaneous fat, may require prior authorization
    - Cautions!
      - Fevers, has to be stuck to the SKIN, anasarca/edema

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Rotating Opioids

Reminder…home regimen

- Oxycodone ER 80 mg q12h ⇨ 160 mg
- Oxycodone 20 mg q3h PRN… 6–8× day ⇨ 120–160 mg
  - ~ 320 mg/day and NOT effective

Dose Conversion Table for Selected Opioids

Hydromorphone (mg/day)		Morphine (mg/day)		Fentanyl transdermal patch (mcg/hr)	Oxycodone (mg/day)
IV	PO	IV/IM	PO		PO
2.5	12.5	17	50	25	30
5	25	33	100	50	65
7.5	37.5	50	150	75	100
10	50	67	200	100	130
12.5	62.5	83	250	125	165
15	75	100	300	150	200
17.5	87.5	117	350	175	230
20	100	133	400	200	265
22.5	112.5	150	450	225	300
25	125	167	500	250	330
27.5	137.5	183	550	275	360
30	150	200	600	300	400

Note: This chart is based on equianalgesic studies conducted on conversion of *oral morphine to transdermal fentanyl patch*. However, there is no data on conversions from the patch to any oral opioid. There is also potential inter-patient variability in absorption of transdermal fentanyl. Clinicians may therefore consider a dose reduction (~25%) when converting a patient *from a patch to an oral opioid*.

Phantumvanit V, et al. Pain Management Tables and Guidelines. DFCI/BWH Palliative Care Program/ BWH Pain Committee. 2013.

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So What's Next?

Methadone

- Low cost, widely available, pill or liquid availability
- Potent mu-opioid receptor agonist
- Inhibits reuptake of norepinephrine and serotonin (similar to the action of some antidepressants [e.g., venlafaxine] that are effective against neuropathic pain)
- Binds to NMDA receptor, known modulator of neuropathic pain; also plays a role in preventing opioid tolerance and potentiating opioid effects
- No active metabolites, mostly hepatic metabolism, no adjustments needed in renal failure
- Able to discharge home with hospice with stable methadone dose, infrequent PRN usage

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Methadone

Cautions

- Complex conversions: Need palliative care/pain management consultation
- Patient and family education: Many stigmas
- Extended terminal half-life of 190 hr can lead to increased risk of sedation and/or respiratory depression with rapid dose adjustments or poor compliance
- High doses can be associated with QT interval prolongation: Caution with certain chemotherapies/clinical trials
- Not indicated in situations where pain is poorly controlled and rapid dose adjustments are needed, no more than every 4 days

Equianalgesic Conversion for Methadone
Dose-dependent potency changes well established in the literature

Oral Morphine Equivalent	Mg of oral Methadone	= (ratio)	Mg of oral Morphine
<100 mg/day	1		4
101-300 mg/day	1		8
301- 600 mg/day	1		10
601-800 mg/day	1		12
801-1000 mg/day	1		15
>1000 mg/day	1		20
IV methadone is twice as potent as oral methadone			

Determine the starting dose of oral methadone by:

- Reducing the calculated oral methadone dose by 30-50%.
- Dividing the resulting reduced daily dose by 3.
- This is the every 8-hour dose of oral methadone in milligrams.

Phantumvanit V, et al. Pain Management Tables and Guidelines. DFCI/BWH Palliative Care Program/ BWH Pain Committee. 2013.

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Which of these is a permanent side effect of all opioids?

A. Somnolence
B. Nausea
C. Confusion
D. Constipation

"We can give you enough medication to alleviate the pain but not enough to make it fun."

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Case #2: Mr. C

- 55-year-old male with locally advanced pancreatic cancer
- Several admissions for epigastric abdominal pain
- Still working as a successful businessman, owns several companies
- Can get adequate pain relief from transdermal fentanyl patch and oral hydromorphone but hates the side effects
  - Impaired mental clarity
  - Constipation

What can we offer Mr. C?

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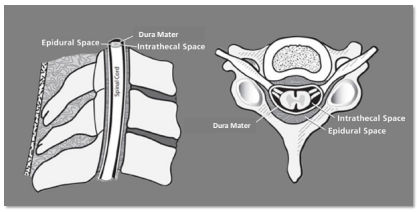
Anesthesia Pain Interventions

- Steroid injections
- Intralesional injections
- Nerve blocks
  Ex. intercostal, brachial plexus, celiac plexus, hypogastric plexus
- Epidural injections or catheters
- Intrathecal catheters

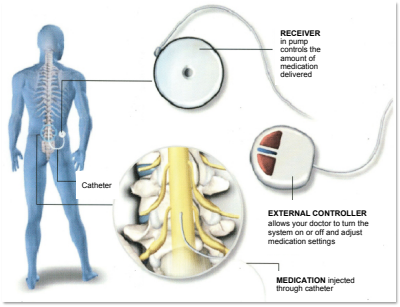
Case #2: Mr. C (cont)

- Had 3 celiac plexus blocks with effective but short-lived relief
- Elective admission to intensive palliative care unit for epidural catheter placement and trial
- If effective, plans made for intrathecal pump placement



http://www.flowonix.com/spinalanatomy.htm

Intrathecal Pump



Berardoni N, et al. Intrathecal pumps (ITPs). http://arizonapain.com/pain-center/pain-treatments/intrathecal-pumps-itps/

Oral vs. Epidural vs. Intrathecal

Analgesic/Route	Relative Potency
Oral	1/3 of IV dose
Epidural	10x greater than IV dose
Intrathecal	100x greater than IV dose
Hydromorphone	5x greater than morphine
Fentanyl	100x greater than morphine
Sufentanil	1,000x greater than morphine
Fentanyl patch	Same as IV fentanyl

*Assume patient requires morphine 10 mg/h IV.

Adapted from Hassenbusch SJ. *Oncology*. 1999;13(5 suppl 2):63–67.

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Case #2: Mr. C (cont)

- Intrathecal pump placed with good effect
- Able to decrease systemic opioids
- 3 wk post IT pump placement, pain is well controlled and palliative chemotherapy is resumed
  - Post-op IT pump care
    - Abdominal binder × 2 weeks, no heavy lifting × 3 months
    - Close follow-up with anesthesia pain service
    - Some patients have a remote to self-bolus their IT pump, great for incidental pain!
    - Pump can be refilled as an outpatient, approximately monthly
    - Some home infusion companies exist that can manage and refill pumps at home
      - Important when approaching end of life or for patients who live far away

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What is the best medication to use in renal failure?

A. Morphine
B. Oxycodone
C. Hydromorphone
D. Fentanyl

"It may surprise you to hear that, actually, morphine is the best medicine."

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Case #3: Mrs. L

- 64-year-old woman with metastatic lung cancer, metastases to brain, bone, liver, and nodes (retroperitoneal). Admitted from home hospice with reports of twitching and increased confusion; she's also been having trouble taking pills.
- Home regimen long-acting morphine 60 mg po q8 with liquid oxycodone 20 mg po q3 PRN
- On admission exam, Mrs. L appears uncomfortable, restless in the bed, dozing off between questions; myoclonic jerking that wakes her from sleep noted in bilateral LE and UE
- Labs: Creatinine is up from baseline and urine output has been decreasing per family's report, LFTs are also on the rise

LE = lower extremity; UE = upper extremity; LFT = liver function test.

Case #3: Mrs. L (cont)

- Family meeting held with primary oncologist, social work, inpatient palliative care team, and Mrs. L's daughter and husband
  - Prognosis is likely days to weeks
  - Family feels unable to care for her at home anymore
- Why is she having myoclonus and somnolence?
  - Retroperitoneal lymphadenopathy is causing obstructive nephropathy
  - Active metabolites of morphine are building up and causing neurotoxicity

Need to rotate opioids

Opioids in Renal Failure

- Morphine: Do not use
- Codeine: Do not use
- Hydromorphone: Use carefully
- Oxycodone: Use carefully; insufficient data
- Methadone: Appears safe, metabolites are inactive, in renal failure mostly excreted into gut
- Fentanyl: Appears safe

Dean M. *J Pain Symptom Manage*. 2004;28(5):497–504.

Case #3: Mrs. L (cont)

- Morphine/oxycodone regimen converted to IV fentanyl continuous infusion and PRN boluses by nursing
- Myoclonus abated, patient able to have more awake and interactive time with family and friends
- Patient discharged to inpatient hospice house with fentanyl PCA

Which opioid can be used at the end of life for "air hunger"?

A. Hydromorphone
B. Fentanyl
C. Morphine
D. All of the above

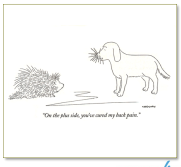
What's New?

- New drugs?
  - NIH study using resiniferatoxin (RTX) which is related to capsaicin
  - Studies underway for neuropathic pain agents using advancing genomics and new targets
    - Voltage-gated ion channels, angiotensin II (Ang II) AT_2 receptors and nerve growth factor
- Research
  - Understanding pain at the molecular and cellular level
    - Ex. How does endothelin-1 (secreted by tumors) interact with nerves and tissues to cause pain?
  - Understanding the psychology of pain using functional MRIs

http://www.brighamandwomens.org/Departments_and_Services/anesthesiology/Pain/PainManagementCenter.pdf

Commonly Used Complementary and Alternative Therapies

- Biologically based practices
- Manipulative and body-based practices
  - Chiropractic and osteopathic manipulation
  - Massage therapy
  - Reflexology
- Mind-body medicine
  - Relaxation therapy
  - Visual imagery, guided imagery
  - Hypnosis
  - Meditation, yoga
  - Biofeedback
  - Cognitive behavioral therapies
- Biofield therapies
  - Acupuncture
  - Homeopathy
  - Therapeutic touch
  - Reiki
- Music therapy, art therapy



Effective Pain Management

Multidisciplinary!

- Physicians
- Physician assistants
- Nurse practitioners
- RNs
- Pharmacists
- Social workers
- Chaplains
- Reiki/massage/acupuncture therapists
- Physical/occupational therapist
- and most importantly…the patient and his or her support system

Palliative Care

Achievement of best quality of life for patients and their families through the…

- Relief of suffering
- Control of symptoms
- Restoration of functional capacity

…while remaining sensitive to personal, cultural, and religious values, beliefs, and practices.

Palliative Care Pearls

- Can be introduced on DAY 1 of diagnosis, even when we're going for a cure!
  Ex: Mucositis pain in head and neck patients or BMT patients
- Does not equal hospice or end-of-life care
- Can be utilized in cardiac units, SICU/MICU, pediatrics, oncology, and general medicine
- Can help open lines of communication with patients and other providers

As APs we are in an ideal situation to broach goals of care and quality-of-life issues…we are often the patient and family's "first line" of communication and may have a more nuanced view of how things are *really* going at home!

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Palliative Care

Studies have shown that palliative care services can:

- Avoid hospitalizations and help the patient remain safely at home
- Improve symptoms
- Lead to better patient and family satisfaction
- Reduce prolonged grief and PTSD among the bereaved
- Lower hospital costs
  - Unnecessary admissions, diagnostic interventions, non-beneficial intensive care
- Metastatic NSCLC study: Patients who received palliative care + standard oncology care had better QOL, less depressive symptoms, and longer median survival
- ASCO recommends combining standard oncologic care with palliative care early for all patients with metastatic disease and/or high symptom burden

NSCLC = non-small cell lung cancer; ASCO = American Society of Clinical Oncology.
Smith TJ, et al. *J Clin Oncol.* 2012;30:880–887; Temel JS, et al. *N Engl J Med.* 2010; 363:733–742.

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Case #4: Mr. S
Sometimes they're zebras…

- 36-year-old male with metastatic sarcoma, large tumor burden in pelvis causing SEVERE pain with ambulation
- Maxed out on oral opioids
- Hospitalized several times requiring IV opioids
- Intrathecal pump placed with temporary good effect
- Rehospitalized with SEVERE pain
  - Tumor has grown and is now causing pain outside of the "range" of the intrathecal pump
  - Anesthesia pain service placed second epidural catheter to cover new areas of pain

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Case #4: Mr. S (cont)

Patient now has the following:

- Implanted intrathecal pump with hydromorphone/clonidine/ bupivacaine
- Temporary epidural catheter with bupivacaine, essentially surgical anesthesia of lower extremities
- Oral methadone and IV dilaudid PCA for any pain not covered by epidural/intrathecal catheters

Still in extremis… ketamine infusion

PCA = patient-controlled anesthesia

Ketamine

- Noncompetitive NMDA receptor antagonist
- Widely used in anesthesia and pediatrics
- Can be administered via intravenous, intramuscular, subcutaneous, oral, rectal, topical, intranasal, sublingual, epidural, caudal
- Indicated for opioid-tolerant patients, those with hyperalgesia and neuropathic pain
- Cautions
  - Increasing recreational use (inhaled, smoked, injected)
  - Dissociative effects (caution with patients w/PTSD or anxiety)
  - Increased intracranial pressure

PTSD = post-traumatic stress disorder
Tawfiq QA. *J Opioid Manag*. 2013;9(5):379–388.

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