Pharmacotherapy of Pain Management in Palliative Care Part I

Mark Holtsman, Pharm.D.
Co-Director, Inpatient Pain Service
Clinical Professor
Anesthesiology and Pain Medicine
UC Davis Medical Center

October 16, 2019

What are the risks to this patient from Uncontrolled Pain?

- Decreased Mobility
- Decreased Pulmonary Function
  - Pneumonia
- Hypercoagulability
  - DVT, PE, MI
- Depression
- Anxiety

Portenoy RK et al. Pain 1999;81(1-2):129-134
Bennett, D et al. P&T 2005 30(5):296-301
Kehlet H. Br J Anaesth 1997;78:606-617

New Developments in Palliative Care Pharmacotherapy

- Pain Management Tools
  - Pain Diary
  - Equianalgesic Conversion Tools
- Advances in Breakthrough Pain Treatment
  - Determine Effective Opioid Doses For Episodic Pain
- Opportunities for Pharmacists
  - Suggest analgesic dose titration for uncontrolled pain
  - Suggest opioid conversion doses when needed
  - Suggest optimal opioid breakthrough pain dose

How Do We Measure Pain?

- Ask!
  - Descriptive terms
    - Burning
    - Shooting
    - Pressure
    - Gnawing
    - Tightness
    - Throbbing
- Does not give information as to degree or intolerability of pain

Pain Assessment in Palliative Care

- Mechanism of Pain – ask questions to determine
  - Inflammatory?
  - Visceral?
  - Neuropathic?
  - Spasm?

What are the questions we need to ask to determine analgesic efficacy?

- Pain Score
  - Pain Score before medication?
  - Pain Score after medication?
- Sleep
  - Does Pain interfere with sleep?
- Mobility
  - Pain before ambulation/deep breathing?
  - Pain after ambulation/deep breathing?
- Diet
  - What percent of diet was eaten?
  - When did patient have their last bowel movement?
- Side effects

What are the questions we need to ask to determine best analgesic?

- Pain Description
  - Throbbing?
  - Burning?
  - Pins and Needles?
  - Tightness?
- What relieves pain?
  - Document OTC analgesics (acetaminophen/NSAID)
- What triggers pain?
- What side effects/responses has patient had in past with medication?
  - Disclosure/Consent

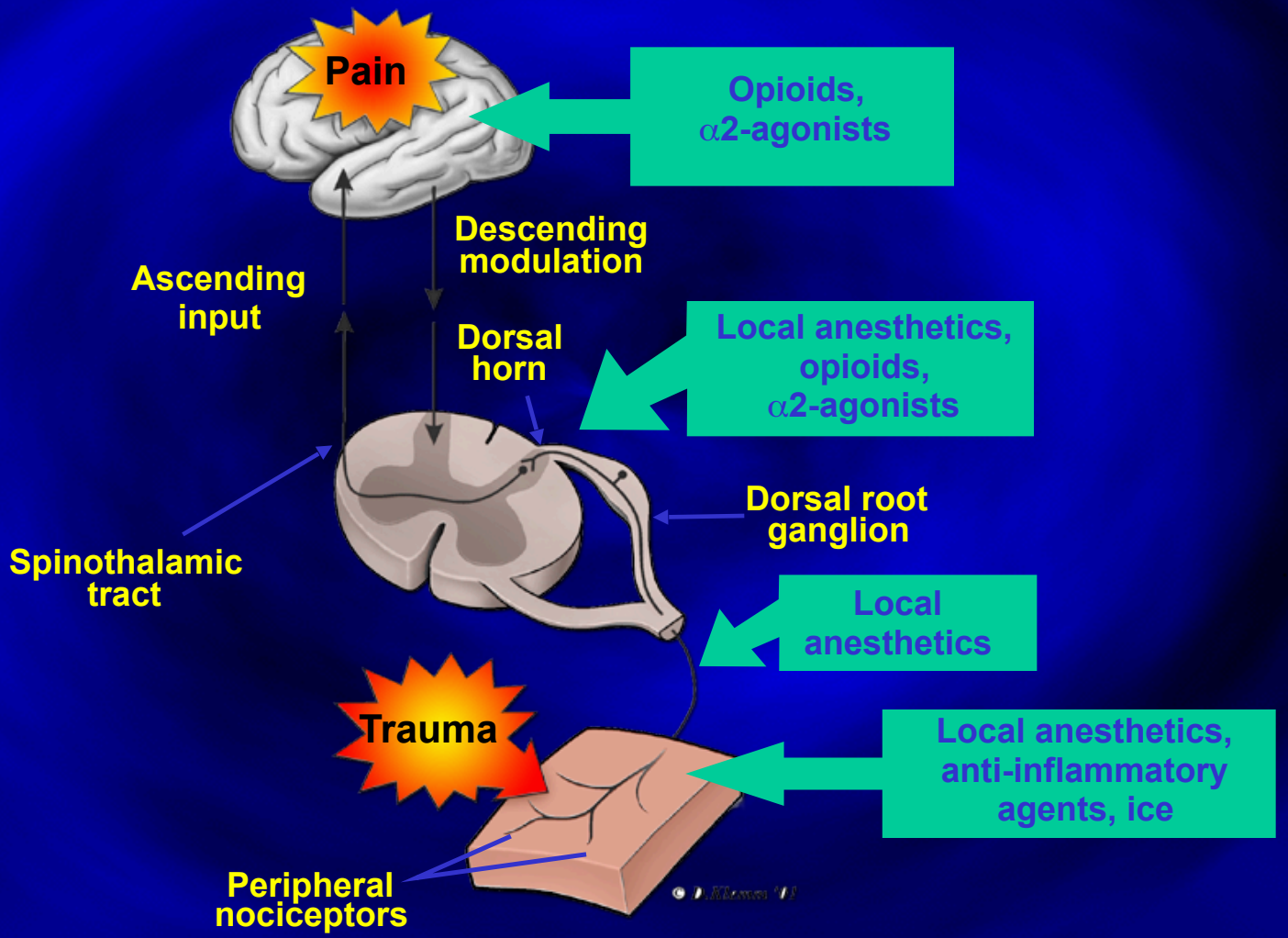
What are the questions we need to ask the patient?

- What functional goals does the patient want to reach?
  - Bronze Medal
    - Do Chores Around House
    - Complete a Physical Therapy Session
  - Silver Medal
    - Work Part-Time
    - Exercise at the Gym
  - Gold Medal
    - Work Full-Time
    - Participate in Favorite Sport Again

Measuring Pain Scores and Function Provides Advantages

- Has meaningful outcomes
- Allows clinician to titrate doses of analgesics up or down based on patients function
- Creates a system for documenting patients progress with therapy.
- Creates a system for documenting discussion of risks/benefits of therapy.
- Creates a system that helps minimize diversion.

Analgesic Interventions and the Transmission of Pain



Adapted with permission from: Kehlet H, Dahl JB. *Anesth Analg.* 1993;77:1049.

Developing a Pain Control Plan

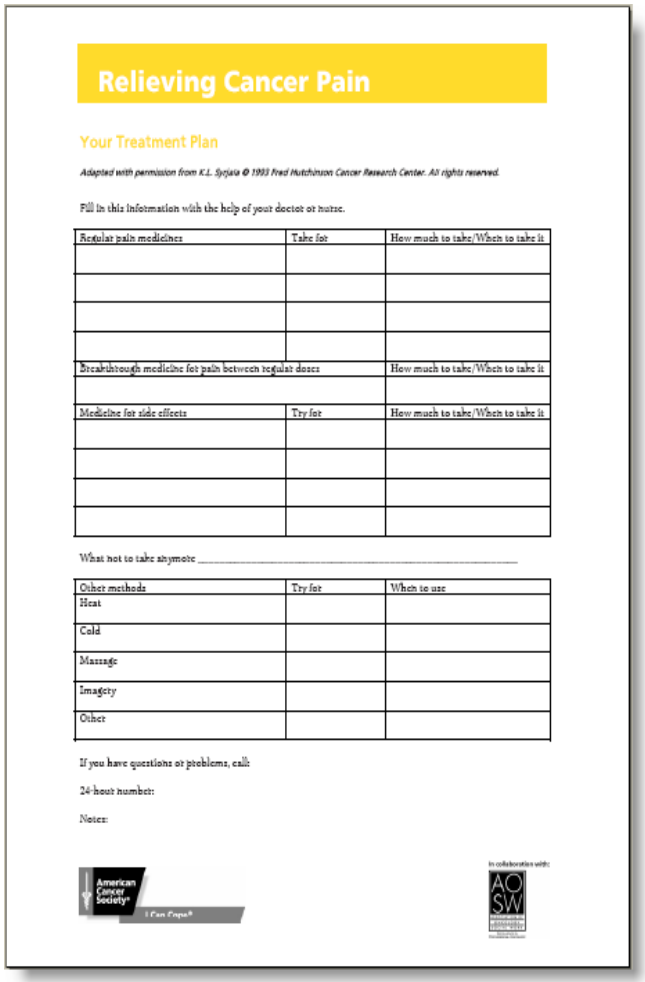
- The person who has the pain is an important member of the health care team; work together to develop a plan that includes…

•When to take medicines & how much to take

•When to use other therapies

•Reports of pain & pain relief

•Name and number of contact person for questions or problems



Relieving Cancer Pain

Your Treatment Plan

Fill in this information with the help of your doctor or nurse.

Regular pain medicines	Take for	How much to take/When to take it
Breakthrough medicine for pain between regular doses		How much to take/When to take it
Medicine for side effects	Try for	How much to take/When to take it

What not to take anymore _____

Other methods	Try for	When to use
Heat		
Cold		
Massage		
Imagery		
Other		

If you have questions or problems, call:

24-hour number:

Notes:

American Cancer Society

I Can Cope

In collaboration with: AOSW

Pharmacologic Approach to Pain Relief

- Non-opioids
  - NSAIDS
  - Adjuvant Analgesics
  - Antidepressants
  - Local anesthetics
    - Bupivacaine, lidocaine, tetracaine, ropivacaine
- Opioids
    - Morphine, fentanyl, oxycodone, hydromorphone

Adjuvant Analgesics

Adjuvant Analgesics for Neuropathic Pain	
CLASS	EXAMPLES
Anticonvulsants	gabapentin, valproate, phenytoin, carbamazepine, clonazepam, topiramate, lamotrigine, pregabalin
Antidepressants	amitriptyline, desipramine, nortriptyline, mirtazapine, duloxetine
Local Anesthetics	mexiletine, lidocaine
Corticosteroids	dexamethasone, prednisolone
α-2 Adrenergic Agonists	tizanidine
NMDA-Receptor Agonists	dextromethorphan, ketamine
Topicals	lidocaine, lidocaine/prilocaine, capsaicin
Miscellaneous	baclofen, calcitonin, methylphenidate

Opioid Dose Titration

- Increase Opioid Dose based on response to previous dose
  - Pain Reduction Less Than 50% -Repeat Same Dose
  - No Pain Reduction – Double the Dose
- Reassess Pain
  - 15 minutes after IV dose
  - 60 minutes after oral dose
- Stop Increasing Dose When
  - patient has adequate analgesia
  - patient has intolerable side effects

Miaskowski, C. et al. (2005) (3) 41-46. Guideline For The Management of Cancer Pain in Adults and Children. American Pain Society. Indelicato, RA, Portenoy RK. J Clin Oncol 2002 20(1):348-352

How fast can you titrate opioids?

Opioid	Half-life (hrs)
– Morphine	2-3.5
– Oxycodone	2-3
– Fentanyl IV	2-3.5
– Transdermal Fentanyl	17

Inturrisi C. The Clinical Journal of Pain 2002;18:S3-S13, Duragesic PI 2001,

Opiate Pharmacology

- Opiates with Active Metabolites
  - Morphine to M6G and M3G
  - Codeine to Morphine
  - Oxycodone to Oxymorphone
  - Oxymorphone to 6-OH-OXM
  - Meperidine to Normeperidine

Davison SN. Am J Kidney Dis 2003 Dec; 42(6):1239-47

Increased Plasma Morphine Metabolites in Terminally Ill Cancer Patients with Delirium

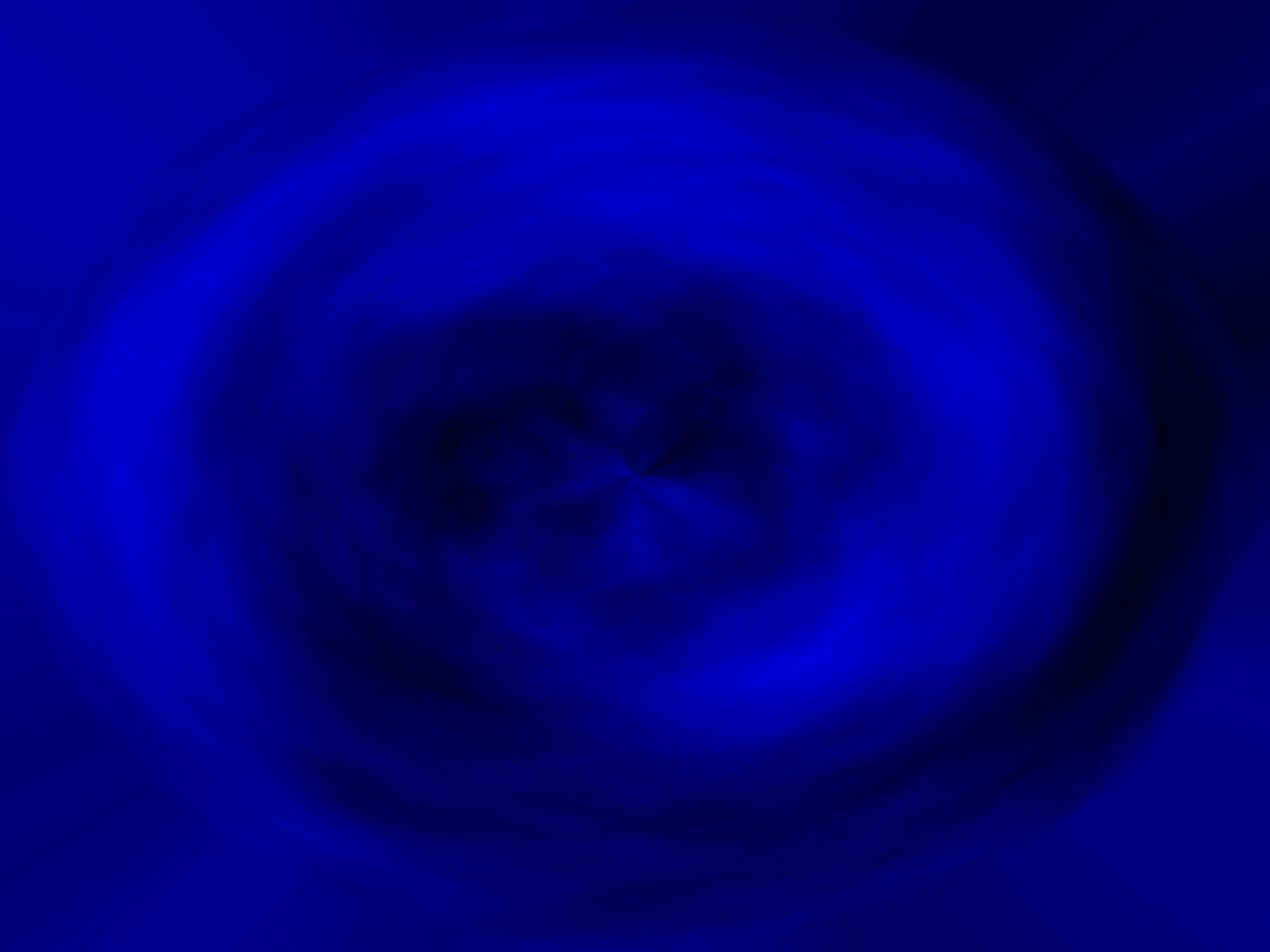
- Investigators looked at 131 consecutive hospice patients
- 8 patients had blood samples drawn before and after development of delirium
- Plasma concentrations of M-6-G and M-3-G significantly increased after development of delirium within the same patient.

Morita, T et al. J Pain Symptom Manage 2002:23:107-113

Potential Mechanisms of Morphine Metabolite Toxicity

Morphine-6-Glucuronide	Morphine-3-Glucuronide
• **Drowsiness**	• Agitation
• Nausea and Vomiting	• **Myoclonus-Seizures**
• Coma	• Hyperalgesia
• Respiratory Depression	• **Delirium**

Mercadante,S *Palliative Medicine* 1999;13:95-104



What is the maximum dose of morphine?

- Pharmacokinetic variability
- Pharmacodynamic variability
- Interpatient Variability with Cesarean Section
  - Morphine PCA (range 0.6 - 5.2 mg/hr)
  - Morphine IM (range 0.75 - 3.5 mg/hr)

Eisenach, et al. Anesthesiology 1988 68:444-448

Developments in the Pharmacogenetics of Pain Management

- Genetic Variations in Endogenous Opioid System
  - Single nucleotide polymorphisms in mu opioid receptor gene.
  - Greater than 20 SNP producing amino acid changes.
  - Most common SNP is A118G.

Somogyi AA et al. Clin Pharmacol Ther. 2007;81(3):429-444

Developments in the Pharmacogenetics of Pain Management

- Genetic Variations in metabolizing enzymes
  - UGT
  - CYP2B6. Greater than 100 SNP identified.
  - CYP3A4
  - CYP2D6
    - Extensive Metabolizers
    - Intermediate Metabolizers
    - Poor Metabolizers
    - Ultra Rapid Metabolizers

Somogyi AA et al. Clin Pharmacol Ther. 2007;81(3):429-444
Totah RA et al. Anesthesiology 2008;108:363-374

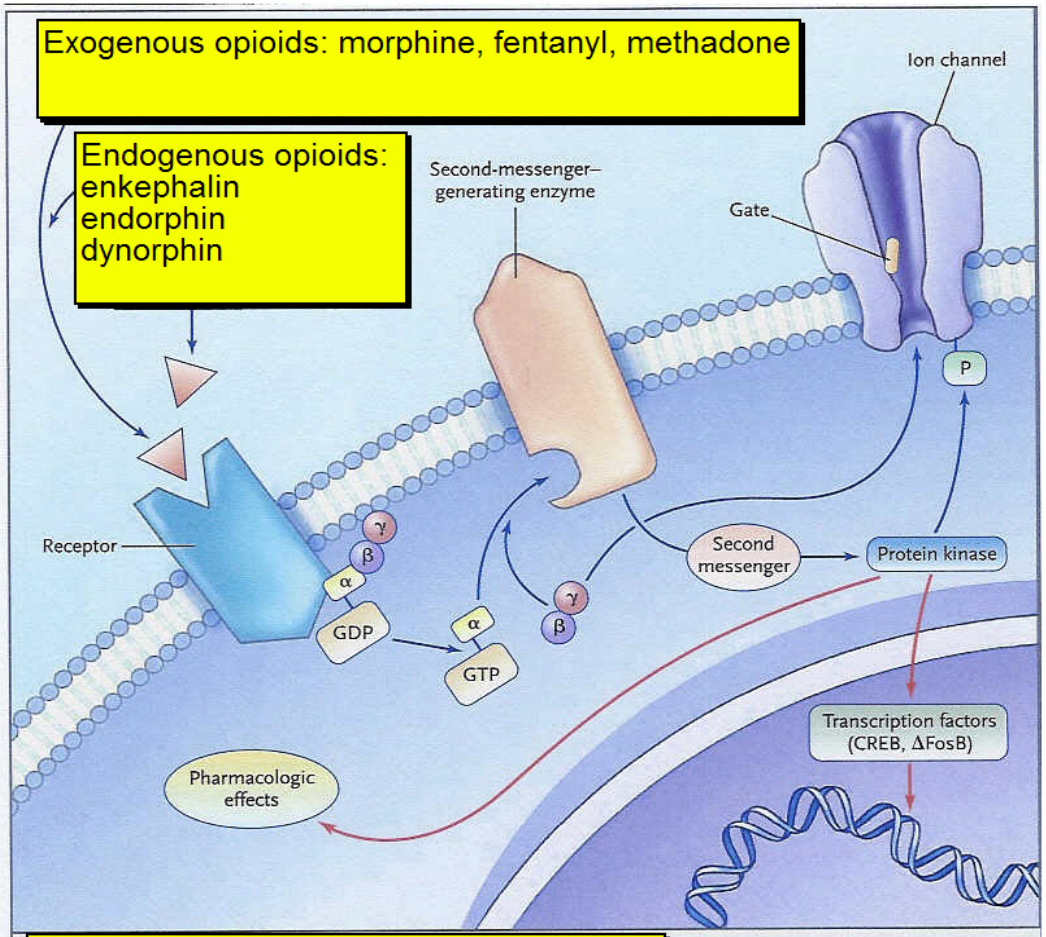


Figure 1. Mechanism of Action of Opioids

Metabotropic (G-protein–coupled) receptors mediate slow synaptic transmission. G proteins are trimeric structures composed of two functional units: an α subunit that catalyzes GTPase activity (converting guanosine triphosphate [GTP] to guanosine diphosphate [GDP]), and a β–γ dimer that interacts with the α subunit when bound to GDP (inactive state). The binding of the agonist activates a nearby G protein. The α subunit bound to GTP subsequently dissociates from its β and γ subunits. Both can activate or inhibit enzymes (adenylyl cyclase or phospholipase C) that synthesize second messengers such as cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate, inositol triphosphate, and diacylglycerol. In addition, the β and γ subunits directly regulate calcium-, sodium-, and potassium-ion channels. Second messengers also regulate ion channels by activating protein kinases, which phosphorylate (P) such channels. Protein kinases induce pharmacologic effects and produce changes in transcription factors such as cAMP-responsive element–binding protein (CREB) and ΔFosB. Opioids bind to opioid receptors (which reduce cAMP levels),

Cami J et al. N Engl J Med 2003;349:975-86

Morphine

- Usual Starting Doses
  - IV 2-6 mg q 1-4 hrs
  - PO 5-30 mg q 2-6 hours
- IV Onset / Duration Oral Onset
  - 15 min / 2-4 hours 30-60 min
- Pearls
  - Has most potential for histamine release and hypotension/ bradycardia (greatest effect in hypovolemia)
  - Metabolites can accumulate in renal dysfxn leading to respiratory depression / prolonged sedation / myoclonus
  - Can decrease myocardial oxygen demand
  - Lack of ceiling effect

Fentanyl

- Usual Starting Doses
  - IV 25-100 mcg q1-2 hours
- IV Onset / Duration
  - 5 min / 1-2 hours
- Pearls
  - relatively short-acting → allows for rapid IV titration
    - Good option for short procedures (ex: dressing changes)
  - ↑↑↑ duration of analgesia and sedation w/ long-term continuous infusion or transdermal use
  - Preferred agent in renal dysfxn due to lack of active metabolites
  - Least amount of histamine release.
    - May be preferred agent in cardiac patients (less hypotension)

Oxycodone

- Usual Starting Doses
  - Immediate release (IR): 5-10 mg po q3-6 hrs
  - Sustained release (SR):10-20 mg po q8-12 hrs ATC
- Onset/Duration
  - IR: 30-60 min / 3-6 hrs
  - SR: 1-2 hours / 8-12 hours
- Pearls
  - Available as PO and recently IV in Japan
  - Elixer 20 mg/ml has rapid onset
  - SR products can not be crushed/administered via NG/G-tube

Palliative Care Terminology

- Tolerance
  - Diminished drug effect from drug exposure
  - Varied types: associative vs pharmacologic
  - Tolerance to side effects is desirable
  - Tolerance to analgesia seldom a problem in the clinical setting
    - Tolerance rarely “drives” dose escalation
    - Tolerance does not cause addiction

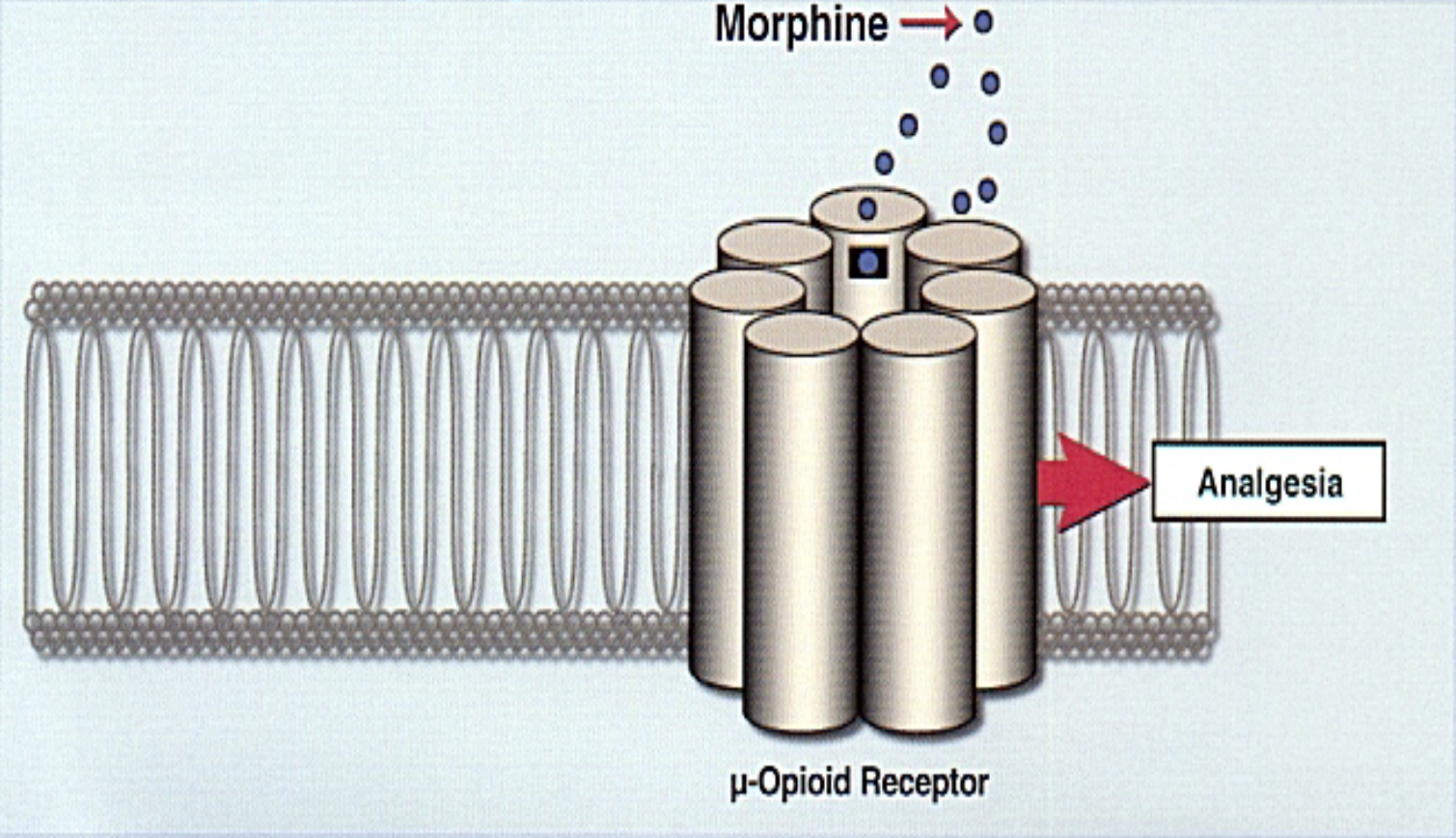
Food and Drug Administration Definition of Opioid Tolerance

- Opioid Tolerance occurs after a patient has taken the equivalent of 60 mg per day of oral morphine for one week.
- This equates to:
  - 40 mg oral oxycodone/day
  - 25 mcg/hr transdermal fentanyl

NMDA-Enhanced Analgesia

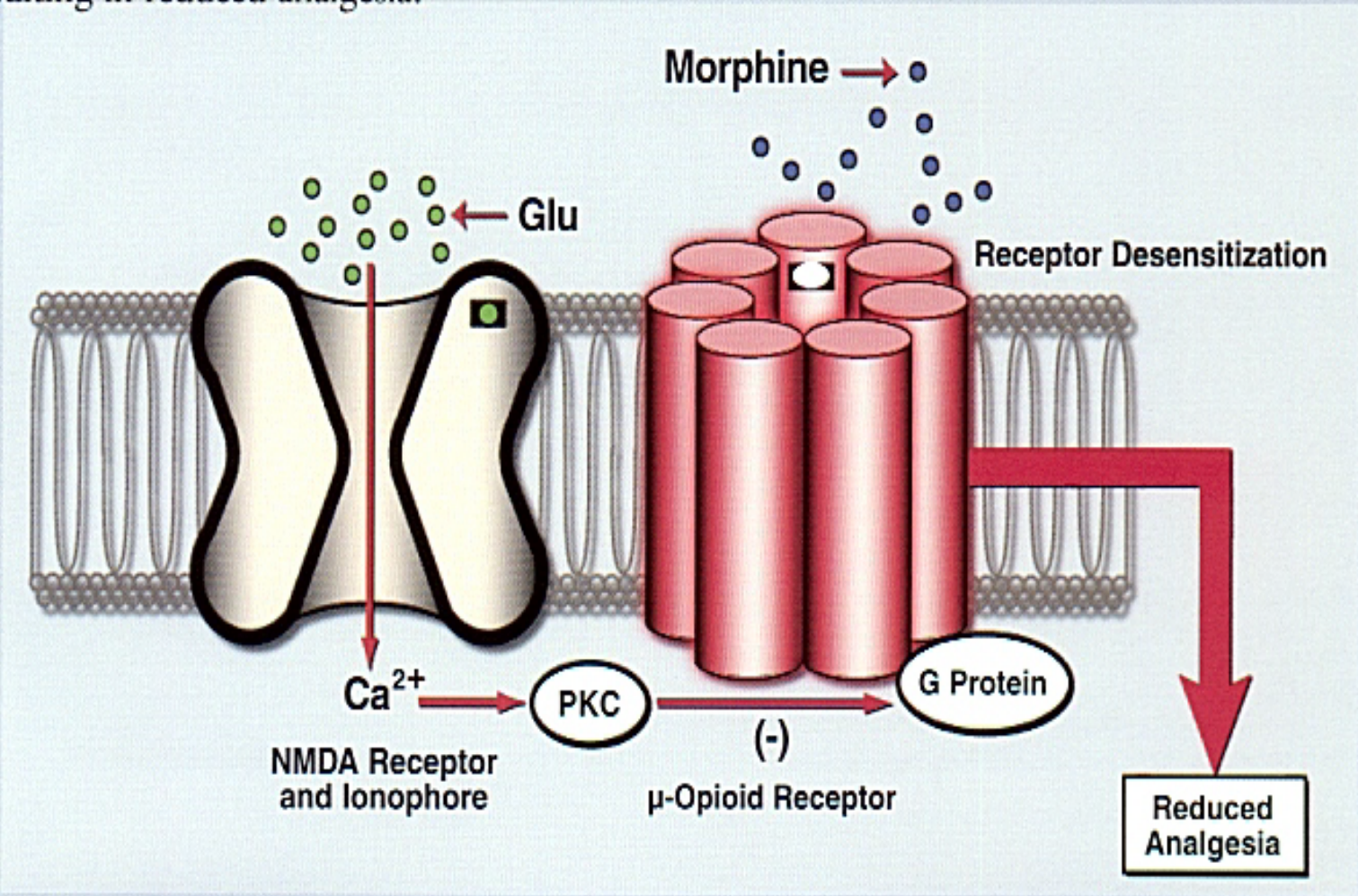
Opioid analgesia: Mechanism of action

The primary mechanism of action of opioid analgesics, such as morphine, involves activation of mu-opioid receptors. When mu-opioid receptors are activated, transmission of painful stimuli is blocked, producing analgesia.



Reduction of analgesia

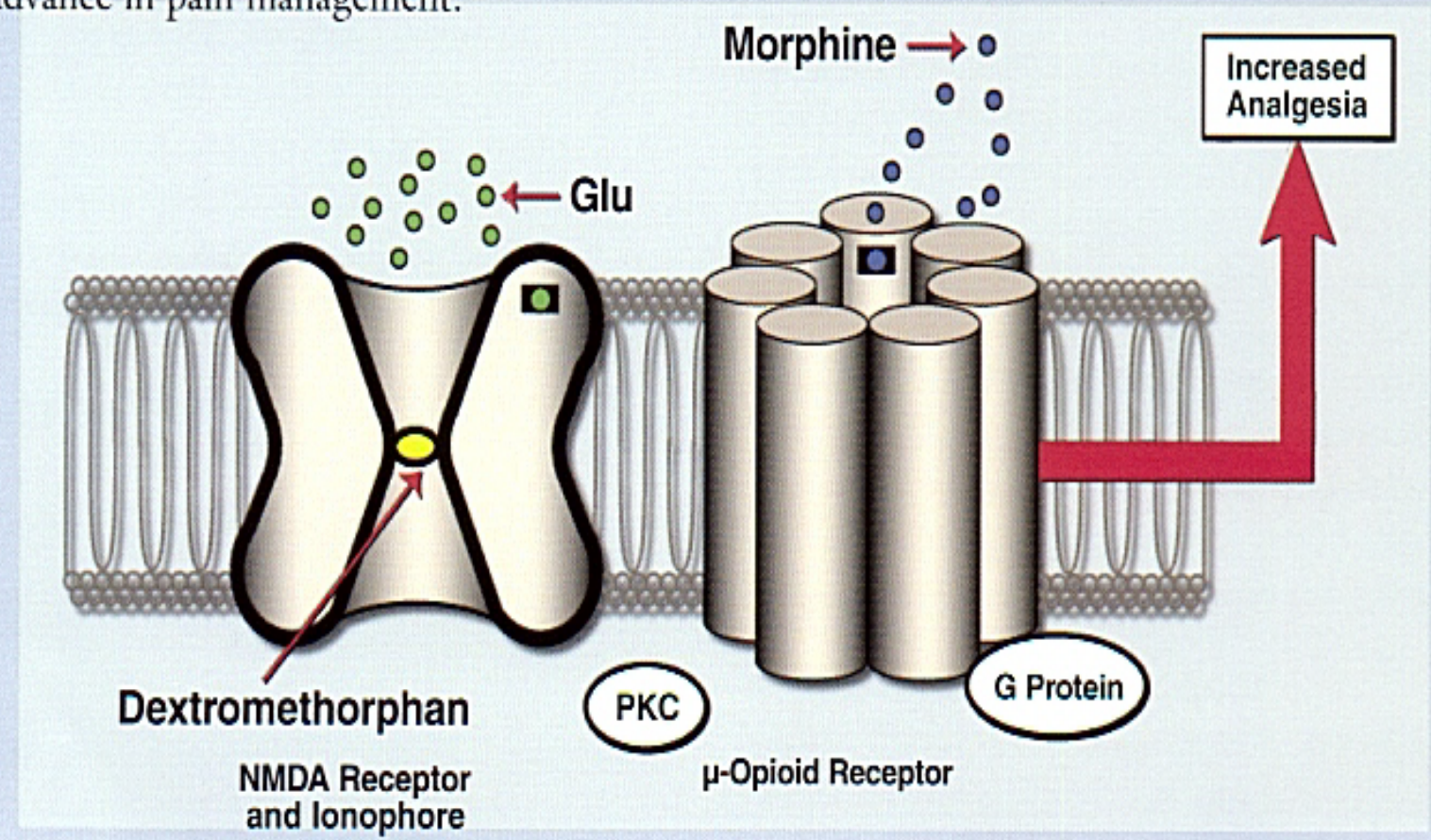
The activation of mu-opioid receptors triggers an intracellular response from *N*-methyl-D-aspartate (NMDA) receptors in the brain and spinal cord. Activated NMDA receptors activate the enzyme protein kinase C (PKC), which desensitizes mu-opioid receptors, resulting in reduced analgesia.



The NMDA-receptor antagonist: Maximizing potential analgesia

As shown in a number of studies,[1-4] the addition of a noncompetitive NMDA-receptor antagonist, such as dextromethorphan, inhibits the activation of PKC and, in turn, prevents the desensitization of mu-opioid receptors to morphine.

Simultaneously blocking the NMDA-receptor-mediated activation of PKC and activating the mu-opioid receptor with morphine increases analgesia, representing an important advance in pain management.



Ketamine Pharmacology

- Non-competitve antagonist NMDA
- Active Metabolite
  - Norketamine
- Norketamine has 1/3 the potency of ketamine at NMDA receptor

Grant et al. Brit J Anesthesia 53:805-809, 1981
Ebert et al. European J Pharmacology 333:99-104, 1997

Ketamine Pharmacology

- Racemic Mix of S(+) and R(-) Ketamine
- S(+) isomer 3-4X more potent as analgesic
- S(+) isomer produces less psychomimetic effects at equianalgesic doses

Schmid et al. Pain 82 (1999) 111-125

Ketamine Pharmacology

- Nicotinic/Muscarinic Receptors
- Sodium Channel Blocker
- Mu opioid receptor agonist-antagonist
- Kappa opioid receptor agonist-antagonist
- Alpha-2 agonist
- 5-hydroxytrypamine agonist

Schmid et al. Pain 82 (1999) 111-125

Ketamine Pharmacokinetics

- Intravenous Bioavailability is 93%
- Oral Bioavailabilty is 16%
- Ketamine undergoes significant first pass hepatic metabolism
- As a result, Norketamine levels are 2-3X higher after oral ketamine than after IV ketamine

Grant et al. Brit J Anesthesia 53:805-809, 1981
Ebert et al. European J Pharmacology 333:99-104, 1997

Ketamine Pharmacokinetics

- After continuous ketamine infusion, blood levels of ketamine and norketamine reach a constant ratio of 3:1

Eide et al. Pain 61:221-228, 1995
Ebert et al. European J Pharmacology 333:99-104, 1997

Ketamine Oral Dosing

- Researchers hypothesized that effective oral dose was about 33% of effective IV dose.
- Series of three patients
  - Patient one -30%
  - Patient two – 37.5%
  - Patient three- 37.5%

Fitzgibbon et al. J Pain Symptom Manage 23:165-170 2002

Ketamine Oral Dosing

- Ketamine IV 0.1 – 0.2 mg/kg q 15 minutes
  - Monitor for pain reduction/side effects
  - Start maintenance infusion based on response to test dose.
- Ketamine Oral 0.08 mg/kg q 1 hour
  - Monitor for pain reduction/side effects
  - Start maintenance dose based on response to test dose
- Lorazepam or clonazepam is usually initiated along with first dose of ketamine.

Ketamine Oral Dosing

- Patient at UCDMC on 480 mg/day IV Ketamine
- Converted to Ketamine 50 mg po q 8 hrs
- Analgesia continued to be effective on new oral dose.

Ketamine Dosing Challenges

- Prevent ketamine psychotomimetic effects
  - clonazepam, lorazepam, haloperidol
- Ketamine Availability
  - Injection, Solution: 10 mg/ml, 50 mg/ml, 100 mg/ml
- Ketamine Stability/Compatability
- Anticipate Need for Opioid Dose Reduction
  - Usual reduction is about 33%

Nonopioid Analgesics

- Acetaminophen
  - Minimal anti-inflammatory effects
  - Fewer adverse effects than other nonopioid analgesics
  - Adverse effects
    - Renal toxicity
    - Risk for hepatotoxicity at high doses
      - Increased risk with liver disease or chronic alcoholism
  - No effect on platelet function

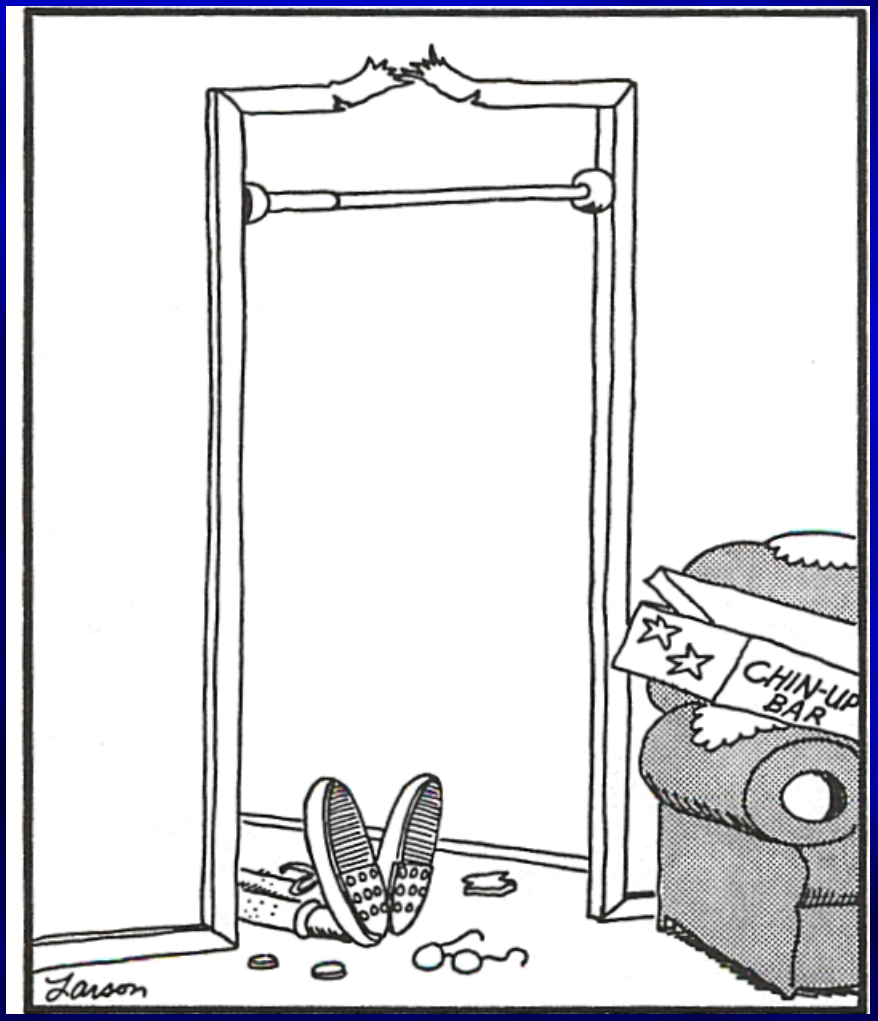
Acetaminophen

- Usual Starting Doses
  - PO/PR 325-1000 mg q 4-6 hrs
  - Onset / Duration
    - <1 hour / 4-6 hours
- Pearls
  - Max Dose 4000 mg/24 hrs from all sources of medications (Med Reconciliation)
  - Reduce dose by 50-75% in patients with hepatic dysfunction
  - Can mask fever in patients with infection
  - Less effective for chronic inflammatory pain

NSAIDS

- Advantages
  - Good for inflammation, post-op, HA, CA and back pain.
  - Additive effect with other analgesic modalities
- Disadvantages
  - Geriatric patients at higher risk for adverse effects
  - NSAIDS indicated in 23.5% of patients age >65 as cause of adverse drug reaction leading to hospitalization
  - Nephrotoxicity
  - Prolonged use can cause GI Bleed
    - Many patients on dual therapy with aspirin for cardioprotection
  - Can increase risk of bleeding through platelet inhibition
  - Ceiling effects

The Ceiling Effect



New Developments in Palliative Care Pharmacotherapy

- Pain Management Tools
  - Pain Diary
  - Equianalgesic Conversion Tools
- Advances in Breakthrough Pain Treatment
  - Determine Effective Opioid Doses For Episodic Pain
- Opportunities for Pharmacists
  - Suggest analgesic dose titration for uncontrolled pain
  - Suggest opioid conversion doses when needed
  - Suggest optimal opioid breakthrough pain dose