

# Advanced Pain Management

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# Objectives

- Describe the importance of pain management
- Define the types of pain
- Discuss opioid pharmacology
- Identify barriers to pain management
- Discuss ethical responsibilities in pain management

# What is Pain?

Pain is what the experiencing person says it is, existing whenever he or she says it does

M. McCaffery

# What is Suffering?

Suffering is a state of severe distress associated with events that threaten the intactness of the person

E. Cassell

# Pain and Suffering

- Pain causes suffering when:
  - a patient feels out of control
  - The pain is overwhelming
  - The source of pain is unknown
  - The meaning of the pain is dire
  - The pain is apparently without end

E. Cassell

# Pain and Suffering

## ■ Patients in pain:

- Learn how little tolerance other people have for their continued report of pain
- Learn that pain becomes less bearable the longer it continues
- Fear the future
- Suffer in the absence of pain because they are anticipating its return

E. Cassell



# Pain and Suffering

Pain, therefore, is perceived as a threat to a patient's continued existence and to a patient's integrity

E. Cassell

# Types of Pain

## ■ Acute pain

- Follows acute injury and disappears when injury heals
- Often associated with autonomic stimulation

It is rarely justified to defer analgesia until a diagnosis is made

# Types of Pain

## ■ Chronic Pain

- Rarely accompanied with signs of sympathetic stimulation
- High incidence of psychological consequences (social behaviors involve the body)
- Develops as a result of sensitization (repeated stimulation of nociceptors) and neuroplasticity (in response to repeated noxious stimuli)

# Types of Pain

## ■ Nociceptive

- Somatic-well localized, constant, gnawing aching (ex: bone mets)
- Visceral-poorly localized, often referred, constant, aching (ex: pancreatic cancer)

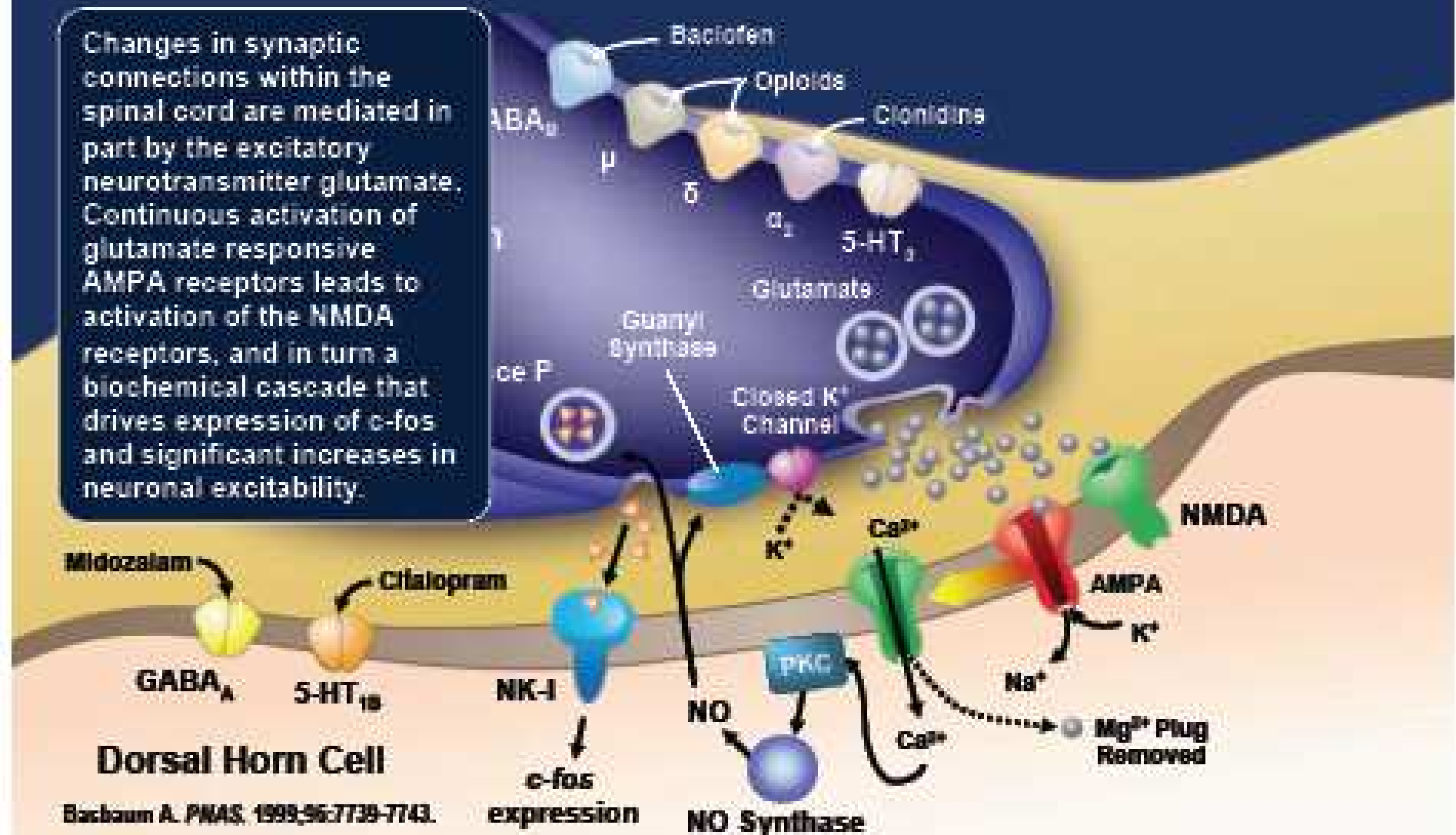
# Types of Pain

## ■ Neuropathic

- Paroxysms of pain, shooting or shock-like, on a background of burning, aching sensation
- Mechanism: spontaneous and paroxysmal discharges in the peripheral and central nervous system
- Example: mets to the brachial or lumbosacral plexus

# Sensitization Acute to Chronic Continuum

Changes in synaptic connections within the spinal cord are mediated in part by the excitatory neurotransmitter glutamate. Continuous activation of glutamate responsive AMPA receptors leads to activation of the NMDA receptors, and in turn a biochemical cascade that drives expression of c-fos and significant increases in neuronal excitability.



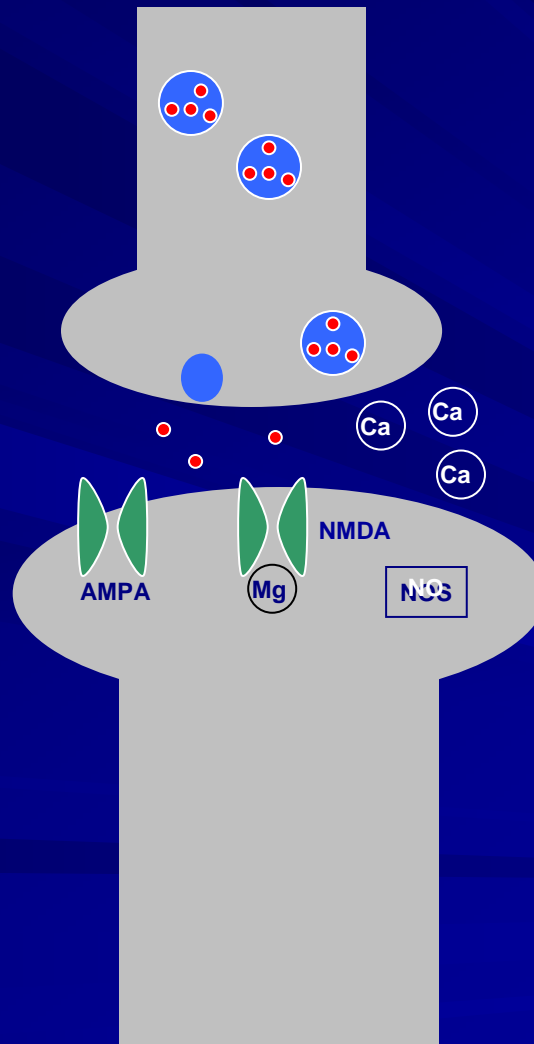
# The NMDA Receptor

- NMDA is a receptor for glutamate
- At resting membrane potentials, NMDA receptor is blocked by Mg ions
- Mg is removed by repeated stimulation (summation) which allows NMDA to be sensitive at resting potentials

# The NMDA Receptor

- Na and Ca influx ► further depolarization  
► further Ca influx ► phosphorylation
- Phosphorylation of NMDA removes Mg
  - **Increased neuronal excitability**
  - **Glutamate stimulation, even at resting membrane potentials**
  - **Production of nitric oxide that potentiates further glutamate stimulation**

# NMDA Receptor



# NMDA Summary

- The NMDA receptor is:
  - A primary cause for the occurrence of neuropathic and chronic pain
  - Involved in the development of hyperalgesia (extreme sensitivity to pain, exaggeration in perception of pain)
  - Involved in the “wind up” phenomenon- progressively greater pain is experienced with repeated pain stimuli of consistent intensity

# NMDA Antagonists

- Methadone
- Ketamine
- Dextromethorphan
- Amantadine
- Memantine



# Mu Opioid Receptor

- Exists mostly presynaptically
- Works by inhibiting GABA mediated synaptic transmission
- Found in mid-brain, spinal cord, medulla, intestines and limbic system

# Mu Opioid Receptor

- Activation by agonist (ex: morphine) causes:
  - Analgesia
  - Sedation
  - Hypotension
  - Itching
  - Nausea
  - Euphoria
  - Decreased respirations
  - Miosis
  - Decreased bowel motility

# Mu Opioid Receptor

- Tolerance develops quickly to sedation, euphoria, and decreased respirations
- Little tolerance develops to analgesia, miosis, and reduced bowel motility

This is due to activation of different Mu receptor subtypes (25 identified)

# Most Common Opioid Mu Agonists

- Morphine
- Hydromorphone
- Oxycodone
- Oxymorphone
- Fentanyl
- Hydrocodone
- Codeine
- Tramadol
- Methadone

# Methadone (Dolophine)

- Is both a mu agonist, NMDA antagonist, norepinephrine and serotonin reuptake inhibitor
- Rapid GI absorption and high bioavailability (85% vs. morphine 35%)
- No active metabolites
- Metabolism is hepatic (via P450)
- Excreted in stool

# Methadone

- Restores opioid responsiveness and prevents opioid-induced hyperalgesia (central activation of NMDA receptors)
- Excellent choice in rotation when opioid induced neurotoxicity occurs

E. Prommer

# Methadone

- Large interindividual variation in the equianalgesic ratio of methadone to other opioids
- Becomes more powerful with increasing prior exposure to other opioids
- Long pharmacological half-life (12-150 hours) but short analgesic half-life (6-12 hours)
- Biphasic elimination



# Problems with Methadone

- Potential for methadone accumulation due to long half life
- Mortality has increased 100% in last 5 years; 50% of methadone deaths occur in first 5-10 days after initiation
- FDA advisory:  
[www.fda.gov/cder/drug/advisory/methadone.htm](http://www.fda.gov/cder/drug/advisory/methadone.htm)

# Methadone and QT Interval

- Methadone can cause prolongation in the QT interval which can lead to a fatal arrhythmia (Torsades de Pointes)
- Critical QT prolongation is rare (>500 msec)
- Most cases involved patients taking >200mg daily
- Rule of thumb: consider getting an EKG if >200mg daily

# Drugs that Prolong QT

- Antibiotics (quinolones, mycins, ampicillin)
- Anticonvulsants
- Antidepressants (SSRI, TCA)
- Antipsychotics (almost all)
- Antifungals (fluconazole)
- Bronchodilators (albuterol)
- Other opioids

# Direct Morphine-Methadone Conversion

## 24 hr total dose morphine

- <30mg
- 31-99mg
- 100-299mg
- 300-499mg
- 500-999mg
- >1000mg

## Conversion ratio morphine to methadone

- 2:1
- 4:1
- 8:1
- 12:1
- 15:1
- 20:1

Fisch and Cleeland 2003

# Morley Markin Model

- Give 10% of total daily morphine dose q3h (hold for sedation)
- Dose should never exceed 30mg q3h to start
- Can give an additional 2 doses prn to bring total daily doses to 10
- Day 6, take the average daily dose given over the last 48 hours; give as divided dose BID or TID

**Notes: You need a very reliable caregiver to use this method!**

# Methadone

- Available in tablet, liquid, and injectable preparations (oral tablets may be used rectally)
- Evidence that sublingual solution can be used for breakthrough pain with median time to pain reduction being 5 minutes

N. Hagen et. al

# Morphine

- Gold standard opioid
- Metabolized into morphine-3-glucuronide primary by the liver (can be neuroexcitatory)
- The most routes of administration of any opioid –oral, sublingual, rectal, IV, IM, SQ
- Long acting preparations available
- Can cause histamine release

# Oxymorphone (Opana)

- New opioid agent for analgesia
- Active metabolite of oxycodone
- Dosage: ER (5,10,20,40) and IR (5,10)-  
also injectable (10mg/ml)
- Oxymorphone:morphine (1:3)
- Must be taken on empty stomach (food  
may lead to increased blood levels)



# Hydromorphone

- 4 times as potent as morphine
- Short half life (2.5 to 3 hr)-  
necessitates frequent administration
- Metabolized to hydromorphone-3-glucuronide (can be neuroexcitatory)
- No long acting available at this time  
(Palladone pulled from market due to dose dumping with alcohol)

# Oxycodone

- 1.5 times greater potency compared to morphine
- No parenteral formulation
- Hepatic metabolism
- Increasing incidence of abuse
- CR is now brand only

# Hydrocodone

- Equianalgesic ratio to morphine 1:1
- No parenteral forms available
- Not available in its pure form- ceiling effect from acetaminophen or NSAID
- No long acting formulation available

# Fentanyl

- Parenteral, transdermal, transmucosal and buccal formulations (GI absorption is poor)
- Transdermal equianalgesic dose 2mg MSO4=1ug fentanyl
- Transdermal fentanyl is released into fat and then into the systemic circulation over 72 hours (20% of patients require application every 48 hours)

# Rapid Acting Fentanyl

- Oral transmucosal formulation (Actiq)
  - Time to peak effect approx 20 minutes
  - Resembles lozenge on a handle
  - Reduced saliva will diminish absorption
- Buccal tablet (Fentora)
  - Peak effect 15 minutes
  - Placed between upper cheek and gum
  - Duration up to 60 min

# Opioid Side Effects

- Cutaneous
  - Pruitus
  - sweating
- Autonomic
  - Xerostomia
  - Urinary retention
  - Postural hypotension
- Gastrointestinal
  - Nausea
  - Vomiting
  - Constipation

# Opioid Side Effects

## ■ CNS

- Drowsiness
- Cognitive impairment
- Hallucinations
- Delirium
- Respiratory depression
- Myoclonus
- Seizures
- Hyperalgesia

# Opioid Side Effects

- Consider dose reduction
- Consider co-morbidity or drug interaction
- Opioid rotation
  - Takes advantage of individual receptor profiles
  - Using opioid conversion tables
  - Incomplete cross tolerance

# Opioids to be Avoided

## ■ Meperidine (Demerol)

- Accumulation of neurotoxic metabolite normeperidine causes seizures
- Normeperidine toxicity cannot be reversed by naloxone (antagonizes seizure suppressing effects of meperidine)
- Normeperidine has a half life 5-10 times longer than meperidine and is renally excreted

# Opioids to be Avoided

- Propoxyphene (Darvon, Darvocet)
  - It is no more effective than acetaminophen
  - It is proarrhythmic due to its effects on Na channels (quinidine-like effect)
  - Cardiac toxicity is not reversed by naloxone

# Barriers to Pain Management

## ■ Health professional

- Paucity of clinical education and training in pain and symptom management

## ■ Caregiver

- Fear of side effects, fear of addiction, PRN

## ■ Patient

- “wimp”, fear of side effects, fear of addiction

# Ethical Responsibilities in Pain Management

- Patients have a right to be free from unnecessary pain
- Pain destroys autonomy
- Pain is dehumanizing
- In its extreme, pain destroys the “soul” itself and all will to live

E. Cassell

# Conclusion

- “If we know that severe pain and suffering can be alleviated and we do nothing about it, then we ourselves become the tormentors”

Primo Levi

# Questions

1. Which one of the four stated issues regarding patients in pain do you believe cause the most suffering?
2. Dextromethorphan is structurally similar to:
  - a. Codeine
  - b. Morphine
  - c. Methadone

# Questions

3. Mortality from methadone over dose has increased by what percentage in the last 5 years?
  - a. 50%
  - b. 100%
  - c. 150%
  
4. Opana costs how much per tablet?
  - a. \$1.69
  - b. \$2.45
  - c. \$4.31