

Pharmacotherapeutic Considerations in Treating Cancer Pain *Focus on Opioids*

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Disclosures

- This lecture is NOT specific to the Dept. of Veterans Affairs Institutions or any other Federal Institution.
- Information provided may be applied to any clinical setting as each attendee deems appropriate.
- Speakers Bureaus
 - Janssen, Merck, Ortho-Biotech, Ortho-McNeil, Pfizer, Purdue Pharma.



Overview of Topics

- Epidemiology
- Adjuvant Medications
- Acute vs. Chronic Pain
- Tolerance vs. Addiction
- Review of Opioids/Opiates
 - chemistry
 - therapeutics
 - advantages/disadvantages
 - costs



Cancer Pain

Epidemiology

- **Cancer pain is highly prevalent**
 - **30%-50% of those in active therapy**
 - **75%-90% of those with advanced disease**
 - **approximately 25% of those in nursing homes**

(Bernebel et al, 1998; Caraceni et al, 1999; Cleeland et al, 1994; Heim et al, 1993; Portenoy, 1994; Portenoy et al, 1992; Serlin et al, 1995)



Cancer Pain

Inferred Pathophysiology

- **Nociceptive: deemed consistent with apparent degree of tissue injury**
 - **Somatic:** related to ongoing activation of somatic primary afferents
 - **Visceral:** related to activation of primary afferent neurons that innervate viscera
- **Neuropathic: sustained by aberrant somatosensory processing in the peripheral nervous system or CNS**

(Portenoy, 2000)

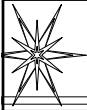


Cancer Pain

Diagnosis: Clinical Considerations

- **Acute or chronic**
- **Nociceptive, neuropathic or mixed pain**
 - **tumor-related** (e.g., metastatic bone disease, nerve compression or infiltration)
 - **treatment-related** (chemotherapy, radiation or surgery)
 - **unrelated to cancer or treatment**

(Portenoy, 2000; Portenoy et al, 1996)

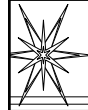


Cancer Pain

Principles of Assessment

- > **Pain History**
 - > chronicity
 - > intensity and severity
 - > pathophysiology and mechanism
 - > tumor type and stage of disease
 - > pattern of pain and syndrome
- > **Physical and Neurologic Examination**
- > **Radiographic Findings**

(Cleeland CS et al. 1992; Jacox et al. 1994; Portenoy et al. 1999; Turk et al. 1994; Wall et al. 1994)

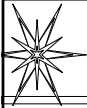


Cancer Pain

Treatment Considerations

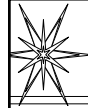
- > **Identify the cause of the pain**
- > **Primary treatment if indicated**
- > **WHO ladder combined with etiology-specific therapies for syndromes**
 - > pharmacological and nonpharmacological interventions
 - > long-acting + short-acting opioids
 - > adjuvant medications for neuropathic pain
 - > NSAIDs and steroids can be helpful when there is an inflammatory component to pain

(Jacox et al. 1994)



Adjuvant Medications for Neuropathic Pain

1. TCA's (amitriptyline)- first line???
2. Elderly (frail) patients TCA vs. SNRIs
3. Tramadol (Ultram®)
4. Gabapentin (Neurontin®)
5. Topiramate (Topamax®)
Oxcarbazepine (Trileptal®)
6. Anti-arrhythmics: Mexiletine (Mexitil®)- ECG



Anti-inflammatory Use in Cancer Pain

- > Traditional NSAIDs (+ protection?)
- > COXIBS
 - > Celecoxib
 - > Rofecoxib
 - > Valdecoxib
- > Steroids



WHO Guidelines for Cancer Pain

GOAL:
Freedom From Pain

STEP 3

Pain Persists

STEP 2

Pain Persists

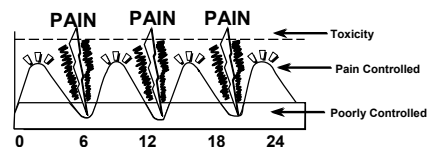
STEP 1

- > **Step 3:** Opioids for moderate-to-severe pain +/- non-opioid +/- adjuvant therapy
- > **Step 2:** Opioids for mild-to-moderate pain +/- non-opioid +/- adjuvant therapy
- > **Step 1:** Non-opioid +/- adjuvant therapy

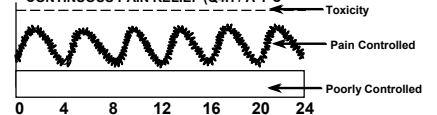
(Adapted from Portenoy et al. 1997)

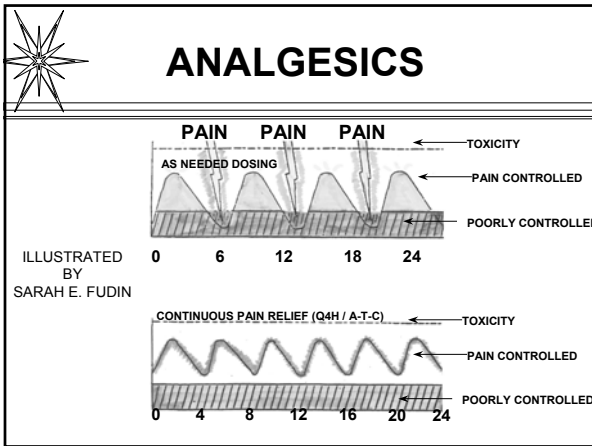
Analgesics

AS NEEDED DOSING



CONTINUOUS PAIN RELIEF (Q4H / A-T-C)





The Terminology of Abuse

- **Tolerance**
 - > Diminished drug effect from drug exposure
 - > Varied types: associative vs. pharmacological
 - > Tolerance to analgesia is seldom a problem in the clinical setting:
 - Tolerance rarely “drives” dose escalation
 - Tolerance does not cause addiction
- **Pseudoaddiction**
 - > Aberrant drug-related behaviors driven by uncontrolled pain
 - > Reduced by improved pain control
 - > Complexities
 - How aberrant can behavior be before it is inconsistent with pseudoaddiction?
 - Can addiction and pseudoaddiction coexist?

(Passik et al., 1998; Passik et al., Portenoy RK, 1996)

Risk Assessment for Addiction

Low Addiction Risk

- Acute pain
- Cancer pain
- Patients without abuse background or psychopathology

Chronic Noncancer Pain

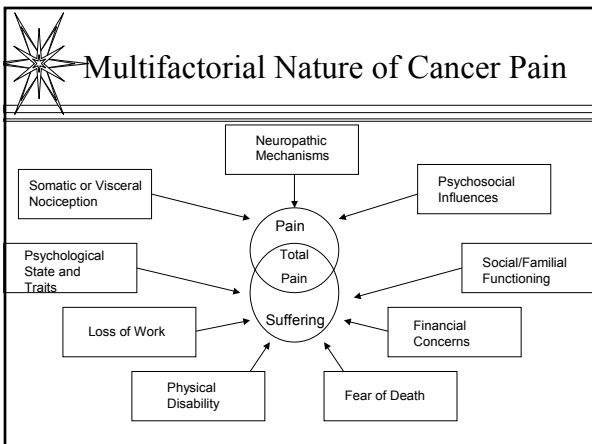
- Probability of addiction is small
 - surveys that include patients with abuse or psychopathology show mixed results
- Predictors of addiction may include
 - history of substance abuse
 - Age
 - personality factors
 - family dynamics and social factors

(Passik et al., 1998; Passik et al., 1998)

Tramadol (Ultram®)

Recent Data Addressing Clinician Concerns

- > Cicero TJ, Adams EH, et al. A postmarketing surveillance program to monitor ultram (tramadol hcl) abuse in the united states. Drug and Alcohol Dependence 57 (1999) 7-22.
- > Petrone D, Kamin M, Olson W. Slowing the titration rate of tramadol hcl reduces the incidence of discontinuation due to nausea and/or vomiting: a double-blind randomized trial. Journal of Clinical Pharmacy and Therapeutics (1999) 24, 115-123.
- > Gassa C, Derby L, Vasilakis-Scaramozza C, Jick H. Incidence of first-time idiopathic seizures in users of tramadol. Pharmacotherapy 2000;20 (6):629-634.



Goals of Therapy for Acute Vs Chronic Pain

Levy, 1985

	<u>ACUTE</u>	<u>CHRONIC</u>
Therapeutic Goal	Pain relief	
Sedation	Often desirable	
Rapid Onset of Effect	Important	
Desired Duration of Effect	2-4 hours	
Timing	PRN	
Dose	Usually standard	
Route	Parenteral / Oral	

Chemical Classes of Opioids

PHENANTHRENES BENZOMORPHANS PHENYLPIPERIDINES DIPHENYLHEPTANES



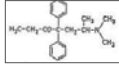
MORPHINE
morphine
codeine
hydrocodone*
hydromorphone*
levorphanol*
oxycodone*
oxymorphone*
buprenorphine*
nalbuphine
butorphanol*
naloxone*



PENTAZOCINE
pentazocine
diphenoxylate
loperamide



MEPERIDINE
meperidine
fentanyl
sufentanil
alfentanil
remifentanyl



METHADONE
methadone
propoxyphene

Rx EXAMPLES >

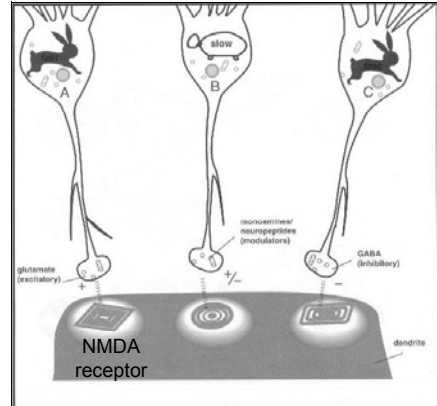
X-SENSITIVITY >

PROBABLE POSSIBLE LOW RISK LOW RISK

*These agents lack the 6-OH group of morphine, possibly decreasing cross-sensitivity within the phenanthrene group.
Reisine T, Pasternak G. Opioid analgesics and antagonists. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed. New York, NY: McGraw-Hill Companies; 1996:521-555.
Willette RE. Analgesic Agents. In: Delgado JN, Remers WA, eds. Wilson and Griswold's Textbook of Organic Medicinal Chemistry, 9th ed. JB Lippincott Company, Philadelphia, Pa. 1991:629-654.

Courtesy of Dr. J. Fudin 2003

Neurotransmitter Signals



Narcotic - Induced Side Effects in Chronic Pain Syndrome

- > Sedation
- > Constipation
 - > Stool softener
 - > Bulk laxative
 - > Stimulant laxative
 - > Motility agents (metoclopramide)
- > Macrolides
- > Osmotic Agents

General Principals / Specific Rx

- > morphine
- > hydromorphone (Dilaudid®)
- > fentanyl (Duragesic®)--dosing
- > levorphanol (Levo-Dromoran)
- > codeine
- > oxycodone (alone and combination)
- > methadone (Dolophine®)
- > meperidine Demerol® (Sphincter of Oddi) - ???
 - > Ref. 92: Isenhower HL, Mueller BA. 1998

QUESTIONS?

www.paindr.com