



Opioids

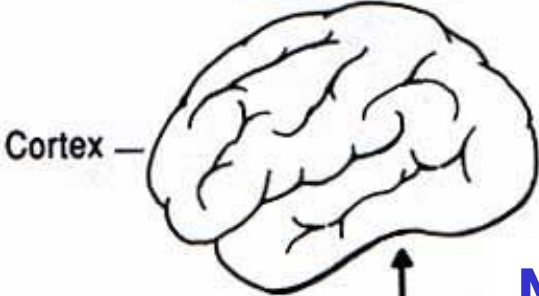
Andrea L. Cheville, M.D., M.S.C.E
Professor of Physical Medicine and Rehabilitation
Research Chair
Mayo Clinic
Rochester, MN

Pathophysiological distinction

- Nociceptive pain - Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.
 - Somatic
 - Visceral
- Neuropathic pain - Pain caused by a lesion or disease of the somatosensory nervous system.

International Association for the study of pain. Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Defi...isplay.cfm&ContentID=1728. Accessed September 8, 2011.

Perception



Thalamocortical projections
Thalamus

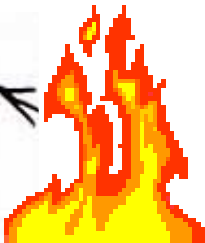
Modulation

Transmission

Transduction

Spinothalamic tract

Primary Afferent Nociceptor



Balanced analgesia

Rationale analgesia

Rationale polypharmacy

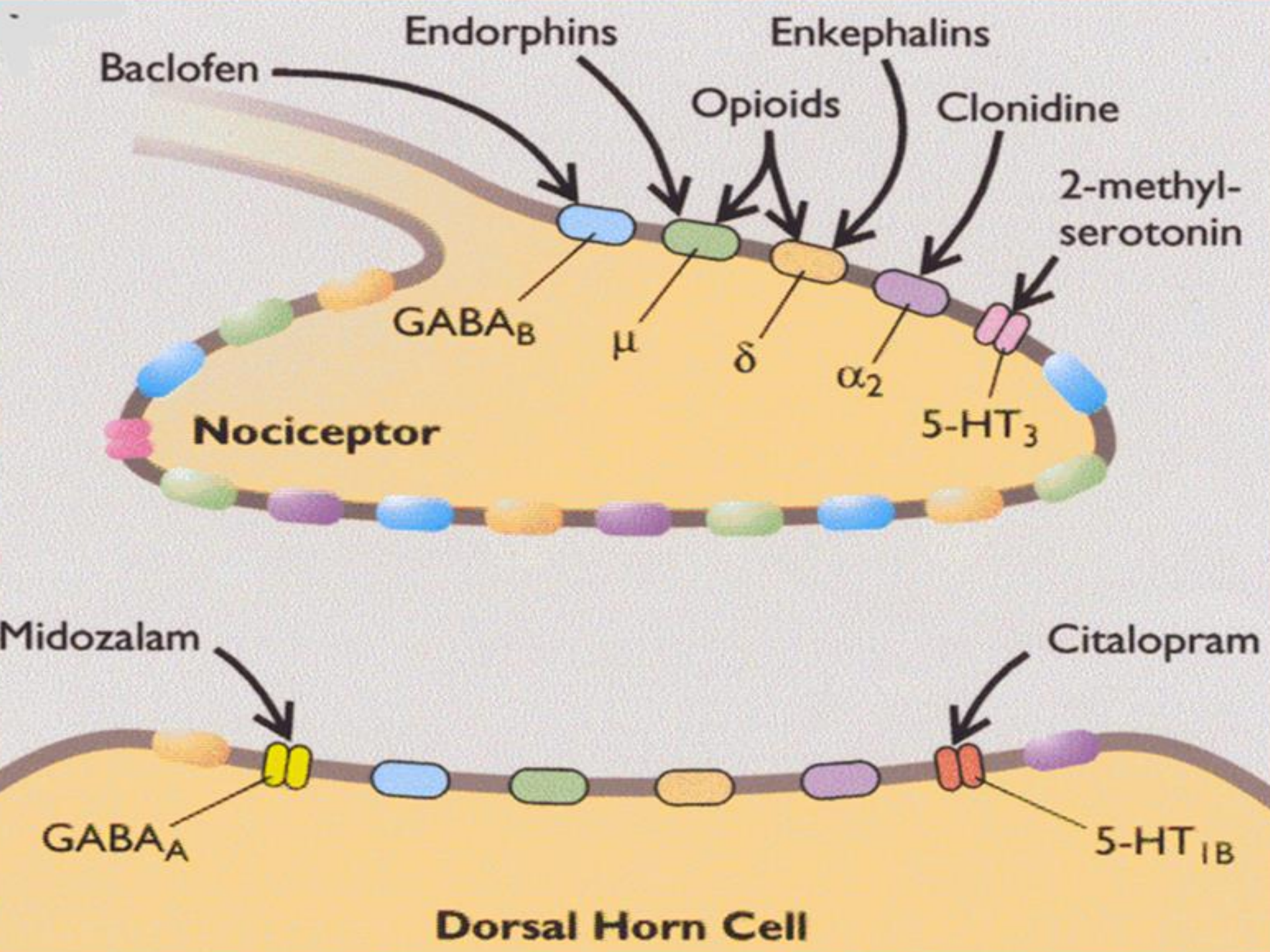
- Capitalizes on complementary mechanisms¹
- Minimizes toxicity associated with individual agents²
- Potential synergies
- Limitedly validated in cancer^{3,4}

1. Gilron I, Max MB. Combination pharmacotherapy for neuropathic pain: current evidence and future directions. *Expert Rev Neurother*. Nov 2005;5(6):823-830.

2. Jackson KC, 2nd. Pharmacotherapy for neuropathic pain. *Pain Pract*. Mar 2006;6(1):27-33.

3. Arai YC, Matsubara T, Shimo K, et al. Low-dose gabapentin as useful adjuvant to opioids for neuropathic cancer pain when combined with low-dose imipramine. *J Anesth*. Jun;24(3):407-410.

4. Keskinbora K, Pekel AF, Aydinli I. Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain: a randomized open trial. *J Pain Symptom Manage*. Aug 2007 ;34(2):183-189.



Analgesic Classes

- Non-opioid analgesics
- Adjuvant analgesics
- Opiate analgesics

Properties of opioid receptors

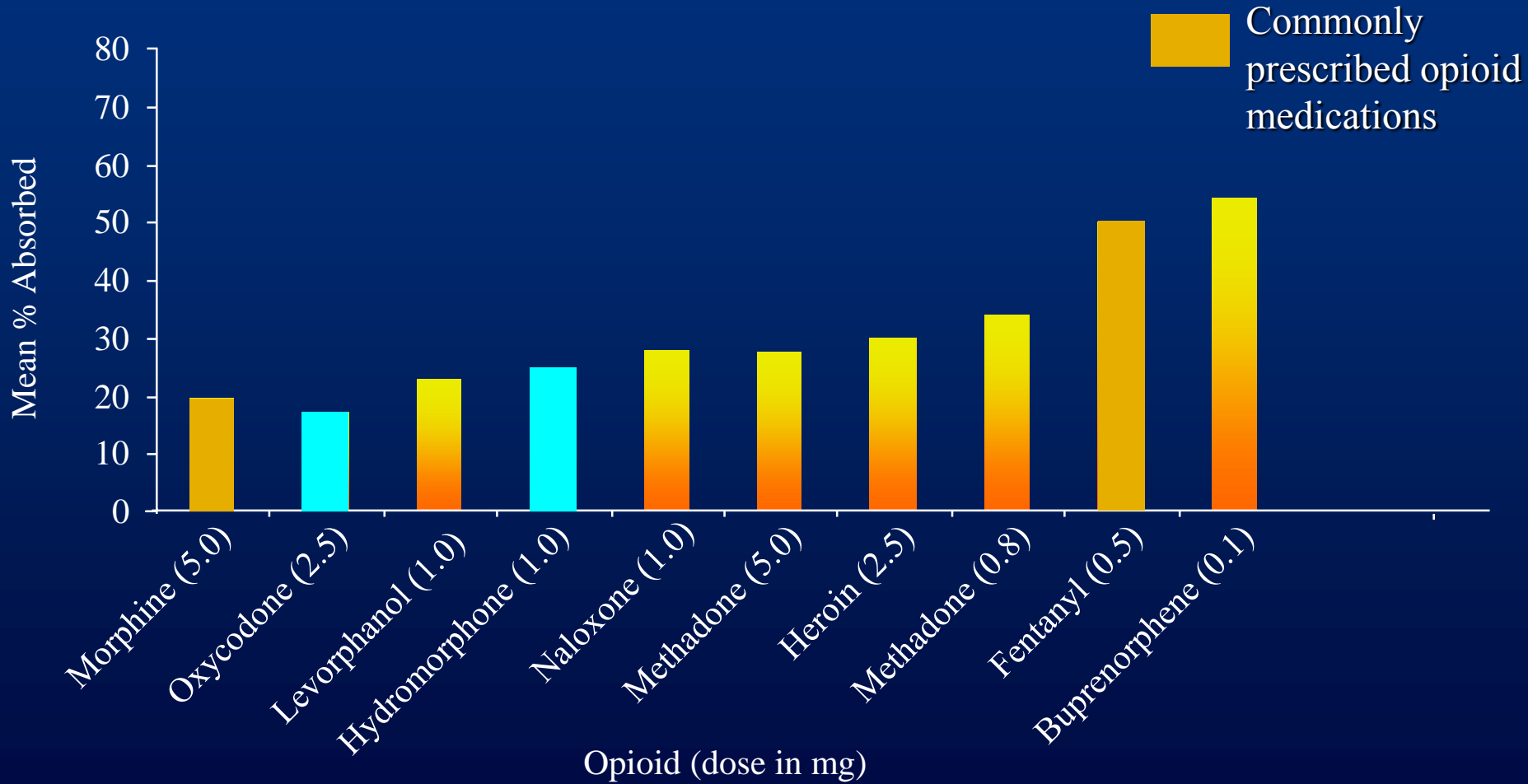
	Mu	Delta	Kappa
Endogenous Ligand	Endorphins	Enkephalins	Dynorphins
Selective Agonist	Morphine		
Effector	cAMP G protein opens K⁺ channel	cAMP G protein opens K⁺ channel	G protein closes Ca²⁺ channel
Subtypes	1 and 2	1 and 2	1, 2, and 3

Opioid characteristics differ

- Metabolite profile*
 - Pro-drugs
 - Toxic breakdown products
- Clearance*
- Fat solubility*
- μ -Receptor affinity*
- Degree of serum protein binding
- Cross reactivity with other receptors
 - NMDA

Lipophilicity

Absorption of Opioids From Oral Mucosa



Adapted from Weinberg DS, et al. *Clin Pharm Ther.* 1988;44:337.

μ -Receptor Affinity

Pure agonists

- Preferred agents - especially for cancer pain
- Many different agents available in the US
- Tramadol - not officially an opioid
 - weak mu agonist
 - monoamine reuptake inhibitor

Opioid Selection

Pure agonists

- Normal release preparations
 - MSO₄
 - Oxycodone
 - Hydromorphone
 - Fentanyl
 - Methadone
 - Levorphanol
 - Oxymorphone
 - Meperidine ☹️
- Controlled release preparations
 - MSO₄
 - Oxycodone
 - Fentanyl
 - Hydromorphone (discontinued...)
 - Methadone

Try to stay with the same opioid!

NOT Recommended

- Mixed agonist-antagonists
 - pentazocine, butorphanol, nalbuphine, dezocine
 - compete with agonists → withdrawal
 - analgesic ceiling effect
 - high risk of psychotomimetic effects

Metabolism & Clearance

Logistics...

Available Formulations

Combined opioid/non-opioid preparations

- Available formulations
 - Codeine → Tylenol #3 & #4
 - Hydrocodone → Lorcet, Lortab, Vicodin, Vicoprofen
 - Propoxyphene → Darvon, Darvocet
 - Oxycodone → Percocet, Percodan
- Potential non-opioid toxicity
 - Hepatotoxicity
 - Nephrotoxicity
- Ceiling conferred by non-opioid
- Limitation on choice of non-opioid

Opioids

Nonoral dosing

- IV/SC
 - MSO₄
 - oxymorphone
 - levorphanol
 - hydromorphone
 - fentanyl
 - meperidine ☹️
 - methadone
- Transmucosal
 - fentanyl

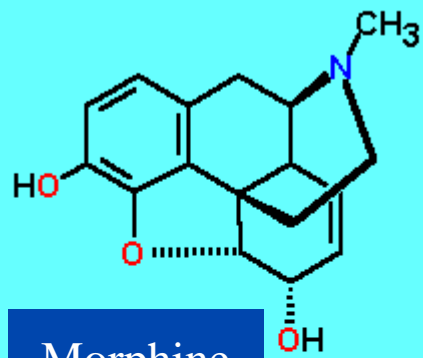
Opioids

Nonoral dosing

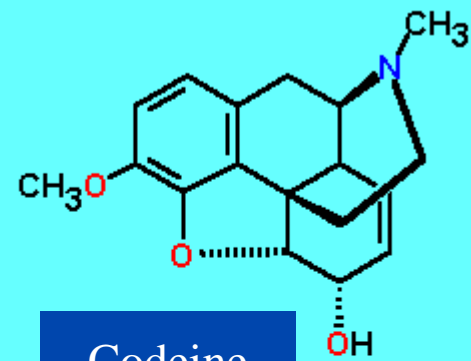
- Transdermal
 - fentanyl
- Suspensions (PEG use)
 - MSO₄
 - oxycodone
 - IV fentanyl
- Rectal suppositories
 - MSO₄
 - oxymorphone

Opioids Derivation

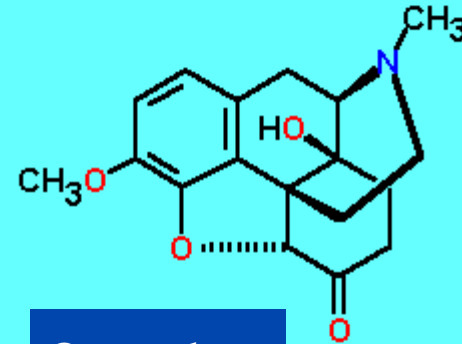
- Naturally occurring
- Semi-synthetic
- Synthetic



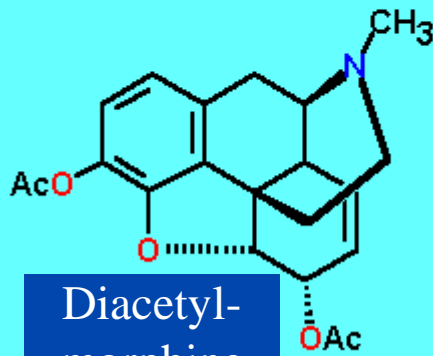
Morphine



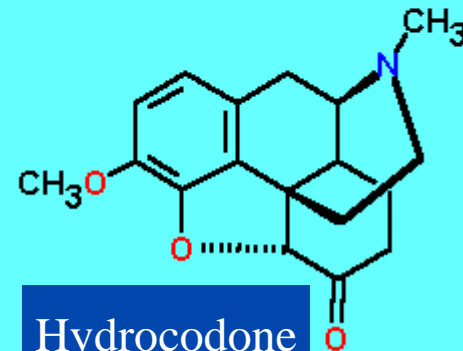
Codeine



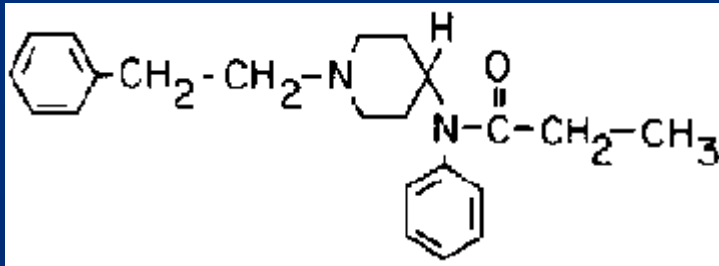
Oxycodone



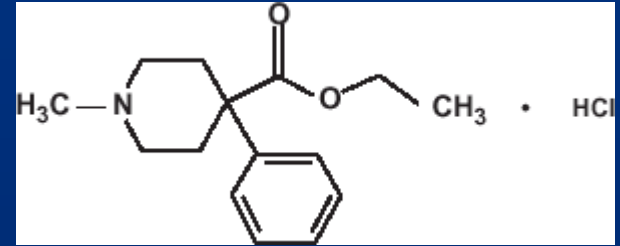
Diacetyl-
morphine



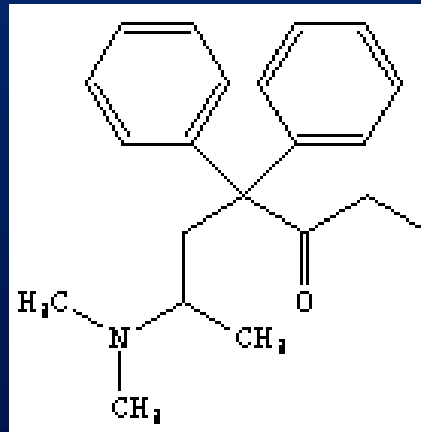
Hydrocodone



Fentanyl



Meperidine



Methadone

Topicals

- Desirable systemic toxicity profile
- Evidence inconclusive in cancer
 - Lidocaine patch ineffective for post-surgical cancer pain¹
 - Baclofen, amitriptyline HCL, and ketamine gel “somewhat” effective for CIPN (p=0.053)²

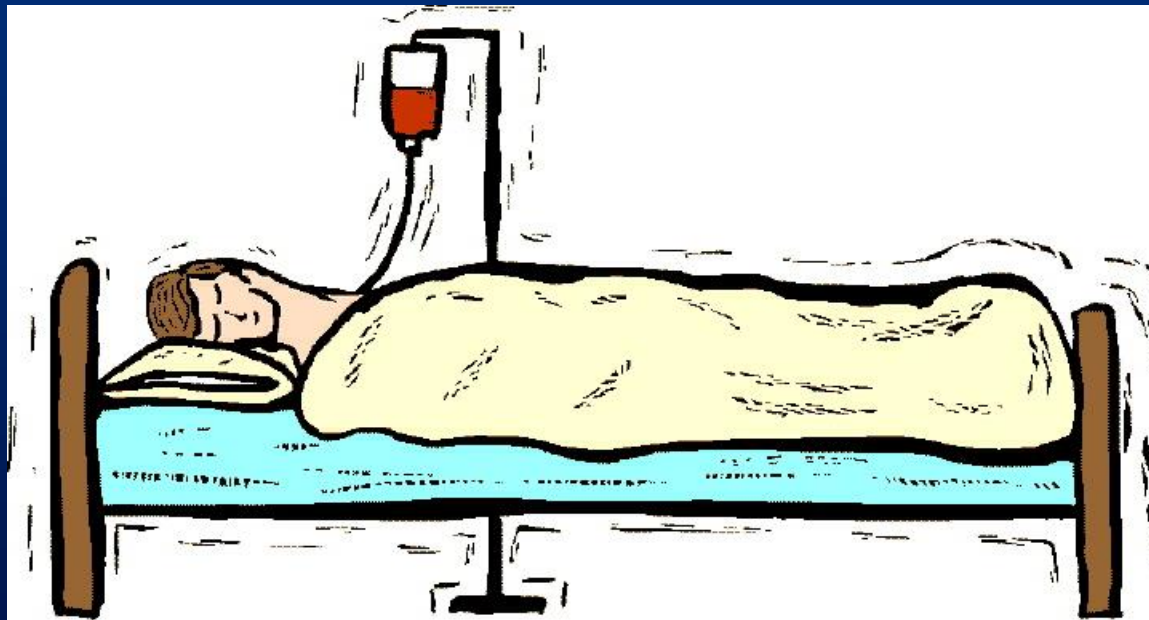
1. Cheville AL, Sloan JA, Northfelt DW, et al. Use of a lidocaine patch in the management of postsurgical neuropathic pain in patients with cancer: a phase III double-blind crossover study (N01CB). *Support Care Cancer*. Apr 2009;17(4):451-460.
2. Barton DL, Wos EJ, Qin R, et al. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy-induced peripheral neuropathy: NCCTG trial N06CA. *Support Care Cancer*. Jun; 19(6):833-841.

Opiophobia

“failure to administer legitimate opioid analgesics because of a fear of the power of these drugs to produce addiction.”

Morgan, J.P., & Puder, K.S. 1989. Postoperative analgesia: variations in prescribed and administered opioid dosages. In C.S. Hill Jr. & W. S. Fields (Eds.), Advances in pain research and therapy (Vol. II). New York: Raven Press.

What cancer patients have taught us about opioids



Opioid Therapy for Nonmalignant Pain: Case Series

AUTHOR	PT. #	OPIOIDS	DAILY DOSE EQUIVALENT	DURATION
Taub (1982)	313	Mixed	10-20 mg po methdone	Up to 6 yrs.
Tennant & Uelman (1983)	22	Not Stated	Not Stated	Not Stated
Portenoy & Foley (1986)	38	Mixed	10-20 mg IV Morphine	6 mos. - 10 yrs.
Portenoy (1992)	20	Mixed	10-20 mg IV Morphine	6 mos. - 10 yrs.
Tennant et al. (1988)	52	Mixed	10-240mg po methadone	ave. >12yr
Zenz et al. (1992)	100	Morphine, Buprenorphine, Dihydrocodeine	20-2000mg Morphine	Mean 224

Opioid Trials

- Establish ground rules
 - Designate pharmacy
 - Sole provider
- Think of it as a diabetic or antihypertensive
- Dose to Effect or Side effect
 - NO Ceiling Effect
- Ongoing outcome assessment

Pain Assessment

- Measurement Tools

- Likert - type scales
- Visual analogue scales
 - poor inter-rater reliability
 - good intra-rater reliability



- Assess variability

- pain “on average”
- pain “at worst”
- pain “at least”
- pain “right now”



Iatrogenic addiction

- True incidence unknown
- Signs & symptoms - 5 Cs
 - impaired **C**ontrol over drug use
 - **C**ompulsive use
 - **C**ontinued use despite harm
 - **C**raving
 - **C**hronic

Differences Between a Chronic Pain Patient and Drug Seeking Behavior (Addicted Patient)

Pain Patients

1. Not out of control with medications
2. Medications improve quality of life
3. Will want to decrease medication if side effects are present

Addicted Patient

1. Out of control with medications
2. Medications cause decreased quality of life
3. Medication continues or increases despite side effects

Differences Between a Chronic Pain Patient and Drug Seeking Behavior (Addicted Patient)

Pain Patients

4. Concern about the physical problem
5. Follows the contract for the use of the opioids
6. Frequently has medicines left over

Addicted Patient

4. Unaware or in denial about any problems
5. Does not follow the contract for use of the opioids
6. Does not have medicines left over, loses prescriptions, and always has a “story”

Thank you for your attention

- Questions?