



# Pharmacologic Management of Pain

Natalie Keil, Pharm.D.  
NMCSD PGY1 Pharmacy Practice Resident  
Palliative Care Nursing Symposium  
October 14, 2011

The views expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

# Disclosures

- The speaker has nothing to disclose.
- Exhibits coordinated through the Henry Jackson Foundation.
- Refreshments provided through the Henry Jackson Foundation.

# Objectives

- Review the different types of pain
- Apply pain assessment tools and discuss how to correctly assess a patient's pain
- Discuss types of pharmacologic agents used in pain management
  - NSAIDs and acetaminophen
  - Opioids
  - Gabapentin and pregabalin
- Review the role we can play in managing a patient's pain

# Pain as the 5<sup>th</sup> Vital Sign

- Joint Commission on Accreditation of Healthcare Organizations (JCAHO) recognizes pain as a 5<sup>th</sup> vital sign
  - Require that health care staff record pain assessment each time vital signs are recorded
    - Temperature, blood pressure, respirations, pulse

# Types of Pain

- Nociceptive
- Neuropathic

# Nociceptive Pain

- Somatic pain
  - Arises from skin, bone, joint, muscle, or connective tissue
  - Throbbing, dull, aching
  - Well localized
- Visceral pain
  - Arises from internal organs
  - Diffuse, deep, aching
  - Poorly localized and feeling as if it is coming from other structures

# Neuropathic Pain

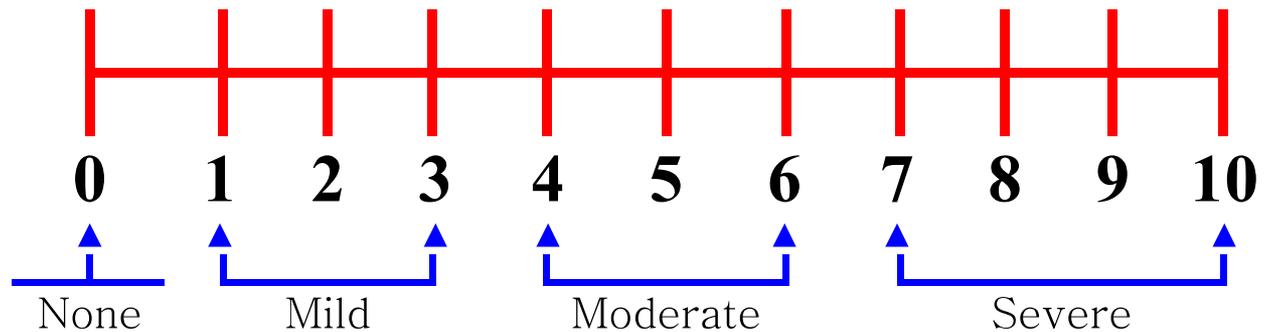
- Pain sustained by abnormal processing of sensory input
- May be caused by nerve damage or persistent stimulation
- Burning, shooting, pricking, numbness, tingling sensation

# Objectives

- Review the different types of pain
- **Apply pain assessment tools and discuss how to correctly assess a patient's pain**
- Discuss types of pharmacologic agents used in pain management
  - NSAIDs and acetaminophen
  - Opioids
  - Gabapentin and pregabalin
- Review the role we can play in managing a patient's pain

# Pain Assessment Tools

- Numerical rating scale (NRS)



# Pain Assessment Tools

- Visual Analogue Scale

**Place a vertical mark on the line below to indicate how bad you feel your pain is today**

No pain



Worst pain  
imaginable

Visual Analog Scale (VAS) (10 cm line).

[Score = 0 - 100 mm] - measuring in millimeters from the left hand end of the line to the point that the patient marks.

# Objectives

- Review the different types of pain
- Apply pain assessment tools and discuss how to correctly assess a patient's pain
- **Discuss types of pharmacologic agents used in pain management**
  - **NSAIDs and acetaminophen**
  - **Opioids**
  - **Gabapentin and pregabalin**
- Review the role we can play in managing a patient's pain

# Nonopioid agents

- Acetaminophen
- Aspirin
- Nonsteroidal anti-inflammatory drugs (NSAIDs)

# Acetaminophen (Tylenol®)

- Properties
  - Analgesic and antipyretic
  - Lacks anti-inflammatory activity or effects on platelet function
- Preferred for
  - Patients whom aspirin is contraindicated
  - Patients with underlying renal disease

# Acetaminophen (Tylenol®)

- Dosage
  - PO/rectal: 325 – 650 mg q4-6 hrs prn
  - IV: 1000 mg q6 hrs prn
- Available dosage forms
  - Oral tablets, capsules, solution
  - Rectal suppository
  - **IV solution (Ofirmev®) – 1000mg/100ml**

# Acetaminophen (Tylenol®)

- Maximum dose
  - Current recommendations are 4000 mg/day
  - Suggestions to decrease maximum dose to 3,000 mg/day
    - FDA asked drug manufacturers to limit strength of APAP in prescription drug products to 325 mg/tablet

# Acetaminophen (Tylenol®)

- Side effects

## Oral/Rectal Administration

Rash/pruritis (5%)      Hypersensitivity reactions (<1%)

Increased LFTs (with higher acute overdoses (>7.5g) and chronic doses > 4 g)

## Intravenous Administration

Headache (10%)      Gastrointestinal (>10%)      Edema (1%)

- Nausea
- Vomiting
- Constipation
- Diarrhea

Anemia (<10%)      Increased LFTs (<10%)

# Aspirin

- Properties
  - Analgesic, antipyretic and anti-inflammatory
  - Affects platelets so useful in preventing or reducing risk of myocardial infarction
  - Not too useful for pain because requires high doses
- Also useful for
  - Juvenile arthritis
  - Rheumatoid arthritis
  - Osteoarthritis

# Aspirin

- Dosage
  - PO/rectal: 325-650 mg q4 hrs prn
  - Max dose: 4000 mg/day
- Available dosage forms
  - Oral tablets – 81 mg, 325 mg, 650 mg
  - Rectal suppository – 300 mg, 600 mg

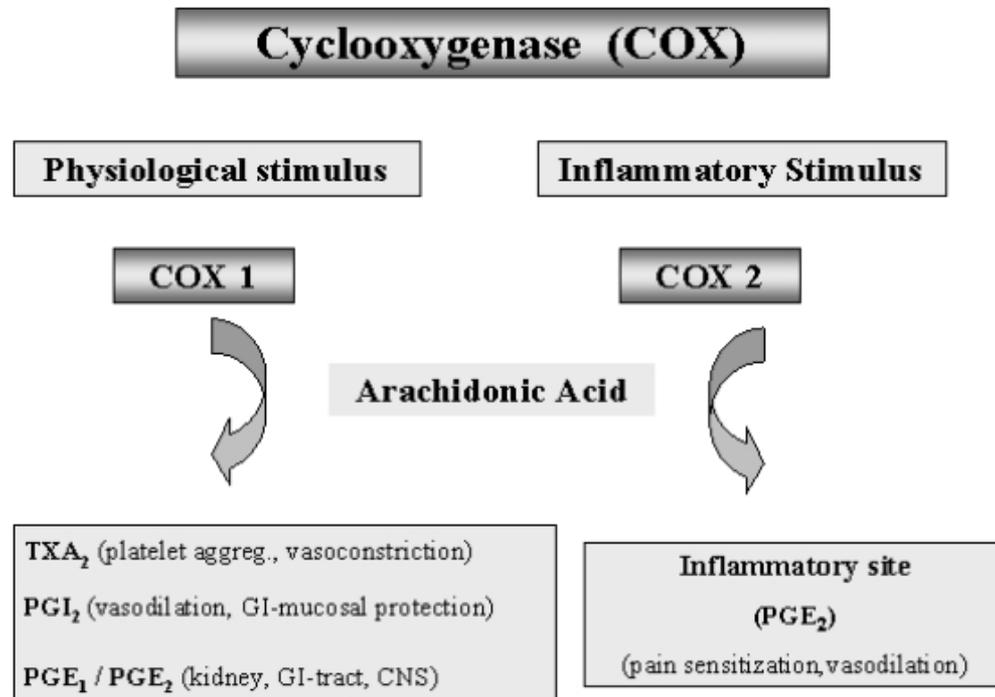
# Aspirin

- Side effects

Oral/Rectal Administration		
Bleeding	Rash	Gastrointestinal <ul style="list-style-type: none"><li>• Nausea</li><li>• Vomiting</li><li>• Heartburn</li></ul>
Anemia	Increased transaminases	Tinnitus
Increased serum creatinine	Bronchospasm	Reye's syndrome

# Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- Properties
  - Analgesic, antipyretic and anti-inflammatory



# Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- Indications
  - Mild to moderate pain
- Available dosage forms
  - Many types of NSAIDs and forms available
    - Capsules, tablets, oral suspension, intravenous solutions

# Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Acetic Acid Derivatives		
Diclofenac (Voltaren®)	Etodolac (Lodine®)	Indomethacin (Indocin®)
Ketorolac (Toradol®)	Sulindac (Clinoril®)	Tolmetin (Tolectin®)
Carboxylic acid derivatives		
Diflunisal (Dolobid®)	Salsalate (Disalcid®)	
Enolic acid derivatives		
Meloxicam (Mobic®)	Piroxicam (Feldene®)	Nabumetone (Relafen®)
Naphthylkanone derivatives		
Nabumetone (Relafen®)		
Propionic acid derivatives		
Flurbiprofen (Ansaid®)	Ibuprofen (Motrin®)	Ketoprofen (Orudis®)
Naproxen (Naprosyn®)	Oxaprozin (Daypro®)	

# Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

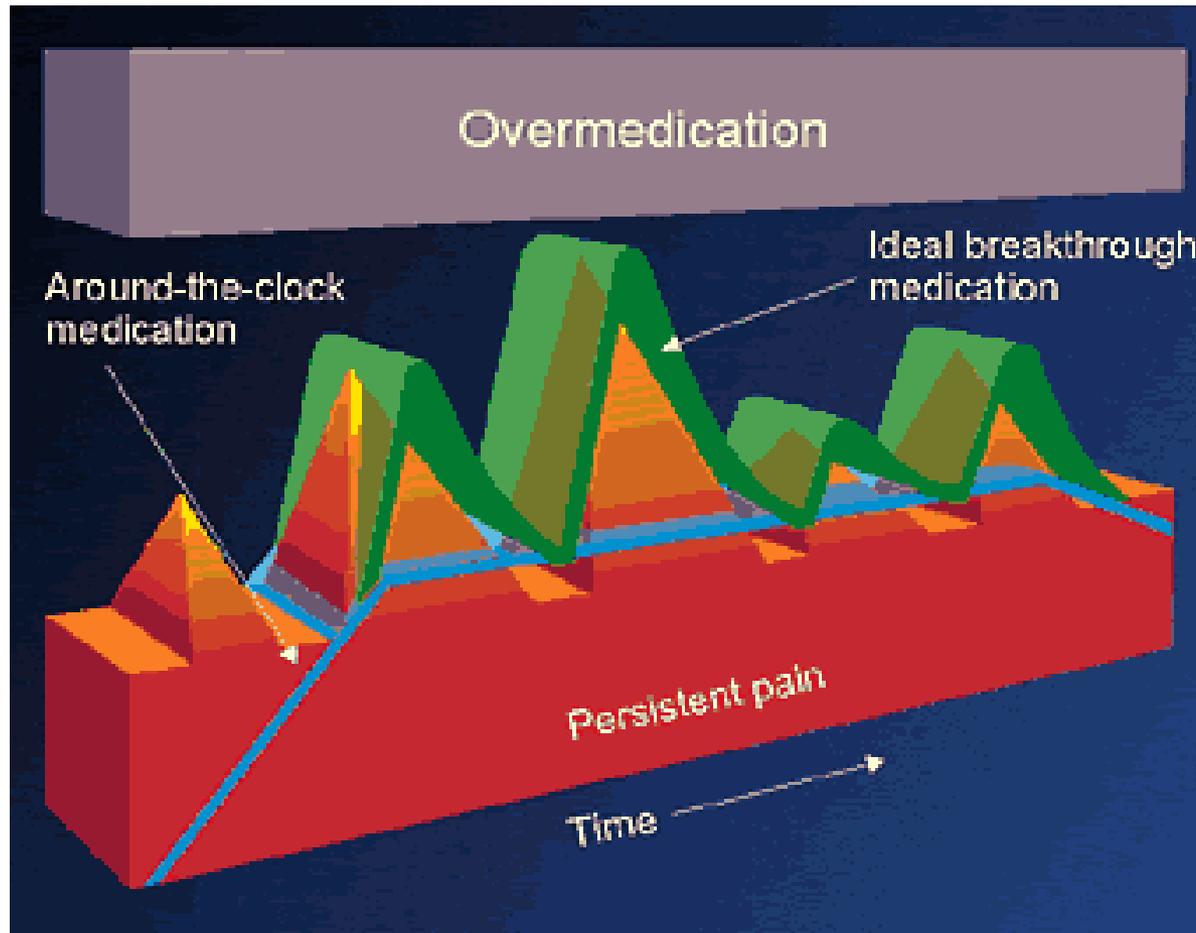
- Adverse Effects

Gastrointestinal <ul style="list-style-type: none"><li>• Heartburn</li><li>• Abdominal pain</li><li>• Diarrhea</li><li>• Vomiting</li></ul>	Fluid retention	Renal complications <ul style="list-style-type: none"><li>• Decreased renal blood flow</li></ul>
Platelet dysfunction	Bronchospasms	Hypersensitivity

# Gastrointestinal Side Effect

- Patients at high risk for GI SE
  - Advanced age
  - Alcoholic liver disease
  - History of gastric ulcers
  - Alcohol ingestion
  - Higher dose
  - Longer duration

# Treating Pain



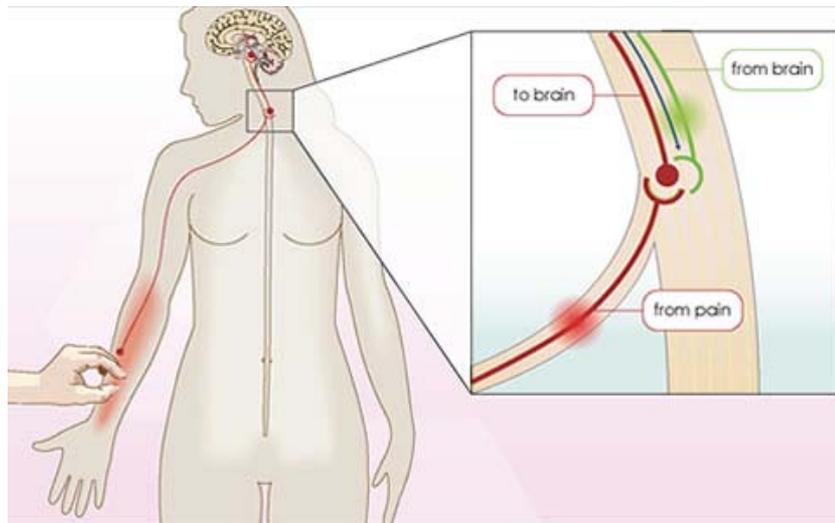
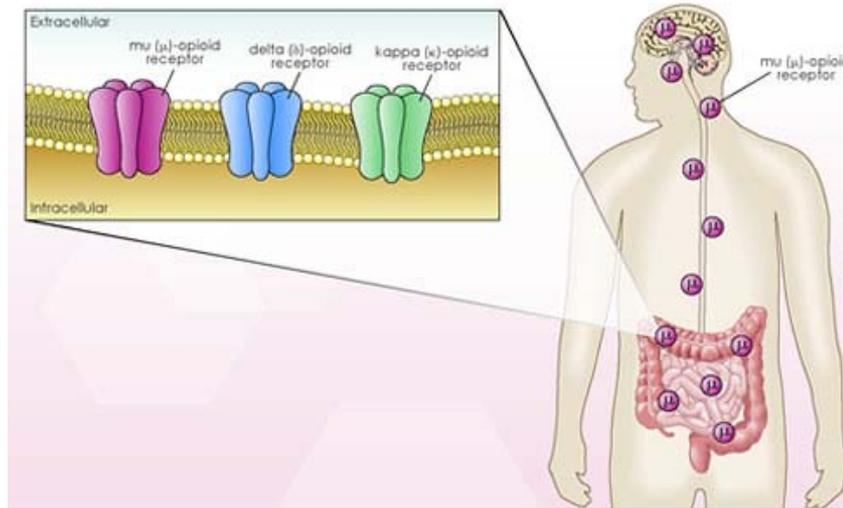
# Opioids

- Indications
  - Severe forms of acute pain
  - Cancer pain
- Binds to opiate receptors to block perception of pain

# Opioids

- Onset of analgesic effects
  - PO:
    - Immediate release: 15-30 minutes
    - Controlled release: 30 min-2 hours
  - IM/SC: 15-30 minutes
  - IV: about 5 minutes
- No ceiling effect
  - No maximum dose
  - Titrate based on pain scale

# Opioid Mechanism of Action



# Opioid Receptors

<b>3 Main Receptor Subtypes</b>	<b>Action</b>
$\mu 1$	Analgesia Bradycardia Sedation
$\mu 2$	Respiratory depression Euphoria Physical dependence
$\delta$	Analgesia Respiratory depression
$\kappa$	Analgesia Respiratory depression Sedation

# Opioid Classes

Phenanthrenes (morphine-like agonists)		
Morphine (MS Contin, Kadian, Oramorph®)	Hydromorphone (Dilaudid®)	Oxymorphone (Numorphan, Opana ®)
Codeine	Hydrocodone (Vicodin, Norco, Lortab®)	Oxycodone (Oxycontin®)
Phenylpiperidines (meperidine-like agonists)		
Meperidine (Demerol®)	Fentanyl (Actiq, Fentora, Duragesic ®)	
Diphenylheptanes (methadone-like agonists)		
Methadone (Methadose, Dolophine®)		
Central Analgesic		
Tramadol (Ultram®)		

# Opioids

- Side Effects

Short term		
Sedation	Constipation (do not develop tolerance)	Nausea/Vomiting
Pruritus	Hypotension	

Long term	
Cognitive Disturbances	Dependence
Addiction	Tolerance

# Opioids

- Side effects
  - Overdose: respiratory depression
    - Administer opioid antagonist (ie: naloxone)
      - Important to assess patient if low respiratory rate

# Opioids

- Side effects
  - Tolerance develops to most side effects **EXCEPT** constipation
    - Almost all patients will require a stool softener (ie: docusate) and a mild stimulant laxative (ie: senna, bisacodyl)

# Opioid Allergies

- True allergy to opioids are rare
- Use agent from a different class of opioids
  - Morphine-like
  - Meperidine-like
  - Methadone-like
  - Central analgesic

# Specific Opioid Agents

- Morphine (MS Contin, Kadian, Oramorph®)
  - Metabolites
    - Morphine-6-glucuronide → more potent than parent compound
    - Morphine-3-glucuronide → side effects
  - Excreted renally
    - Requires dosage adjustment in renal impairment
  - Caution in renal dysfunction and elderly

# Specific Opioid Agents

- Codeine
  - Mild to moderate pain
  - Pro-drug → metabolized to morphine
    - Avoid use in hepatic impairment
  - Used in combination with NSAIDs, aspirin, acetaminophen
  - Has antitussive properties

# Specific Opioid Agents

- Hydromorphone (Dilaudid®)
  - 7x more potent than morphine
  - May cause less constipation
  - Metabolized in liver via glucuronidation
  - No active metabolite
    - May be better for renal and hepatic insufficiency

# Specific Opioid Agents

- Hydrocodone (Vicodin, Norco, Lortab®)
  - Only available in combination products
  - NOTE: combinations contain acetaminophen so careful with overdose
    - Dose limiting factor acetaminophen dose

# Specific Opioid Agents

- Oxycodone (Oxycontin®)
  - Most effective when used with NSAIDs, aspirin, acetaminophen
  - Severe chronic pain
- Oxymorphone (Opana®)
  - Metabolite of oxycodone
  - Not used much
  - No pharmacologic advantage over morphine

# Specific Opioid Agents

- Meperidine (Demerol®)
  - Not used for chronic pain
  - Used for rigors
  - Toxic metabolite – normeperidine
    - Can cause seizures
    - Not reversible by naloxone (Narcan®)
    - Renally excreted
  - Max use of 3 days

# Specific Opioid Agents

- Fentanyl (Actiq, Fentora, Duragesic®)
  - No active metabolites
  - Preferred in renal insufficiency
  - Many available formulations
    - IV, PO, transdermal
  - No histamine release → decreased pruritis

# Specific Opioid Agents

- Fentanyl
  - Patch (Duragesic®)
    - Patient must be opioid tolerant
      - Equivalent of oral morphine 60 mg for 7 days or longer
    - Applied every 72 hours
    - Takes up to 12-24 hours to work
    - Heat increases absorption
    - Risk of burns during MRI
  - Oral lozenge (Actiq®)
  - Buccal tablet (Fentora®)

# Opioid Naïve vs. Tolerant

- Naïve
  - Patients who are not chronically receiving opioids on a daily basis
- Tolerant
  - Patients chronically receiving opioids
  - Equivalent daily opioid dosing
    - 60 mg oral morphine
    - 30 mg oral oxycodone
    - 8 mg oral hydromorphone
    - 25 mcg/hr fentanyl patch

# Specific Opioid Agents

- Methadone (Methadose, Dolophine®)
  - Used for chronic pain
  - Also used to treat opioid abuse
    - Lacks profound euphoria
    - Withdrawal symptoms milder than morphine
  - Duration of action a lot shorter than elimination half-life
  - Careful in hepatic impairment

# Specific Opioid Agents

- Tramadol (Ultram®)
  - Synthetic codeine analogue
  - Weak affinity for opioid receptor
  - Active metabolite renally excreted
    - Careful in renal impairment

# Principles of Opioid Rotation

- Practice of switching to a different opioids when dose-limiting toxicities lead to poor responsiveness
- Should NOT be initiated in patients stable on their medication
- Genetic polymorphisms in genes for mu-receptor subtypes lead to different responses in each individual

# General Opioid Conversions

Equianalgesic Dosing		
10 mcg IV Fentanyl	1 mg IV Morphine	0.2 mg IV hydromorphone (Dilaudid®)
0.2 mg IV hydromorphone (Dilaudid®)	1 mg PO hydromorphone (Dilaudid®)	
1 mg IV Morphine	3 mg PO morphine	
10 mg PO oxycodone	15 mg PO morphine	15 mg PO hydrocodone

For methadone or assistance, contact the pharmacist at 619-532-8596

# Opioid Conversion Example

- Patient receives 0.5 mg/hr of hydromorphone (Dilaudid®) from PCA
- How many mg of morphine is 12 mg of IV hydromorphone equivalent to?

$$12 \text{ mg IV hydromorphone} \times \frac{1 \text{ mg IV morphine}}{0.2 \text{ mg IV hydromorphone}} = 60 \text{ mg IV morphine}$$

$$60 \text{ mg IV morphine} \times \frac{3 \text{ mg PO morphine}}{1 \text{ mg IV morphine}} = 180 \text{ mg PO morphine}$$

# Opioid Overdose

- When to administer naloxone (Narcan®)
  - Patient nonresponsive
  - Severe respiratory depression
- Goal is to restore adequate spontaneous respirations
  - Monitor for respiratory changes and opiate withdrawal symptoms
    - Anxiety, hypertension, tachycardia, diarrhea, seizures

# Naloxone (Narcan®)

- Use lowest possible dose that maintains adequate ventilation
- Dose
  - 0.4-2 mg IV/IM/SQ titrated to effect; doses can be repeated every 2-3 minutes
    - IV route preferred because more rapid
    - IM and SQ routes have erratic absorption

# Agents used for Neuropathic Pain

- Gabapentin(Neurontin ®)
- Pregabalin (Lyrica®)

# Gabapentin (Neurontin ®)

- Dosing
  - Requires dose titration and multiple daily doses
  - Typically use 300-600 mg three times daily
  - Dosages 1,800-3,600 mg per day were effective
- Adverse Effects
  - Fatigue, weight gain, back pain, somnolence, dizziness
- Use with caution in renal impairment
- Well-tolerated

# Pregabalin (Lyrica ®)

- Maximum FDA approved dose is 300 mg daily
  - Initiate at 50 mg TID and increase within 1 week
- Adverse effects
  - Dizziness, somnolence, peripheral edema, blurry vision, weight gain
- Requires dosage adjustments in renal impairment

# Objectives

- Review the different types of pain
- Apply pain assessment tools and discuss how to correctly assess a patient's pain
- Discuss types of pharmacologic agents used in pain management
  - NSAIDs and acetaminophen
  - Opioids
  - Gabapentin and pregabalin
- **Review the role we can play in managing a patient's pain**

# Our Role

- Type of pain
- Frequent assessment of patient's pain
- Choice of agent
  - Mild to moderate – NSAIDs, aspirin, acetaminophen
  - Severe – opioids
- Opioid naïve vs. tolerant
- Administration
- Monitoring for side effects

# References

- Baumann, TJ. Pain Management. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. New York, NY: McGraw-Hill; 2005:161.
- Cadet. Mu opiate receptor subtypes. © *Med Sci Monit*, 2004; 10(6): MS28-32
- Chou, R, Qaseem, A, Snow, V, et al. Diagnosis and treatment of low back pain; a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med* 2007; 147:478-40
- Clinical Pharmacology Web site. <http://www.clinicalpharmacology-ip.com/default.aspx>. Accessed September 5, 2011.
- Corbett AD, Henderson G, McKnight AT, Paterson SJ (2006). "75 years of opioid research: the exciting but vain quest for the Holy Grail". *Br. J. Pharmacol.* 147 Suppl 1: S153-62.
- Cupp, M. Analgesic Options for Patients with Allergic-Type Opioid Reactions. *Pharmacist's Letter/Prescriber's Letter* 2006; 22(2):22021
- FDA Drug Safety Communication available online at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm239955.htm> (Accessed on October 1, 2011).
- Joint Commission on Accreditation of Healthcare Organizations (2000), *Implementing the new pain management standards*. Oakbrook Terrace, Ill.: JCAHO
- Lanas et al. A nationwide Study of Mortality Associated with Hospital Admission due to severe gastrointestinal events and those associated with non-steroidal anti-inflammatory drug use. *Amer J Gastroenterology*. Aug 2005; p 1685-93
- McCaffery, M., & Beebe, A. (1993). *Pain: Clinical Manual for Nursing Practice*. Baltimore: V.V. Mosby Company.
- NCCN. *Clinical Practice Guidelines in Oncology. Adult Cancer Pain.V.1.2010*. Available at: [http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Accessed September 5, 2011
- Naesh, O. Back to the future: postoperative pain management beyond COX-2 inhibitors. *Journal of the New Zealand Medical Association* (2006) 119: 1242
- Wewers M.E. & Lowe N.K. (1990) A critical review of visual analogue scales in the measurement of clinical phenomena. *Research in Nursing and Health* 13, 227±236.
- NCCN. *Clinical Practice Guidelines in Oncology. Adult Cancer Pain.V.1.2010*. Available at: [http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Accessed September 5, 2011