Management of the Opioid-Tolerant Patient

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Learning Objectives

• Review the clinically-relevant pharmacology of opioids

• Review concepts of tolerance and addiction

• Discuss management options for patients on chronic opioids
Mechanisms of Postoperative Pain

- Nociceptive
  - Somatic
    - Incisional
  - Visceral
    - Ileus
- Neuropathic
  - Direct nerve damage

OPIOID RECEPTORS
Opioids Effect Descending Modulation

Facilitation

Inhibition

Glutamate
Cholecystokinin
Galanin (2)
Melanocortin
Substance P
Dynorphin (NMDA)
5-HT (1A)
Norepinephrine ($\alpha_1$)
Acetylcholine (nicotinic)
Histamine ($H_1$)

GABA
Glycine
Galanin (1)
Neuropeptide FF
Neurotensin
Orphanin FQ
Dynorphin ($\kappa$OR)
$\beta$-Endorphin
Enkephalin
Acetylcholine

Dopamine ($D_2$)
5-HT (1B/3)
Norepinephrine ($\alpha_2$)
Acetylcholine

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Opioids Effect Descending Modulation

Descending Inhibition
- GABA
- Glutamate (NMDA/AMPA)
- Neurotensin (NT2)
- Substance P
- Dynorphin (κOR)
- Acetylcholine (nicotinic/muscarinic)
  NO

Descending Facilitation
- GABA
- Glutamate (NMDA)
- Cholecystokinin (CCK2)
- Neurotensin (NT1)
- Opioids (μOR)
- Norepinephrine (α1)
- Cannabinoids (CB1)
  NO

DIRECT
- Galanin
- Melanocortin
- Neuropeptide VF
- Orphanin FQ
- Dynorphin (κOR)
- β-Endorphin (μOR)
- Enkephalin (δOR)
- Endomorphin (μOR)
- Histamine (H2)
- Cannabinoids (CB1)
- BDNF

INDIRECT
Perioperative Opioid Analgesia

- Patient-Controlled Analgesia (PCA)
  - Emphasis on patient satisfaction
  - Management of undesirable side effects
    - Peripherally-acting opioid antagonists
- **Acute Pain Services**

Perioperative Opioid Use

• Patient on pre-admission opioid regimen
  • Prescription vs. illegal
  • Duration of use
  • Stable vs. escalating
  • Adverse effects
Perioperative Opioid Use

• Patient on pre-admission opioid regimen
  • Multimodal analgesia
  • Opioid-induced hyperalgesia
    • Animal evidence
    • Occurs after short term administration of opioids
    • Persists after discontinuation of opioids

Mitra S, Sinatra RS. Anesthesiol 2004; 101:214-27
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Tolerance to Chronically-Administered Opioids

- NMDA antagonists
- AMPA antagonists
- CCK antagonists
- CGRP antagonists
- Ca\(^{2+}\) channel blockers
- Dynorphin antiserum
- NOS inhibitors
- PKC inhibitors
- PKA inhibitors
- COX inhibitors
- Glutamate transporter activator
- I\(_2\) Imidazoline agonists
- Orphanin FQ/nociceptin
- Benzodiazepine antagonists

Neuroplasticity
Terminology

• **Tolerance**
  - Organ system differences
  - Cross tolerance (e.g., ethanol)
  - Opioid induced hyperalgesia

• **Dependence**
  - Physical
  - Psychological

• **Withdrawal syndrome**
Case - Active Opioid User

- 55-year-old man for ventral hernia repair
- PMH significant for chronic low back pain. L3-L5 lumbar fusion 2 years ago. Has not worked since.
- Current medications include gabapentin 600 mg q 8 hrs, fentanyl patch 100 mcg/hr, oxycodone 15 mg q 3-4 hrs prn
Terminology

Addiction  Pseudoaddiction
Aberrant Behavior Less Suggestive of Addiction

- Aggressive complaining about the need for more drugs
- Requesting specific drugs
- Resistance to change in therapy

Seppala M, Martin DP. Pain Free Living For Drug-Free People: A Guide to Pain Management in Recovery, 2005
Aberrant Behavior More Suggestive of Addiction

- Multiple or nonmedical sources of prescriptions
- Concurrent abuse of alcohol or illicit drugs
- Functional deterioration
- Repeated resistance to changes in therapy

Seppala M, Martin DP. Pain Free Living For Drug-Free People: A Guide to Pain Management in Recovery, 2005
Opioid Conversions

• Route
  • Fentanyl patch unpredictable
  • Oral may not be available

• Incomplete cross tolerance

• Web conversion calculator: http://www.globalrph.com/narcoticconv.htm
Case - Active Opioid User

• Plan:
  • Continue:
    • Fentanyl patch
    • Gabapentin
  • Regional / local anesthesia
  • iv PCA hydromorphone
Tolerance: Treatment

• Ketamine
  Subramanian K et al. *Anesth Analg* 2004;99:482-95

• Clonidine / Dexmedetomodidine

• COX-2 inhibitors:
  • Parecoxib
    Tröster A et al. *Anesthesiol* 2006;105:1016-23
Opioid Tolerance

- Organ specific:
  - Euphoria
  - Nausea / Vomiting
  - Sedation
  - Cognitive impairment
  - Analgesia
  - Respiratory depression
  - Constipation

Collett BJ. *Br J Anaesth* 1998;81:58-68

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Opioid Cautions

• **Meperidine**
  - Normeperidine: neurotoxic
  - Avoid in renal failure or elderly

• **Methadone**
  - Partial NMDA antagonist effects
  - May lead to overdose

• **Mixed agonist / antagonists**
  - May lead to withdrawal
Characteristics of Methadone

• High bioavailability (80%)
• Long half-life: 30 ± 16 h
• Interpatient pharmacokinetic variability: CYP3A4 & CYP2B6
• No active metabolites
• Poorly defined equi-analgesic potency
Morphine:Methadone Ratio
Daily Oral Morphine Equivalent

Symptoms of Opioid Withdrawal


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Opioid Cautions

- **Meperidine**
  - Normeperidine is neurotoxic
  - Avoid in renal failure or elderly patients

- **Methadone**
  - Has partial NMDA antagonist effects
  - May lead to overdose in tolerant patients

- **Mixed agonist / antagonists**
  - May lead to withdrawal
Alternatives to Opioids

- Regional Anesthesia
  - Local anesthetics
- NSAIDS and Acetaminophen
- Anticonvulsants
- Antidepressants

Non-pharmacologic
- Acupuncture
- Hypnosis
- Meditation
- Physical Therapy / Massage
Conclusions
• Develop a plan in advance, if possible
• Continue baseline medications
  • Change route if necessary
• Increased doses may be needed
• Consider nonpharmacologic and nonopioid analgesics
• Provide psychosocial support
https://youtu.be/I6FRSU9vodQ