Management of Malignant Pain in the Era of an Opioid Epidemic

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Objectives

- Review the pathophysiology of pain
- Explain the mechanisms of action of opioid and non-opioid analgesics
- Compare and contrast characteristics of analgesics and their place in therapy
- Recognize risk factors for opioid misuse

What is Pain?

- International Association for the Study of Pain
  - "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"
- Whatever the patient feels it is

The Problem

- Approximately 1.7 million new cases of cancer will be diagnosed in the US in 2012
- 30-50% of these patients will experience pain during their treatment
- Of those with advanced cancer, 70-90% will experience pain
- WHO estimates that 50% of individuals with cancer worldwide will die with pain not controlled
- Many patients with cancer pain will be prescribed opioids

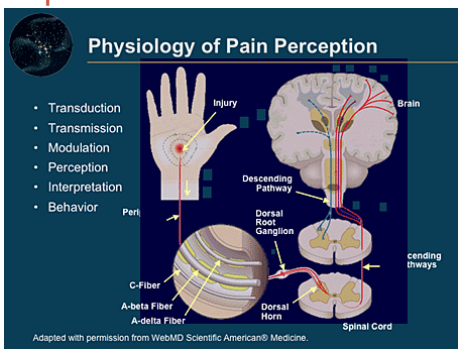
ACS Facts and Figures 2012
Cohen M, et al. J Pain Symptom Manage 2003;25:519-527.

PAIN PATHOPHYSIOLOGY

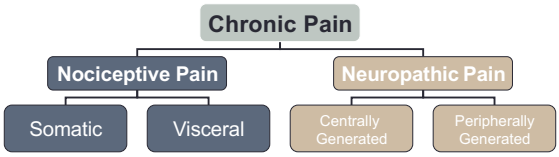
Pain Pathophysiology

- **Stimulation** of receptors causing release of neural chemicals that stimulate/sensitize receptors producing an action potential.
- **Transmission** of the action potential to the dorsal horn then ascending to the thalamus → cortex for processing
- **Perception** of the action potential/interpretation as pain
- **Modulation** by the descending neurons to the spinal cord releasing endogenous opioids, serotonin and norepinephrine that inhibit further transmission of nociceptive impulses (← site of action of opioids)

Perception of Pain



Classification of Pain



Nociceptive vs. neuropathic

- Nociceptive
  - Associated with ongoing tissue damage
  - Typically resolved when stimulus is removed
  - Responds well to opioids
- Neuropathic
  - Result of injury or malfunction of nerves (peripheral or central)
  - Poor response to opioids alone
  - Numbness, burning, tingling, electric-like

Somatic vs. visceral

- Somatic
  - Injury to tissue → stimulation of nerves
  - Bones, joints, muscle, skin, soft tissues
  - Localized to injured area
  - Throbbing, aching, dull, gnawing
- Visceral
  - Internal organ stretching or inflammation
  - Pancreas, stomach, intestine, other visceral organs
  - Can be localized or diffuse
  - Deep, cramping, "pressure" sensation

Malignant vs. non-malignant

- Malignant pain (usually cancer related)
  - Often presents over weeks to months
  - Often rapidly changing
  - Can be related to…
    - Malignancy itself (tumor invasion)
    - Secondary to the treatment
- Non-malignant
  - Management is more complex
  - Often presents over years
  - Often stable in nature
  - Pain contracts are common
  - Issues regarding efficacy and safety of chronic opioid therapy are unresolved and poorly studied

Acute vs. Chronic

- Acute Pain
  - Usually quick in onset
  - Lasts for a short period of time
- Chronic Pain
  - Constant an prolonged
  - Lasts for at least 3 months beyond the usual course of an acute disease

ASSESSMENT AND TREATMENT

Assessment of Pain: PQRSTU

- P = Palliating/precipitating factors
- Q = Quality (i.e. burning, stabbing, shooting)
- R = Region and/or radiation
- S = Severity
- T = Temporal nature
- U = Impact on "U"

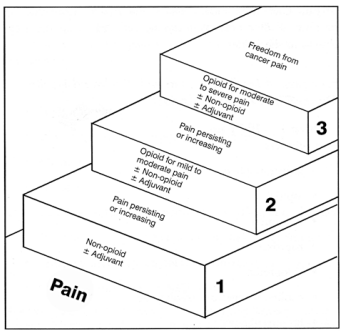
Gammaitoni A et al. Clin Journal Pain 2003;19:286-97

World Health Organization (WHO) Principles of Pharmacologic Management

- By the mouth
- By the clock
- By the ladder
- For the individual
- With attention to detail

World Health Organization. Cancer pain relief: with a guide to opioid availability, 2nd ed, 1996.

WHO Pain Relief Ladder



Pharmacologic Options

- Adjuvants
  - *Note: Use is off-label*
  - Antidepressants
  - Anticonvulsants
  - Local Anesthetics
  - Bisphosphonates
  - Calcitonin
  - Corticosteroids
- Non-Opioids
  - Acetaminophen (APAP)
  - NSAIDs
  - COX-2 Selective Agents
- Opioids
  - See upcoming slides

Pereira A et al. *Pain* 2013; 154:345-9.

NSAIDs

- Antipyretic, analgesic, anti-inflammatory activity
- Nociceptive pain responds best
- 1 week for maximum anti-inflammatory effects
- Response may vary with different NSAIDS
- Choice of a particular agent is largely determined by dosage frequency and cost
- Use caution in patients receiving myelosuppressive chemotherapy: masks FEVER!

Acetaminophen

- Unknown central mechanism
- Antipyretic and analgesic
- Nociceptive pain
- Often in combination with opioid
- Side effects
  - Overdose is hepatotoxic
  - Max 3-4 g/day from all sources…remind patient about OTC cough/cold products

Opioid Medications

- Clinical Indications:
  - Analgesia
  - Anti-tussive
  - Anti-diarrheal
  - Treatment of opioid addiction
- Available preparations:
  - Oral
    - short-acting (IR) and long-acting (ER or SR) formulations
  - Transdermal
  - Transmucosal
  - Parenteral

Opioids

- Mechanisms of Action:
  - Mu opioid receptor agonist
    - Stimulate central and peripheral opioid receptors
    - Decreases messages reaching the brain where pain is perceived
    - Inhibit intestinal motility
- Potential Side Effects:
  - Constipation
  - Nausea
  - Sedation, cognitive defects
  - Respiratory depression
  - Tolerance, physical dependence, hyperalgesia

Opioid Options

Mild-Moderate Pain
- Hydrocodone/APAP*
- Oxycodone/APAP*
- Codeine

*Combination products have variable amounts of opioid

Severe Pain
- Morphine
- Oxycodone
- Hydromorphone
- Methadone
- Fentanyl
- Oxymorphone

Available Preparations

Short-acting opioids
- Morphine (liquid, tablets, concentrated liquid)
- Oxycodone (+/- APAP; liquid, tablets)
- Hydrocodone/APAP
- Hydromorphone (liquid, tablets)
- Oxymorphone
- Transmucosal fentanyl (**Note: ultra-rapid acting)

Long-acting Opioids
- Morphine (MS Contin®, Kadian®)
- Oxycodone (Oxycontin®)
- Methadone
- Oxymorphone (Opana®)
- Hydromorphone (Exalgo®)
- Hydrocodone (Hysingla ER®, Zohydro ER®)
- Fentayl patch (Duragesic®)

Considerations prior to prescribing opioids

- Medication allergies
- Previous opioid exposure and preference
- Severity and nature of disease
- Age of patient
- Extent of cancer, particularly hepatic and renal involvement altering opioid pharmacokinetics
- Comorbid disease states
- Dosage form and route of administration

Tolerance and Dependence

- Tolerance
  - Increased dosages are needed over time to achieve the adequate analgesia
- Physical dependence
  - Stopping the opioid results in withdrawal
- Psychological dependence
  - Behavioral pattern characterized by cravings and preoccupation with obtaining the drug

Opioid Conversions

- Establish Indication for Change
  - Lack of Efficacy
  - Intolerable Side Effects
  - Change in Patient Status
  - Practical Considerations
- Gather Pertinent Patient Information
  - Cause of Pain and History
  - Pain Rating
  - Concomitant Disease States
  - History of Allergies (Preferences) with Opioids

Opioid Conversions

- Determine Total Daily Usage with Opioids
  - All long acting opioids in past 24 hours
  - Total prn opioids in last 24 hours
- Determine New Regimen with Desired Opioid
  - Convert total daily usage to desired opioid equivalent
    - See institution specific conversions
  - Individualize dosage to meet patient needs
    - Cut back 25%, Straight Conversion, Increase 25%
  - Determine scheduled and prn doses
    - PRN dosing should at least equal 100% of daily scheduled dose
- Follow-up and reassessment

Equianalgesic Dosing Chart: NCCN

OPIOID	ORAL DOSE	PARENTERAL DOSE
Codeine	200 mg	N/A
Hydrocodone	30 - 45 mg	N/A
Oxycodone	15-20 mg	N/A
Morphine	30 mg	10 mg
Hydromorphone	7.5 mg	1.5 mg
Methadone*	*	*
Fentanyl**	N/A	100 mcg
Oxymorphone	10 mg	1 mg

*Ratio of daily oral morphine dose to oral methadone dose may range from 1:1 at low doses of oral morphine up to 20:1 for patients receiving high doses of oral morphine (~300mg/day)
**Fentanyl transdermal systems 30mcg/hr ≈ 60mg PO morphine (round to nearest patch strength)

Barriers to Care:

- Patient-Related
  - Fear of addiction
  - Non-adherence
  - Perceived lack of time with provider to discuss pain
- Provider-Related
  - Fear of legal action
  - Difficulty assessing pain
  - Deficiency in pain management education

THE OPIOID EPIDEMIC

Issues with Opioids

- Opioid-related deaths are on the rise
  - In 2015, more than 33,000 Americans died of opioid over-dose
- An estimated 2 million Americans have a substance abuse disorder related to prescription opioids
- Up to 80 % of people who abuse heroin first abused prescription opioids
- Four North Carolina cities are among the top US Cities for opioid abuse (Wilmington, Hickory, Jacksonville, Fayetteville)

National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services. http://archive.castlighthealth.com/typ/the-opioid-crisis

Who is at Risk for Opioid Misuse?

Moderate Risk

- Remote h/o drug or alcohol abuse
- H/o addiction with sustained period of recovery
- Questionable family h/o alcohol or drug abuse
- Younger age
- Smoker
- H/o physical or sexual abuse
- Involvement with others who engage in drug abuse

High Risk

- Recent h/o or multiple episodes of alcohol or drug abuse
- H/o addiction with limited or no system to sustain recovery
- Strong family h/o drug or alcohol abuse
- History or major psychiatric disorder

Price et al. J Clin Oncol 2016 (24): 1-23

Red Flags of Opioid Misuse

- Early refills
- Use of multiple pharmacies
- Obtaining controlled substances from multiple physicians
- Giving or selling controlled substances to family, friends
- Current/past abuse of alcohol or drugs
- Marijuana use
- Use of street names for medications
- Inconsistent results from urine screens
- Driving long distances to see physician for controlled substances
- Drug overdose

American Academy of Family Physicians; American College of Emergency Physicians; American Medical Association; et al. National Association of Boards of Pharmacy; 2015 Mar

Strategies for Minimizing Abuse Risk

- Prescribe opioids only if benefits outweigh risk
- Utilize prescription drug monitoring program
  - NC Controlled Substances Database
- Consider urine drug screening
- Prescribe small amounts of opioids at short intervals
- Avoid agents with higher abuse potential
- Require the use of one pharmacy
- Initiate written agreement (contract)

Price et al. J Clin Oncol 2016 (24); 1-23

Conclusion

- Many patients with cancer will experience malignant pain
- Opioids remain the mainstay of pharmacologic pain management
- Opioids are associated with risks of abuse and misuse
- Risk mitigation strategies are critical