Pain Management and the Pharmacist's Role in Opioid Use

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Disclosure

The author of this presentation has nothing to disclose concerning possible financial or personal relationships with the commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

Pharmacist Objectives

- Differentiate between the pathophysiology of the characteristic types of pain
- Convert between different opioid-containing formulations and recommend appropriate dosing
- Communicate to physicians and patients on effective strategies for appropriate opioid use, adverse effects, and proper disposal
- Outline risk factors in identifying patients' potential for opioid tolerance and dependence

Definition of Pain

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"

-International Association for the Study of Pain, 1996

"Pain is always subjective. Each individual learns the application of the word through experiences related to injury"

-Merskey, 1991

"Pain is a more terrible lord of mankind than even death itself"

-Dr. Albert Schweitzer, 1931

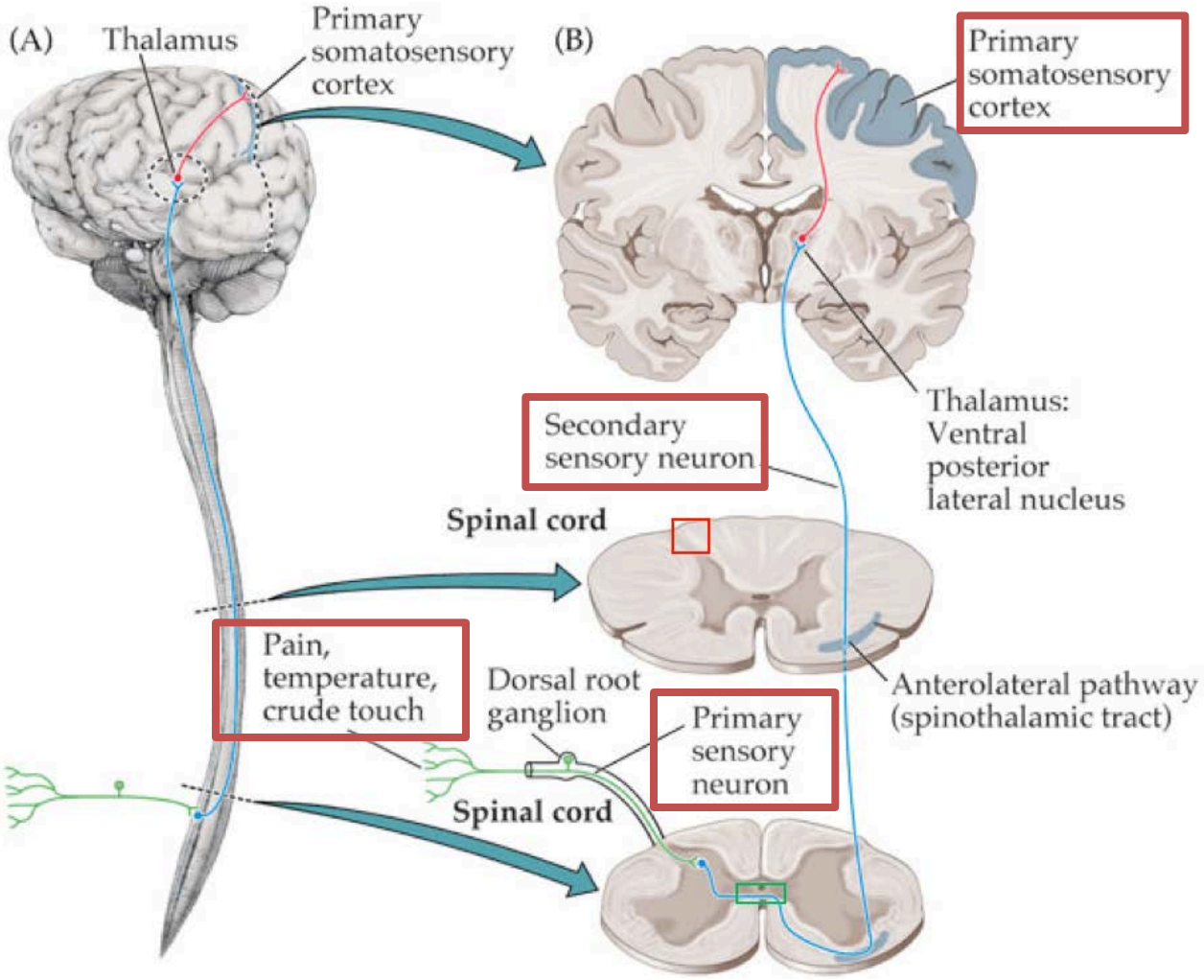
Anand KS, et al. *Pain*. 1996;67:3-6.

Background

- Pain affects more Americans than diabetes, heart disease, and cancer combined
- Most common reason individuals seek medical attention
- National Center for Health Statistics (2006)
  - 76.2 million people in the US have suffered from chronic pain lasting more than 24 hours
- The American Pain Society estimates that the national cost of pain ranges from $560 to $635 billion

Pain management. *NIH.* 2010:1-2.
Gaskin DJ, et al. *J Pain*. 2012;13(8):715-24.

Pathophysiology



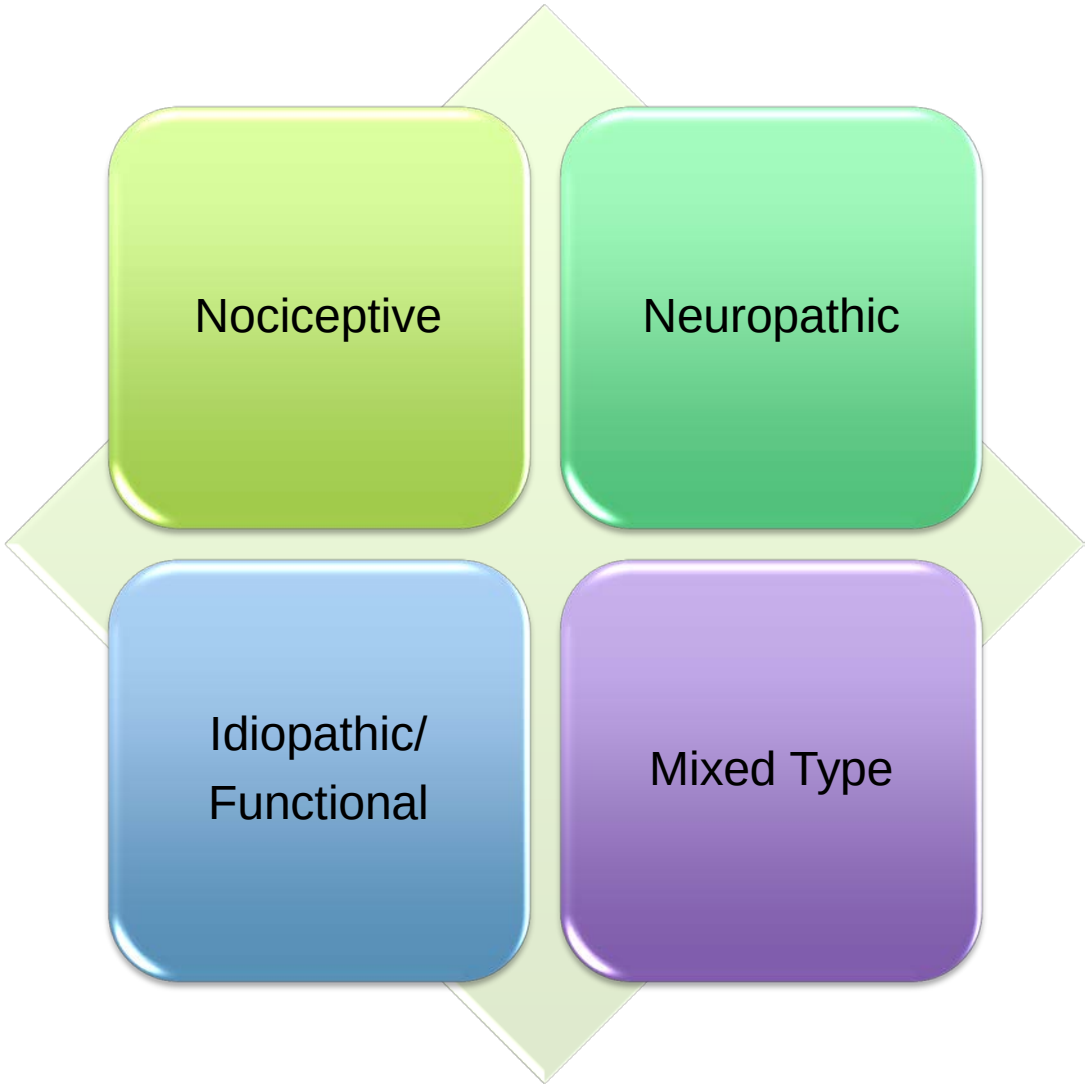
Sinauer Associates, Inc. 2002.

Classification of Pain

Acute	Chronic
• Predicted physiological response to stimulus • Self-limiting • < 3 months duration • Associated with surgery, traumatic injury, tissue damage, and inflammation	• Intractable pain • Does not resolve in response to treatment • ≥ 3 months duration • Cause may or may not be known

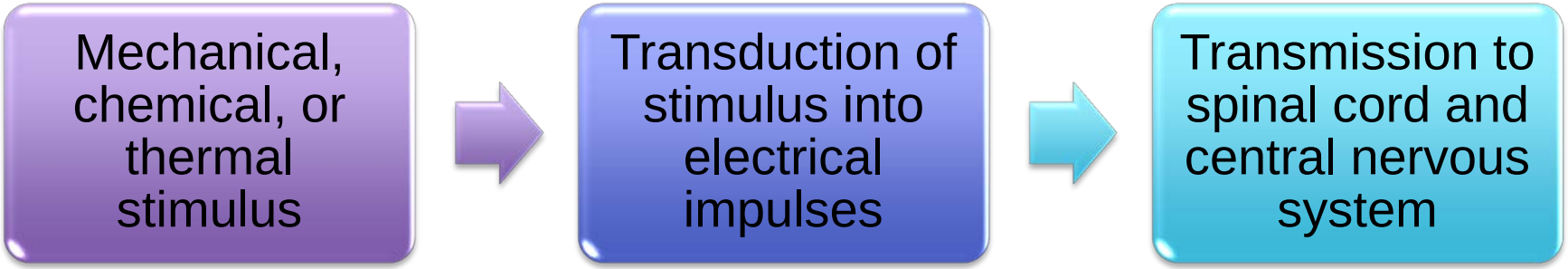
Anwar K. *Dis Mon*. 2016;62:324-29.

Types of Pain



Nociceptive Pain

- Results from the activation or sensitization of nociceptors located in the periphery
- Categorized as somatic and visceral pain
- Examples include trauma, post-operative pain, lower back pain, arthritis and sickle cell crisis



Anwar K. *Dis Mon*. 2016;62:324-29.

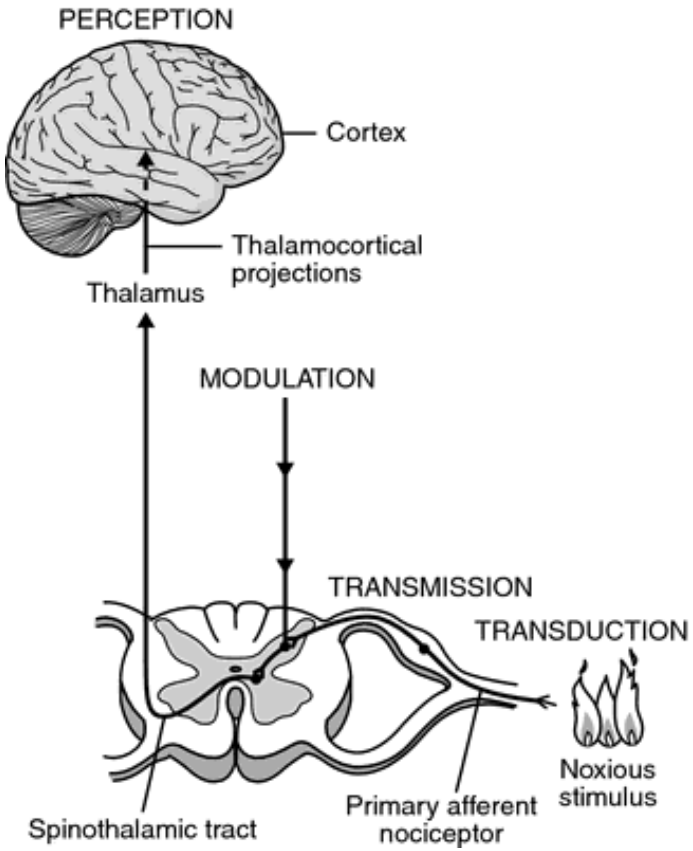
Nociceptive Pain

Somatic

- Excitation and sensitization of nociceptors in bone, peripheral soft tissue, joints, and muscles
- Generally well-localized
- Described as aching, stabbing, gnawing, or throbbing

Visceral

- Produced by organs and referred to other locations
- Diffuse and poorly-located
- Accompanied by motor and autonomic reflexes (i.e. nausea and vomiting)



Anwar K. *Dis Mon*. 2016;62:324-29.

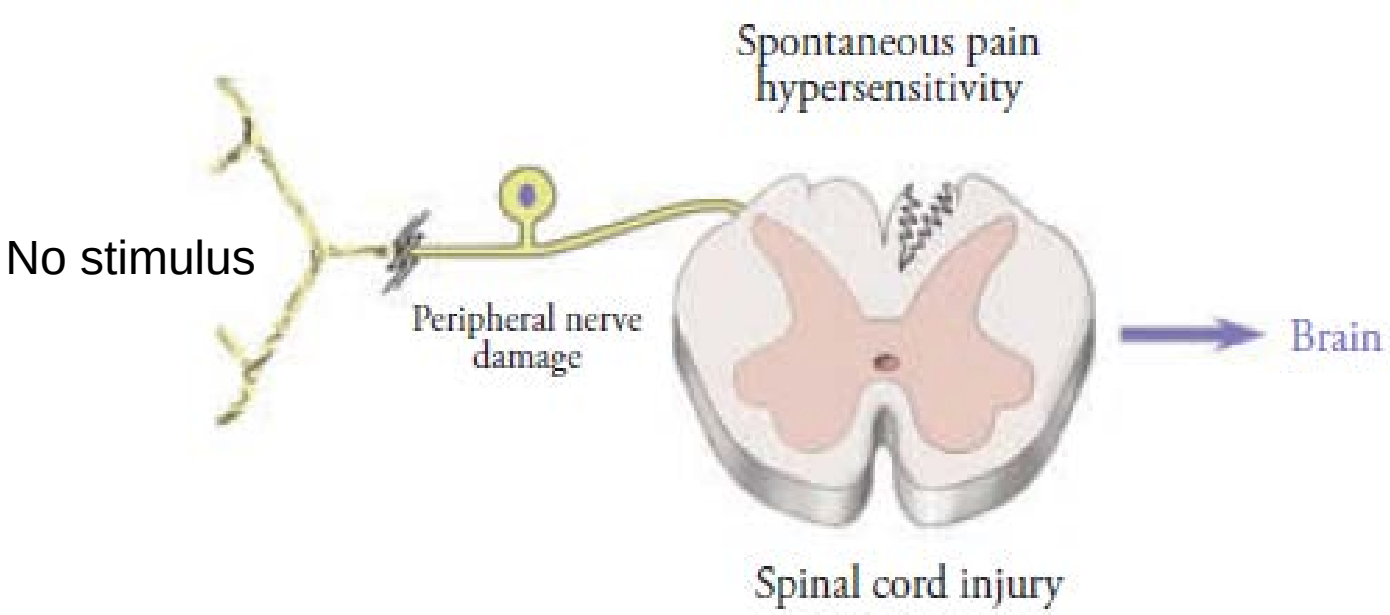
Neuropathic Pain

- Results from injury to neural structures within the peripheral and central nervous system
- Sharp, burning pain caused by aberrant somatosensory processing
- Three types of neuropathic pain
  - Peripherally-mediated (peripheral nerves and brachial plexus)
  - Central pain syndrome (CNS)
  - Sympathetically-mediated (central and peripheral)

Anwar K. *Dis Mon*. 2016;62:324-29.

Neuropathic Pain

- Examples include post-herpetic neuralgia, diabetic neuropathy, central post-stroke pain, post-amputation pain



Anwar K. *Dis Mon*. 2016;62:324-29.

Idiopathic/Functional Pain

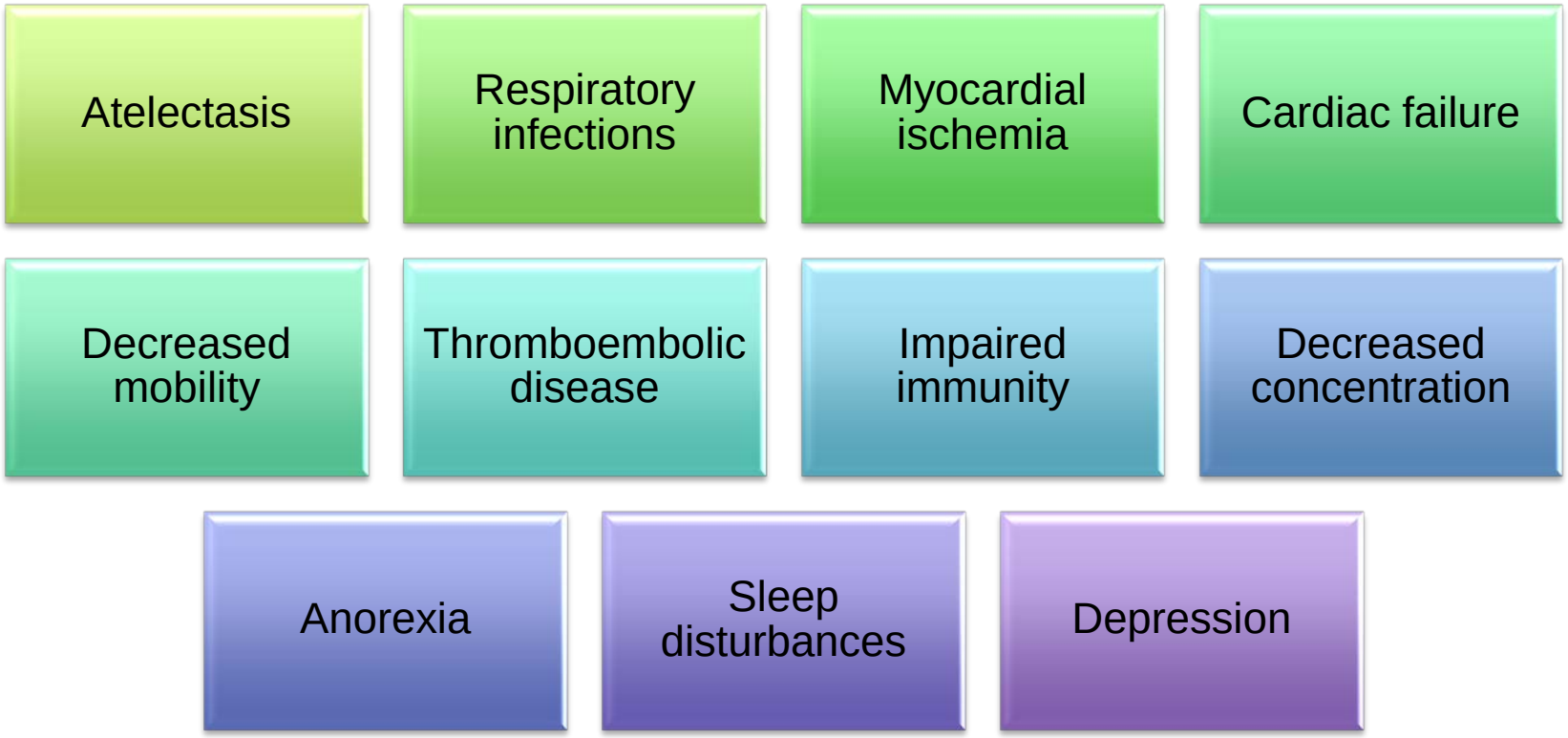
- Pain resulting from an absence of neurologic deficit or peripheral abnormality

- Caused by changes in the nervous system emerging from:
  - Genetic predisposition
  - Anxiety or depression
  - Increased psychosocial stressors
  - Infections
  - Trauma

- Examples include fibromyalgia and tension-type headaches

Schechter NL. *JAMA*. 2014;168(8):693-94.

Clinical Implications of Untreated Pain



King NB, et al. *PLoS Med*. 2013;10(4):1-4.

Goals of Pain Management

- Identify and address cause of pain
- Treat acute pain aggressively
- Prevent chronic pain
- Treat chronic pain continuously
- Improve function to sustain quality of life
- Treat noninvasively if possible

Volochayev R. *NIH.* 1-12.
Gaskin DJ, et al. *J Pain*. 2012;13(8):715-24.

Pain Assessment

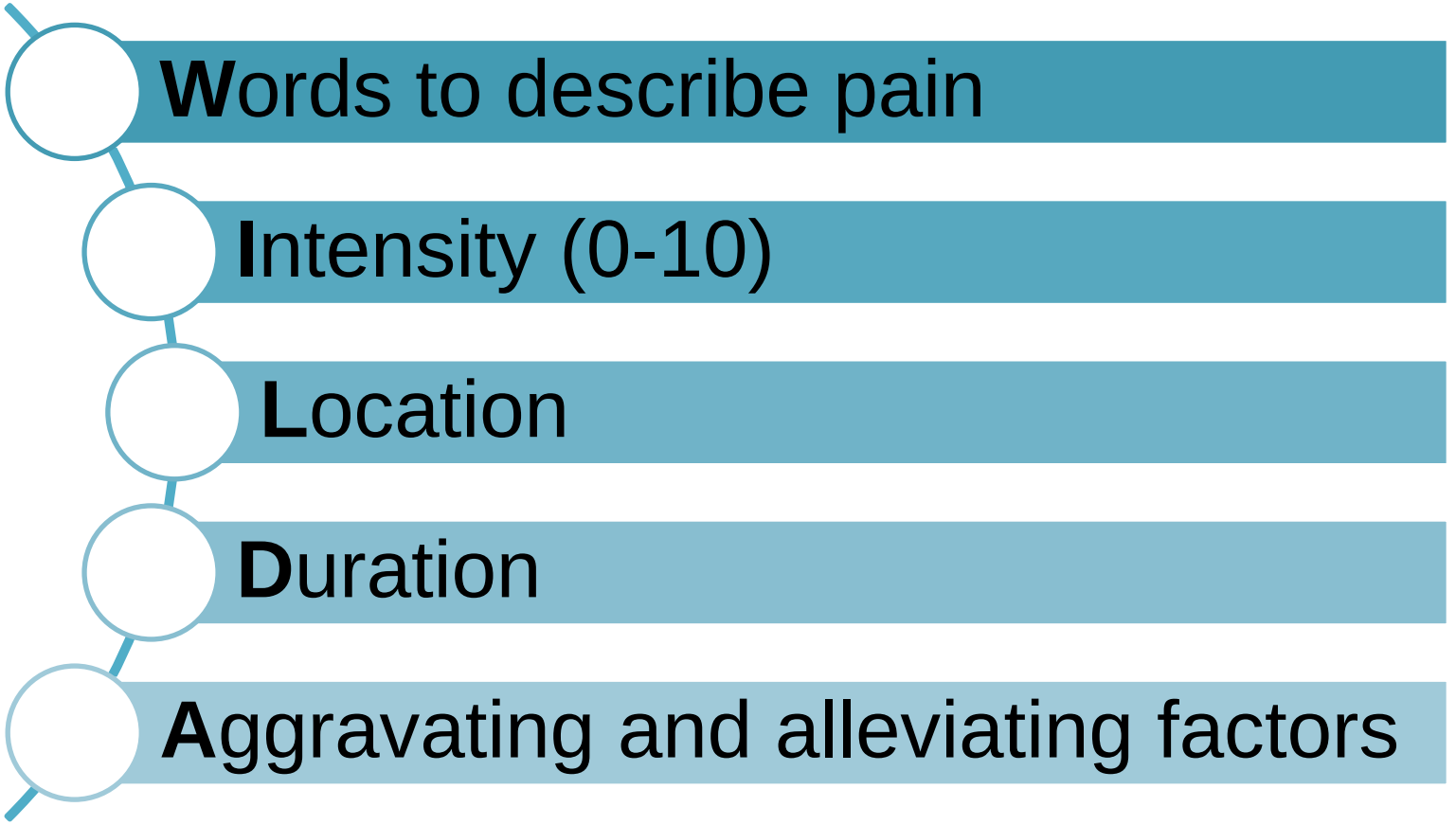
- Cornerstone to optimal pain management

- Subjective approach (clinical assessment)
  - Complete history & physical
    - Medical, social, and psychiatric history
  - Physical examination
  - Laboratory and diagnostic tests (i.e. x-rays, MRI, etc.)

- Objective approach (pain assessment tools)
  - WILDA approach
  - PQRST approach

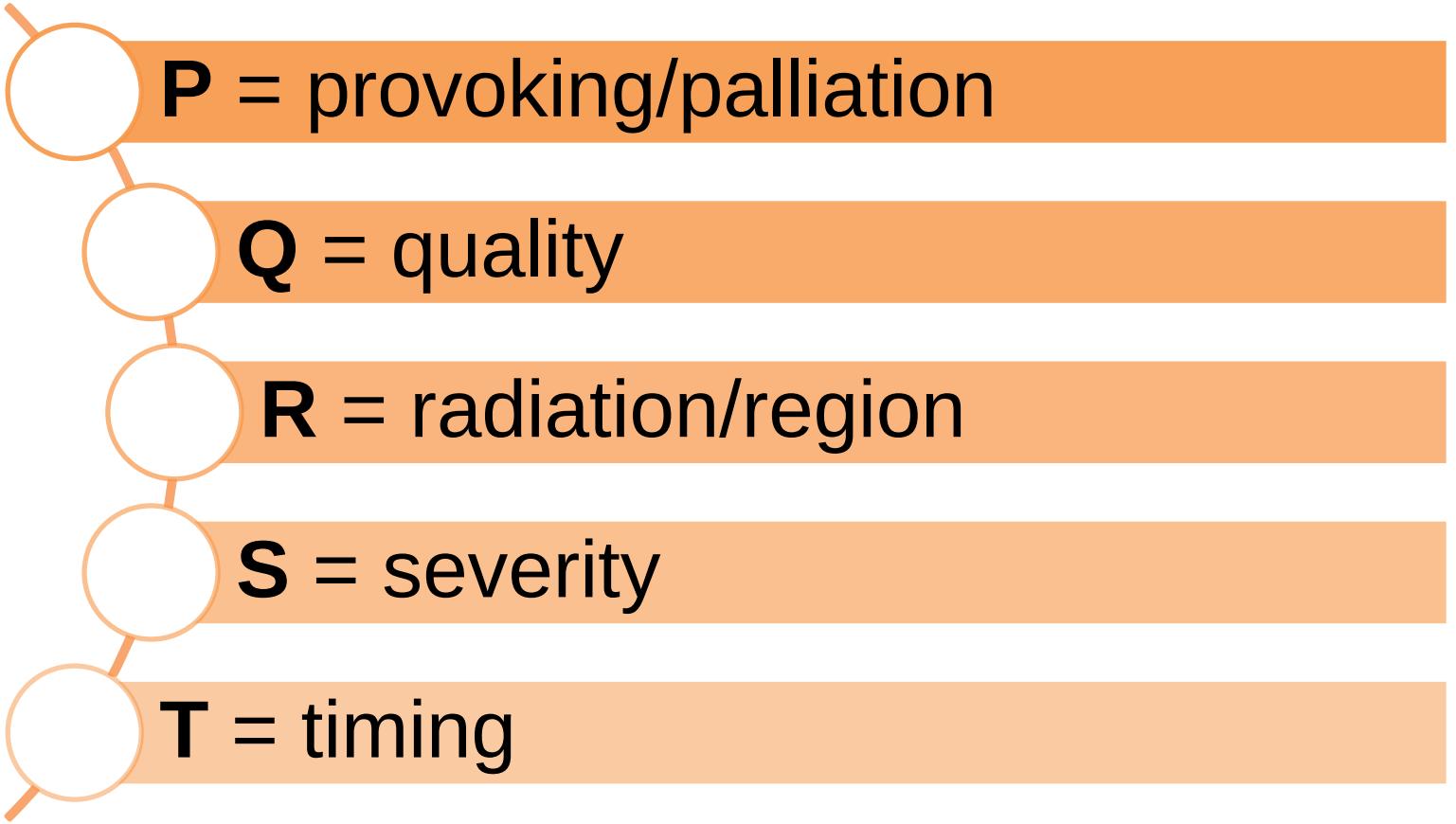
Fink R. *BUMC Proceedings*. 2000;13:236-9.

The WILDA Approach to Pain Management



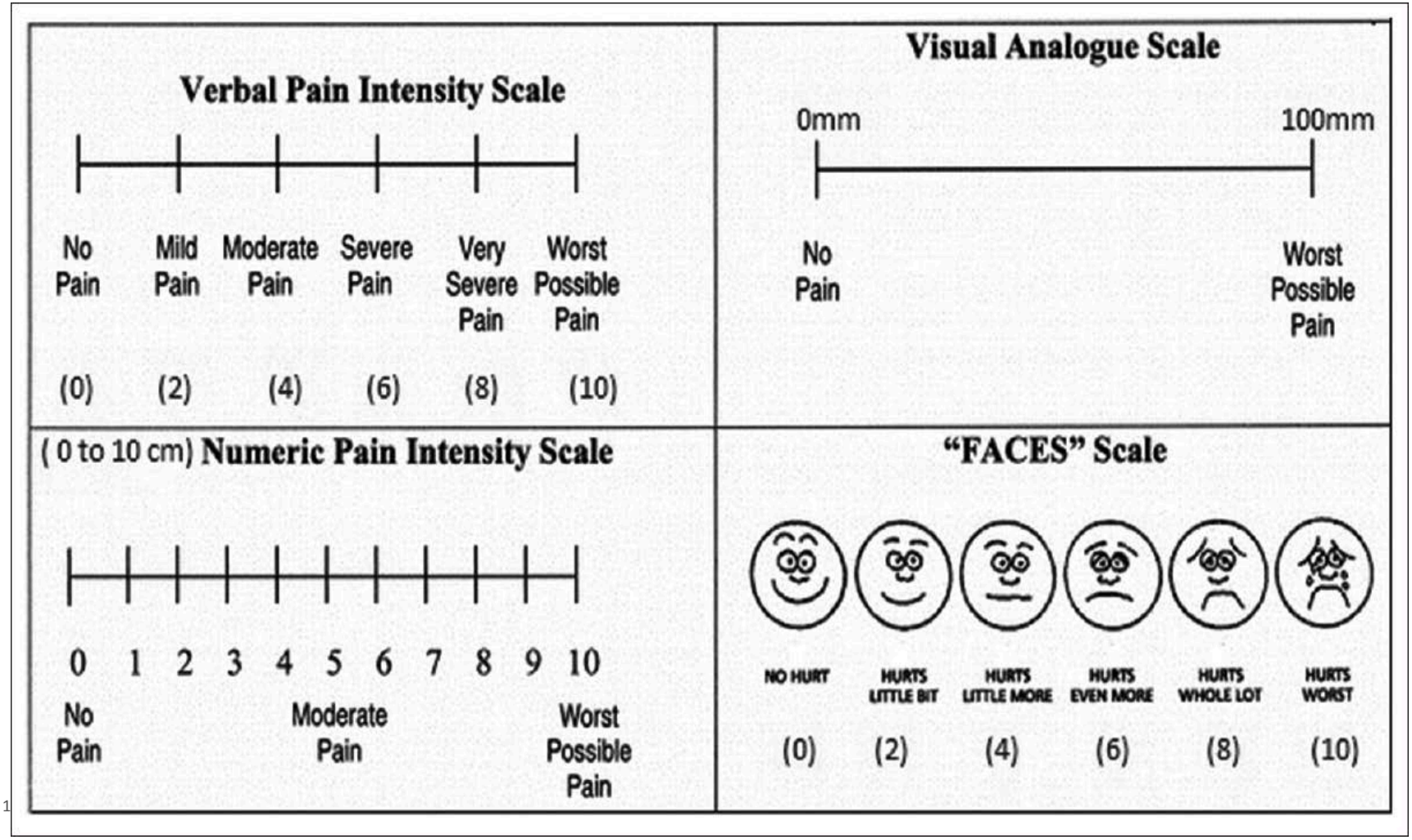
Fink R. *BUMC Proceedings*. 2000;13:236-9.

The PQRST Approach to Pain Management



Fink R. *BUMC Proceedings*. 2000;13:236-9.

Validated Pain Assessment Tools



Williamson A, et al. *J Clin Nurse*. 2005;14(7):798-804.

The Pharmacist's Role

- Utilizing multimodal analgesia to select an appropriate pain regimen
- Understanding the pharmacokinetic and pharmacodynamic properties of analgesics
- Managing adverse effects appropriately
- Recommending potential reversal agents for overdose
- Converting between opioid formulations

Multimodal Treatment Approach

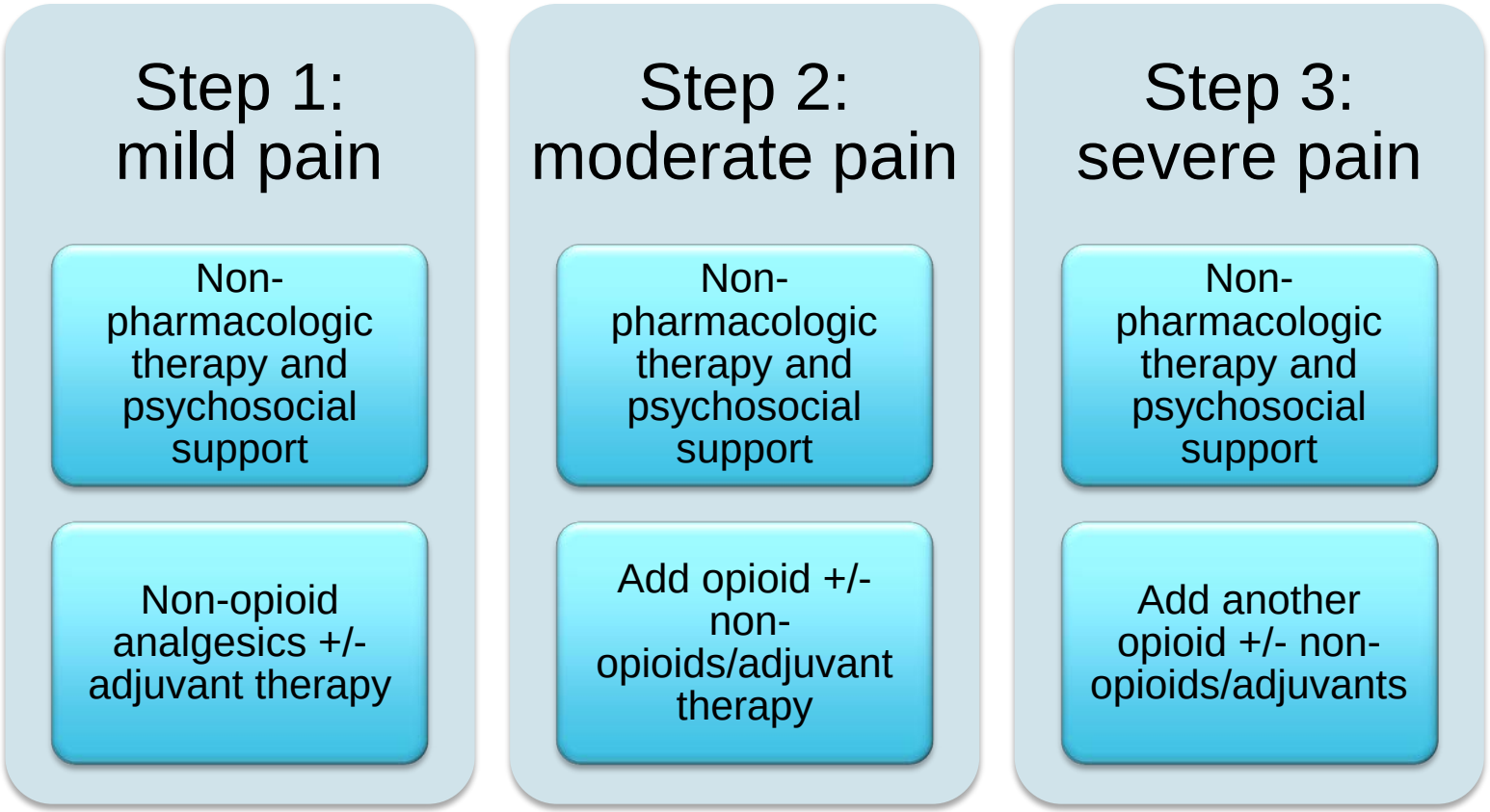
- Use of more than one method or modality of controlling pain
  - Nonpharmacologic and pharmacologic treatment
  - Medications from two or more classes

- To obtain additive beneficial effects, reduce adverse effects, or both

- Clinical benefits of multimodal analgesia
  - Earlier oral intake, ambulation, and hospital discharge
  - Reduction in postoperative morbidity, mortality, and healthcare costs

American Pain Society. *J Pain*. 2014;60-71.

A Stepwise Approach to Multimodal Analgesia



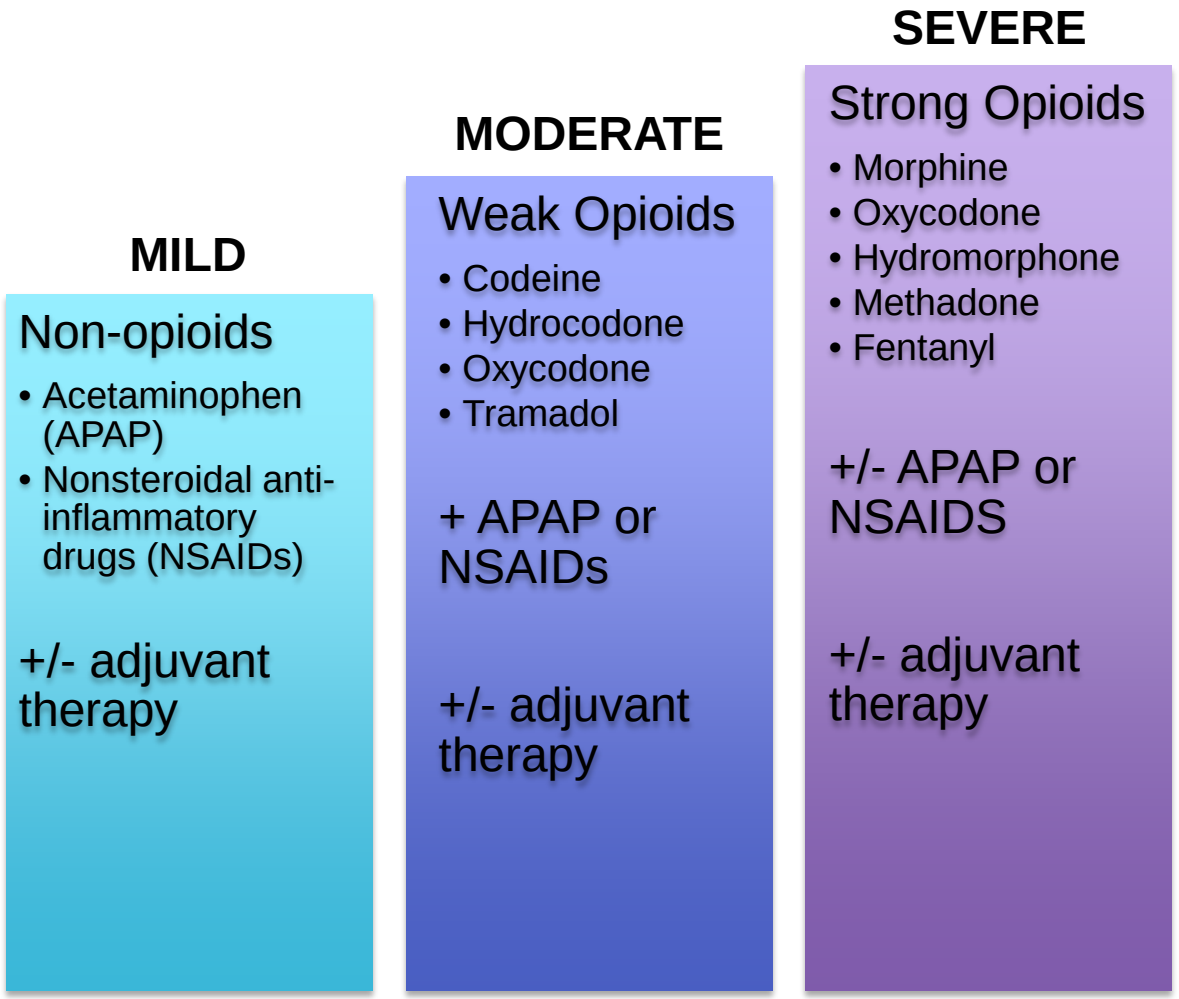
Adjuvant therapy: anticonvulsants (gabapentin, pregabalin), topical agents (lidocaine patch, capsaicin cream, diclofenac gel/cream), muscle relaxants (cyclobenzaprine, metaxalone, baclofen, methocarbamol, carisoprodol), antidepressants (SSRIs, SNRIs, TCAs)

American Pain Society. *J Pain*. 2014;60-71.

Non-Pharmacologic Therapy

Gelinas C, et al. *Nurs Crit Care*. 2013;18(6):307-18.

World Health Organization Analgesic Ladder



World Health Organization (WHO). 2013.

Non-Opioid Analgesics

- **Acetaminophen (APAP)**
  - MOA: inhibition of prostaglandin synthesis in the CNS
  - Blocks peripheral pain impulse generation and increases pain threshold
  - Lacks anti-inflammatory benefit; no effect on platelets
  - Risk for hepatic dysfunction

- **NSAIDs (i.e. ibuprofen, ketorolac, naproxen)**
  - MOA: inhibition of cyclooxygenase (COX) and inhibition of prostaglandin synthesis from arachidonic acid
  - Reduces tissue inflammation and pain
  - Risk for bleeding, cardiovascular events and renal insufficiency

Adjuvant Therapy for Chronic Pain

Anticonvulsants	• Gabapentin, pregabalin
Topical agents	• Lidocaine patch, capsaicin cream, diclofenac gel/cream
Muscle relaxants	• Cyclobenzaprine, metaxalone, carisoprodol, methocarbamol
Antidepressants	• SSRIs, SNRIs, TCAs

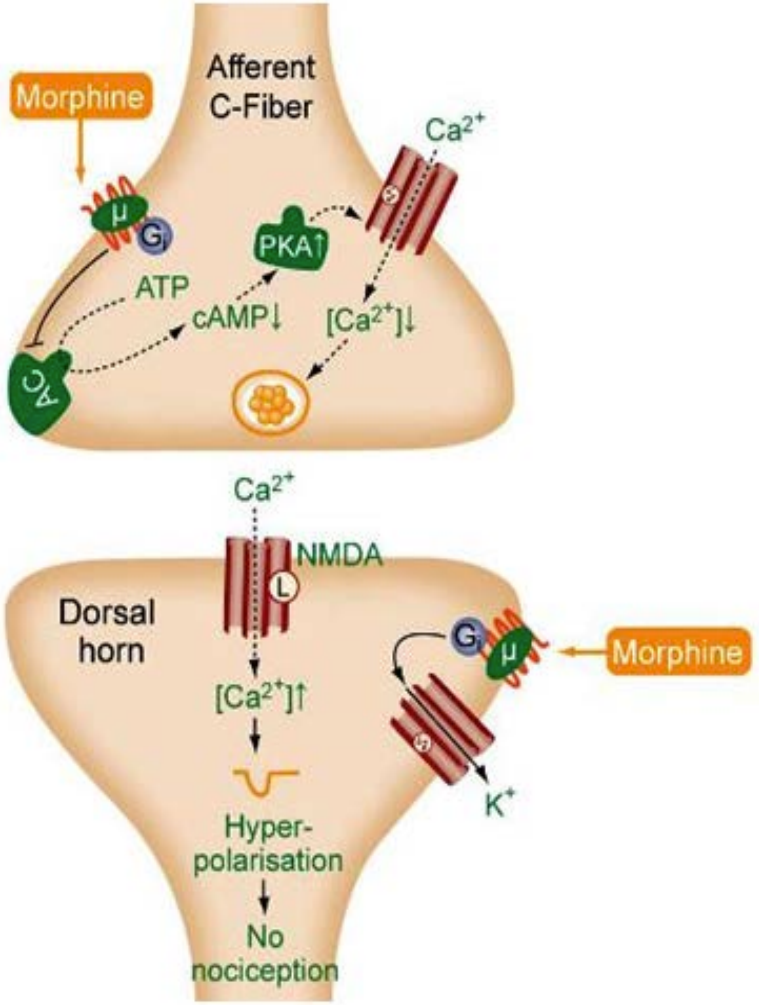
Opioid Analgesics

- MOA: binds to opioid receptors in the CNS, peripheral nerve terminals, and GI tract
  - Interact with mu (μ), delta (δ), or kappa (κ) opioid receptors
  - Decrease release of excitatory neurotransmitters (i.e. glutamate)
  - Decrease post-synaptic response to neurotransmitters
  - Inhibition of ascending pain pathways, which alters response and perception of pain

Bovill JG. *Eur J Anaesthesiol Suppl*. 1997;15:9-15.

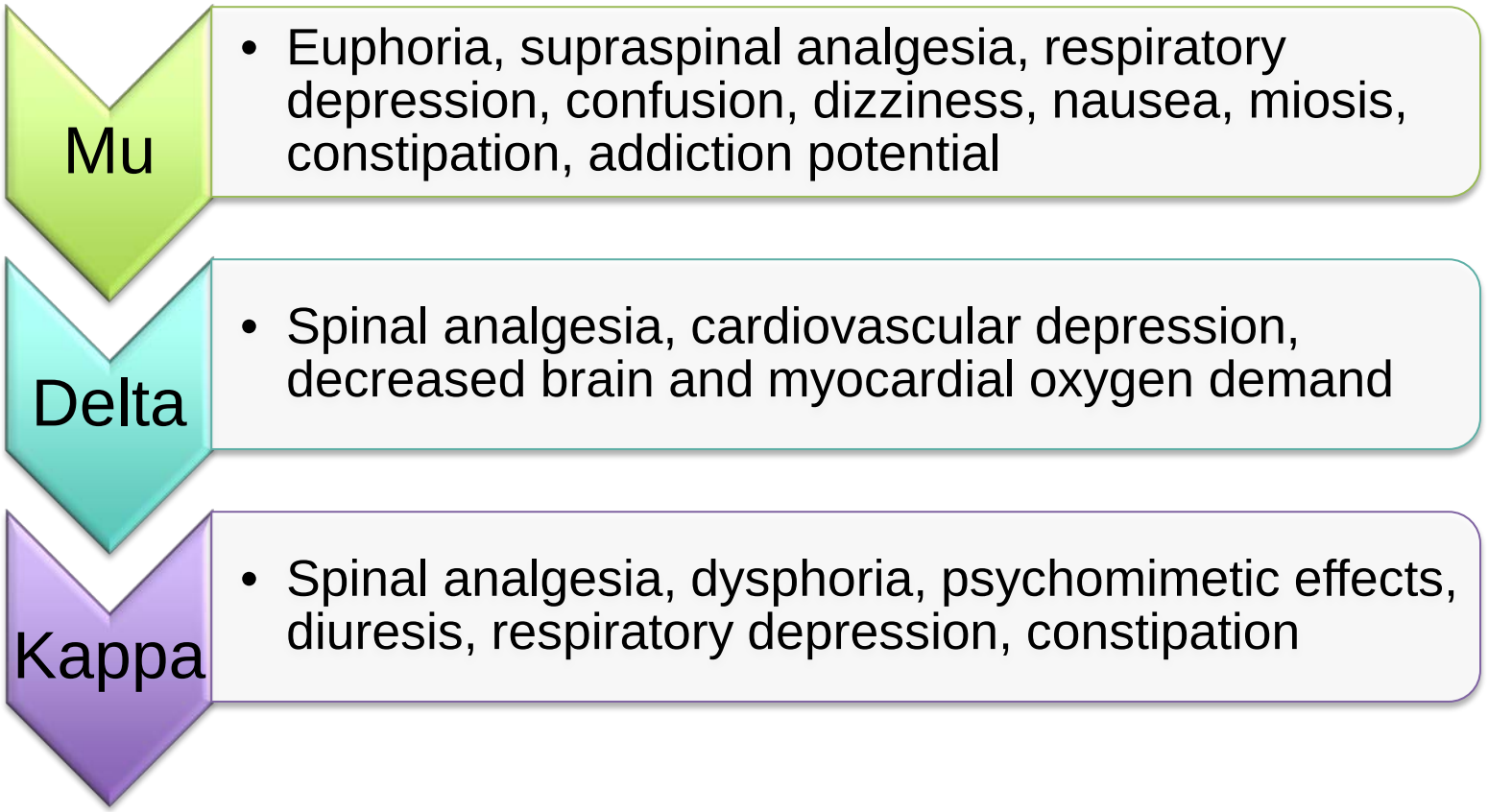
Pharmacology of Opioids

- Opioid receptors coupled to G1 proteins
- Closure of N-type voltage-operated calcium channels
- Opening of calcium-dependent inwardly-rectifying potassium channels
- Hyperpolarization and reduction in neuronal excitability
- ↓ cAMP results in decreased substance P



Bovill JG. *Eur J Anaesthesiol Suppl*. 1997;15:9-15.

Opioid Receptor Effects



Al-Hasani R, et al. *Anesthesiology*. 2011;115(6):1363-81.

Classification of Opioids

Partial agonist	Pure agonist	Agonist/ Antagonist	Antagonist

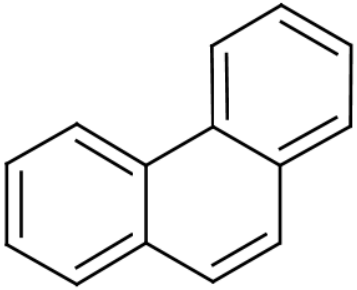
• Buprenorphine	• **Weak**
	  • Tramadol
	  • Codeine
	  • Dextropropoxy-phene
	  • Dihydrocodeine
	• **Strong**
	  • Hydromorphone
	  • Fentanyl
	  • Methadone
	  • Oxycodone
	  • Morphine
		• **Weak**
		  • Nalbuphine
		• **Strong**
		  • Pentazocine
			• Naloxone
			• Naltrexone

Pathan H. *Br J Pain*. 2012;6(1):11-6.

Classification of Opioids

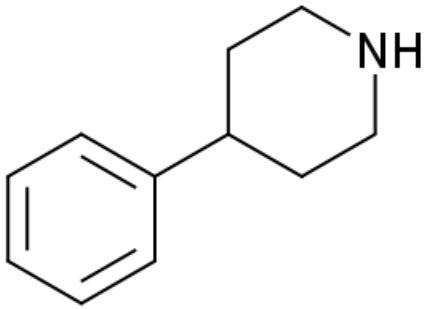
Phenanthrenes

- **Natural**:
  - Codeine, Morphine
- **Semisynthetic**:
  - Hydrocodone, Hydromorphone, Oxycodone, Oxymorphone



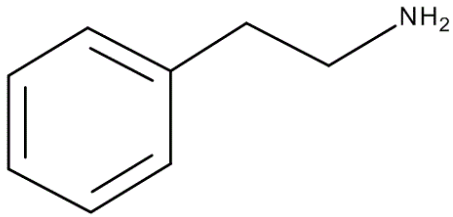
Phenylpiperidines

- Fentanyl, Meperidine, Remifentanil, Sufentanil



Phenylheptylamines

- Methadone, Propoxyphene



Pathan H. *Br J Pain*. 2012;6(1):11-6.

Opioid Allergy vs. Pseudoallergy

- 9 out of 10 patients with a reported allergy to an opioid do not have a true allergy
  - Codeine, morphine, and meperidine cause most allergic-type reactions
- Symptoms resemble an allergic reaction but are actually a "pseudoallergic" reaction due to histamine release
  - Itching, sneezing, flushing, sweating, asthma exacerbation
- Symptoms of a true allergy
  - Hives, maculopapular rash, erythema multiforme, pustular rash, severe hypotension, bronchospasm, angioedema

DeDea L. *JAAPA*. 2012;25(1):17.

Opioid Allergy vs. Pseudoallergy (continued)

- Cross-allergenicity
  - Risk of cross-reactivity between opioids is thought to be less likely among agents from a different structural class

- Initiation of alternative therapy
  - Determine necessity for opioid agent
  - Initiate NSAID or APAP around the clock if no contraindications exist
  - If narcotic is required –
    - Utilize lowest-possible dose (dose-dependent histamine release) OR
    - Utilize high-potency opioid
    - Administer antihistamine concurrently

DeDea L. *JAAPA*. 2012;25(1):17.

Factors to Consider When Selecting An Opioid

Prior opioid exposure	Pain intensity	Acute vs. chronic pain
Type of pain (nociceptive vs. neuropathic)	Allergy history	Metabolic status
Drug interactions	Cost/availability	Tolerability to adverse effects

Opioid Drug Therapies

- Morphine
  - Significant histamine-release reactions (i.e. itching)
  - Active metabolite may accumulate in renal failure → prolonged sedation
  - Available as immediate-release and sustained-release oral formulations

- Hydromorphone
  - 7 times more potent than morphine
  - No formation of active metabolites
  - Good choice for patients with tolerance to morphine or patients experiencing histamine-release reactions

Yaksh TL, et al. *Opioids, Analgesia, and Pain*. 2011.

Opioid Drug Therapies (continued)

- Fentanyl
  - 100 times more potent than morphine
  - Least amount of histamine-release reactions
  - No formation of active metabolites
  - Drug of choice for hemodynamically unstable, mechanically ventilated patients
  - Short duration of effect often requires a continuous infusion
  - Available as a long-acting patch, buccal tablet, and immediate-release dosage forms

Yaksh TL, et al. *Opioids, Analgesia, and Pain*. 2011.

Opioid Drug Therapies (continued)

- Codeine
  - Weak analgesic (often co-formulated with acetaminophen)
  - Prodrug metabolized by CYP2D6 to active metabolites
    - 10% of US population are unable to convert codeine to the active metabolite
- Oxycodone
  - Available as immediate-release and extended-release oral formulations
    - Immediate-release formulation onset of action is 10-15 minutes (may take up to 80 minutes for maximum effect)
  - 5 mg oxycodone = 40 mg codeine

Yaksh TL, et al. *Opioids, Analgesia, and Pain*. 2011.

Opioid Drug Therapies (continued)

- Meperidine
  - Not routinely used for analgesia (active metabolite may accumulate and lead to seizures)
  - Significant histamine-release reactions
  - Several doses may be given for post-operative rigors

- Methadone
  - Strong opioid agonist and n-methyl-D-aspartate (NMDA) antagonist
  - Analgesic effects last 6-8 hours
  - Long terminal half-life (approximately 27 hours)
  - QTc prolongation (interaction with quinolones, macrolides, antipsychotics, and amiodarone)

Yaksh TL, et al. *Opioids, Analgesia, and Pain*. 2011.

Opioid Drug Therapies (continued)

- Tramadol
  - Synthetic analogue of codeine
    - Binds to mu receptors and inhibits norepinephrine and serotonin reuptake
  - Active metabolite that is 6 times more potent
  - May have increased risk of seizures with concomitant MAOI, SSRI, TCA, or opioid administration

- Tapentadol
  - Weak opioid agonist
    - Serotonin and norepinephrine reuptake inhibitor
  - Effective option for patients with GI effects from other opioids
  - Also approved for diabetic peripheral neuropathy

Yaksh TL, et al. *Opioids, Analgesia, and Pain*. 2011.

Pharmacokinetic Properties of Opioids

- Majority of opioids are metabolized through phase I metabolism via CYP450 enzymes 2D6 and 3A4

- Hepatic impairment and cirrhosis
  - Gastritis → delayed drug absorption
  - Ascites → increased volume of distribution → increased adverse effects of hydrophilic opioids (i.e. morphine, oxycodone)
  - Decreased production of alpha-1-acid glycoprotein and albumin
    - Increased free drug levels of highly protein-bound opioids (i.e. methadone and buprenorphine)

START LOW AND TITRATE SLOW!

Gelot S, et al. *US Pharm*. 2014;39(8):34-38.

Dosing Recommendations in Hepatic Impairment

Opioid	Recommended Use	Dosing Recommendations
Morphine	Use cautiously	*Moderate-severe*: increase dosing interval by 2x usual time period
Hydromorphone	Use cautiously	*Moderate-severe*: decrease initial dose by 50%
Oxycodone	Use cautiously	*Severe*: decrease initial dose by 33-50%
Hydrocodone	Use cautiously	*Severe*: decrease initial dose by 50%
Codeine	Use not recommended	---
Methadone	Use not recommended	---
Fentanyl (IV)	Appears safe	No dose adjustment
Fentanyl (Patch)	Use cautiously	*Mild-moderate*: reduce dose by 50% *Severe*: use not recommended

Gelot S, et al. *US Pharm*. 2014;39(8):34-38.

Pharmacokinetic Properties of Opioids (continued)

- Renal impairment
  - Approximately 1/3 of patients with a CrCl < 50 mL/min are administered an opioid for pain

CrCl (mL/min)	Morphine	Hydromorphone	Hydrocodone	Oxycodone	Methadone	Fentanyl (patch)
> 50	No dose adjustment	If CrCl ≤ 60, reduce dose by 25%	No dose adjustment	If CrCl < 60, reduce dose by 50%	No dose adjustment	Reduce dose by 50%
10-50	Reduce dose by 25-50%	Reduce dose by 50%	Reduce dose by 50%			
<10	Reduce dose by 50-75%	Reduce dose by 75%	Reduce dose by 75%	Use not recommended	Reduce dose by 50-75%	Use not recommended

START LOW AND TITRATE SLOW!

Gelot S, et al. *US Pharm*. 2014;39(8):34-38.

Opioid-Related Adverse Effects

- Sedation
  - Results from anticholinergic activity of opioids
  - More common when initiating therapy or when increasing dose
  - Resolves within days to weeks
  - Opioid rotation and dose reduction if possible
  - Psychosomatic simulants (i.e. methylphenidate)

- Nausea and Vomiting
  - Results from direct stimulation of chemoreceptor trigger zone
  - Results within several days
  - Initiation of antiemetic agents (ondansetron, metoclopramide, prochlorperazine, etc.)

Raghavan S, et al. *Anesthesia and Crit Care*. 2011;1:18-21.

Opioid-Related Adverse Effects (continued)

- Constipation
  - Occurs in 40-95% of all patients treated with opioids
  - Results from mu receptor activation in the gastrointestinal tract, leading to decreased gut motility
  - Unlikely to improve over time
  - Long-term consequences
    - Significant morbidity and mortality
    - Decreased quality of life
  - Aggressive prophylaxis
    - Stimulant laxative (i.e. senna or bisacodyl) and a stool softener (i.e. docusate) scheduled around the clock

Raghavan S, et al. *Anesthesia and Crit Care*. 2011;1:18-21.

Opioid-Related Adverse Effects (continued)

- Cardiac effects
  - Not very common
  - Morphine-associated histamine-release and subsequent vasodilation and hypotension
  - QTc prolongation resulting from parasympathetic stimulation and bradycardia
  - Effects are completely reversed with naloxone administration

- Bladder dysfunction
  - Results from inhibition of the voiding reflex
  - More common with postoperative patients
  - Effects are reversible with naloxone

Raghavan S, et al. *Anesthesia and Crit Care*. 2011;1:18-21.

Opioid-Related Adverse Effects (continued)

- Histamine-release reactions
  - Associated with lower potency opioids (i.e. morphine)
  - Flushing, tachycardia, hypotension, and pruritis
  - Utilize lower doses of opioids or switch to a more potent agent (i.e. hydromorphone)
  - If opioid is required, administer an antihistamine

Raghavan S, et al. *Anesthesia and Crit Care*. 2011;1:18-21.

Opioid Addiction

- **Addiction**: complex disease involving physiological, psychological, and social aspects
  - **Pseudoaddiction**: aberrant behavior in patients not truly addicted to opioids
    - Ex. Once patient receives adequate analgesia, the drug-seeking behaviors cease

- Fear of inducing a new addiction with appropriate opioid use should NOT be a barrier to providing adequate pain relief

Kiefer MM, et al. *Pocket Primary Care*. 2014.

Tolerance and Physical Dependence

- **Tolerance**: constant opioid dose provides a decreased effect
  - Opioid-related adverse effects will develop over several days to weeks (with the exception of constipation)
  - More frequent administration of analgesia over time

- **Physical dependence**: predictable pharmacologic effect
  - Withdrawal symptoms after abrupt discontinuation of therapy
  - Commonly occurs after 2 weeks of therapy
  - Symptoms include drug craving, nausea, abdominal cramps, muscle aches
  - Nonverbal patients may appear restless, irritable, dysphoric, anxious, delirious, or have increased pain sensitivity

Kiefer MM, et al. *Pocket Primary Care*. 2014.

Opioid Clinical Pearls in Special Populations

- Methadone maintenance therapy
  - Patients typically have very high tolerance for opioid therapy
  - Indicated for opioid dependence; additional opioid may be added for breakthrough pain
- IV drug abuse (IVDA)
  - High tolerance for opioids and will require higher doses, more potent agents, and more frequent dosing
- Suboxone® or Subutex® therapy
  - Very high affinity for opioids receptors and block analgesic effects of opioids
  - Pain consult recommended

Yaksh TL, et al. *Opioids, Analgesia, and Pain*. 2011.

Opioid Overdose

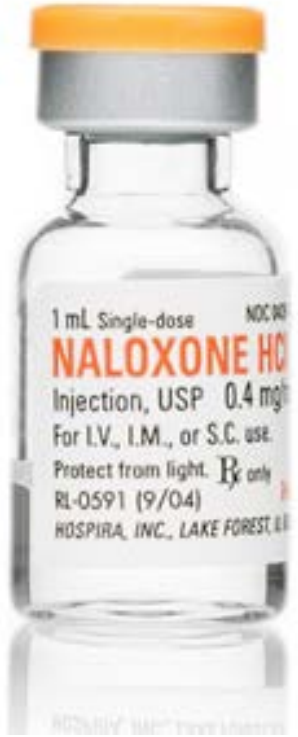
- Preventable and potentially lethal condition resulting from:
  - Prescribing practices
  - Inadequate understanding on risk of opioid misuse
  - Drug administration errors
  - Pharmaceutical abuse

- Clinical implications:
  - Life-threatening toxic effects in multiple organ systems
  - Pharmacokinetic changes leading to prolonged complications
  - Inappropriate treatment decisions

Boyer E, et al. *N Engl J Med*. 2012;367:146-55.

Naloxone: The Antidote for Opioid Overdose

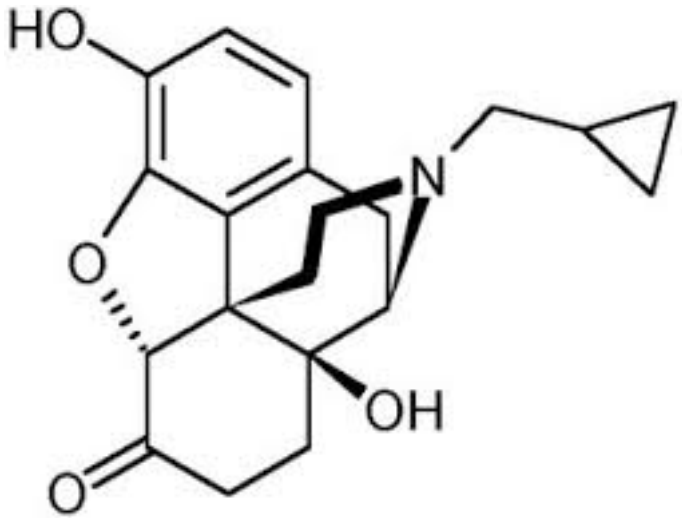
- MOA: competitive μ opioid-receptor antagonist
- Routes of administration:
  - Parenteral
  - Intranasal
  - Pulmonary
  - Oral route (negligible bioavailability)
- Onset of action: < 2 minutes (IV)
- Duration of action: 20 to 90 minutes
- Dosing:
  - Initial: 0.04 mg
  - Increase every 2 minutes, if no response
  - Maximum dose: 15 mg



Boyer E, et al. *N Engl J Med*. 2012;367:146-55.

Naltrexone

- MOA: potent, long-acting, pure opiate antagonist
- Route of administration: oral
- Duration of action: up to 72 hours
- Recommended dosing:
  - Day 1: 25 mg
  - If no withdrawal signs occur, may increase to 50-300 mg/day



Pani N, et al. *Indian J Anaesth*. 2015;59(10):664-69.

Equianalgesia

- Analgesic and sedative effects of opioids are similar when administered in equipotent doses
  - Example: hydromorphone 1 mg = morphine 7 mg

- Special considerations:

Titrate drugs to individual response	Incomplete cross-tolerance (reduce by 25-50%)	Organ dysfunction and clinical situation	Drug-drug interactions

Pharmacist's Letter, August 2012.

Equianalgesic Dosing

	Equianalgesic Doses	
Drug	**PO**	**IV**
Morphine IR *(Roxanol®, MS IR®)*	30 mg	10 mg
Morphine ER *(MS Contin®, Kadian®)*	30 mg	N/A
Hydromorphone IR *(Dilaudid®)*	7.5-8 mg	1.5-2 mg
Oxycodone IR *(Oxy IR®)*	20-30 mg	N/A
Oxycodone ER *(OxyContin®)*	20-30 mg	N/A
Hydrocodone IR *(Vicodin®, Norco®)*	30-45 mg	N/A
Oxymorphone *(Opana®)*	10 mg	1 mg
Codeine	200 mg	100-130 mg
Fentanyl	N/A	0.1 mg
Meperidine *(Demerol®)*	300 mg	75 mg

Pharmacist's Letter, August 2012.

Converting Between Opioids

Steps to convert between opioids:

1. Determine the total 24-hour opioid requirement of current medication
2. Set up equianalgesic equation:

$$\frac{\text{Equianalgesic dose (current drug)}}{\text{Equianalgesic dose (new drug)}} = \frac{\text{Total 24-hour dose (current drug)}}{\text{X mg (new drug)}}$$

3. Solve for X
4. Reduce dose by 25-50% to account for incomplete cross-tolerance
5. Divide the total calculated dose by the frequency

Opioid Conversion Example

RJ is a 54-year old female admitted to the hospital due to progressively worsening back pain. She takes 2 tablets of oxycodone-acetaminophen 5/325 mg every 4 hours, with no relief. The physician wants to start the patient on oral hydromorphone and asks you for a dose recommendation.

Step 1: Determine the 24-hour opioid requirement for the current medication.

2 tablets oxycodone-acetaminophen 5/325 mg Q4H

=

60 mg oxycodone in 24 hours

Opioid Conversion Example

Step 2: Set up the equianalgesic equation.

$$\frac{\text{20 mg PO oxycodone}}{\text{7.5 mg PO hydromorphone}} = \frac{\text{60 mg PO oxycodone}}{\text{X mg PO hydromorphone}}$$

Step 3: Solve for x.

X = 22.5 mg PO hydromorphone in 24 hours

Opioid Conversion Example

Step 4: Reduce dose by 25-50% to account for incomplete cross-tolerance.

22.5 mg PO hydromorphone x 0.25 = 5.625 mg PO hydromorphone

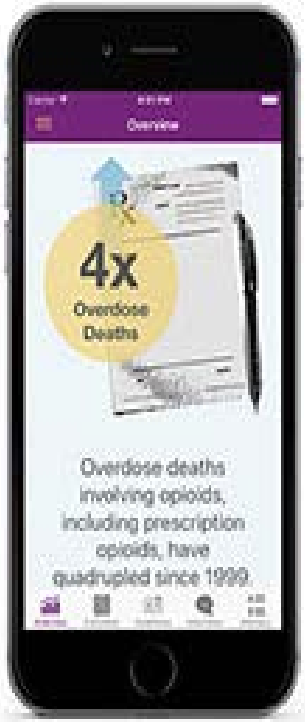
22.5 mg PO hydromorphone – 5.625 mg PO hydromorphone =
16.88 mg PO hydromorphone in 24 hours

Step 5: Divide total calculated dose by frequency (divide by 6 for Q4H dosing)

16.88 mg PO hydromorphone/6 =

2.8 mg PO hydromorphone every 4 hours ≈ **2 mg PO Q4H**

Available Resources



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www.cdc.gov

World Health Organization

PHARMACIST'S LETTER

Summary

- Pain is a complex condition that requires careful and continuous assessment
- Multimodal analgesia should be used if possible, to minimize adverse effects and the potential for abuse
- Pharmacists play a crucial role in opioid education, equianalgesic dosing and optimization of analgesia

Pain Management and the Pharmacist's Role in Opioid Use

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June 14th, 2017

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