



MAYO CLINIC

Management of the Opioid-Tolerant Patient



A black and white photograph of a bronze statue depicting two men in profile, facing right. The man in the foreground is wearing a surgical mask and cap, while the man behind him has a more traditional academic or medical appearance.

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**British-Ukrainian Symposium (BUS – 11):
Innovative Technologies and Techniques
in Anaesthesiology and Intensive Care**

Kyiv, April 18, 2019



Carlos Mantilla. 11-й Британо-Український Симпозіум. Київ, 2019

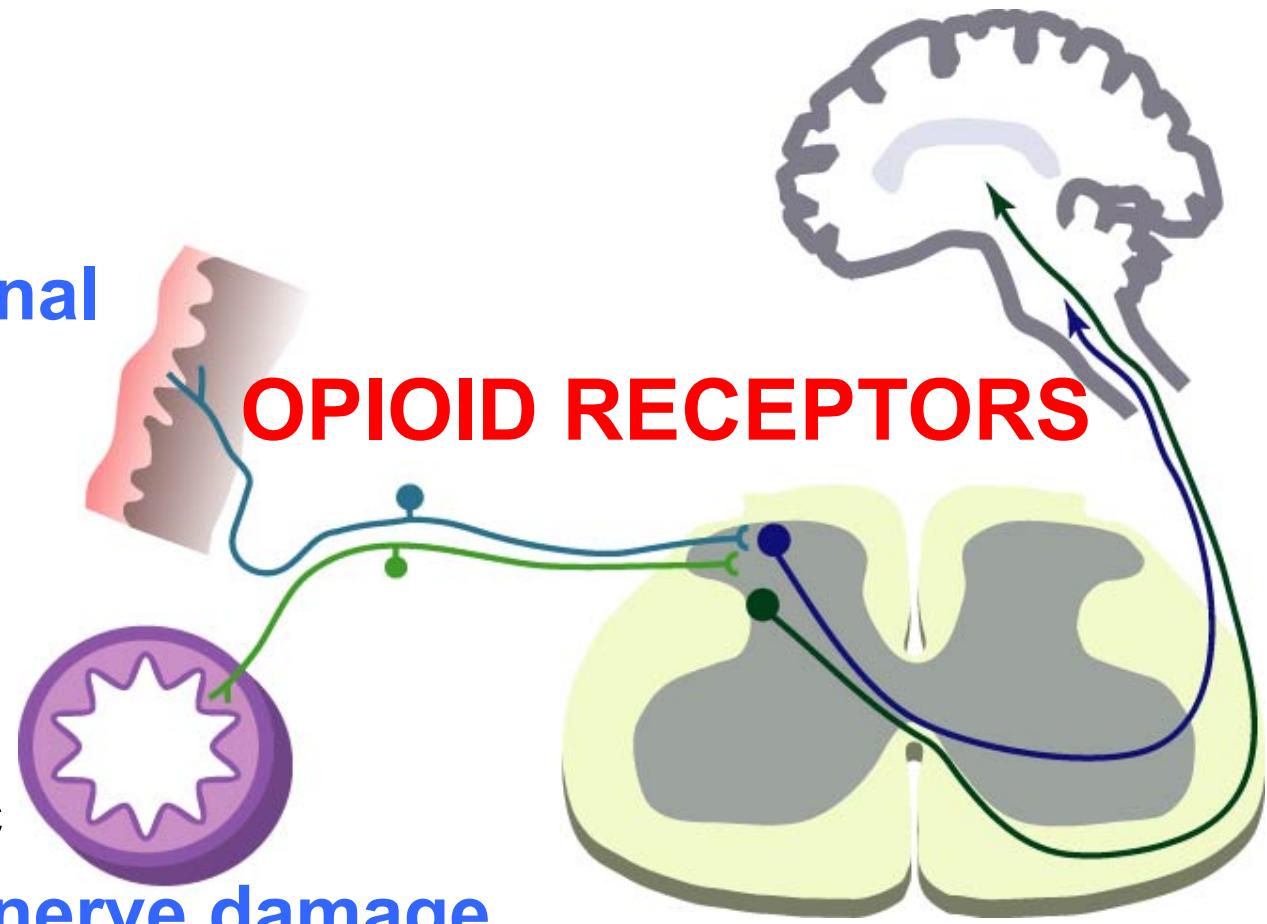
Learning Objectives

- Review the clinically-relevant pharmacology of opioids
- Review concepts of tolerance and addiction
- Discuss management options for patients on chronic opioids

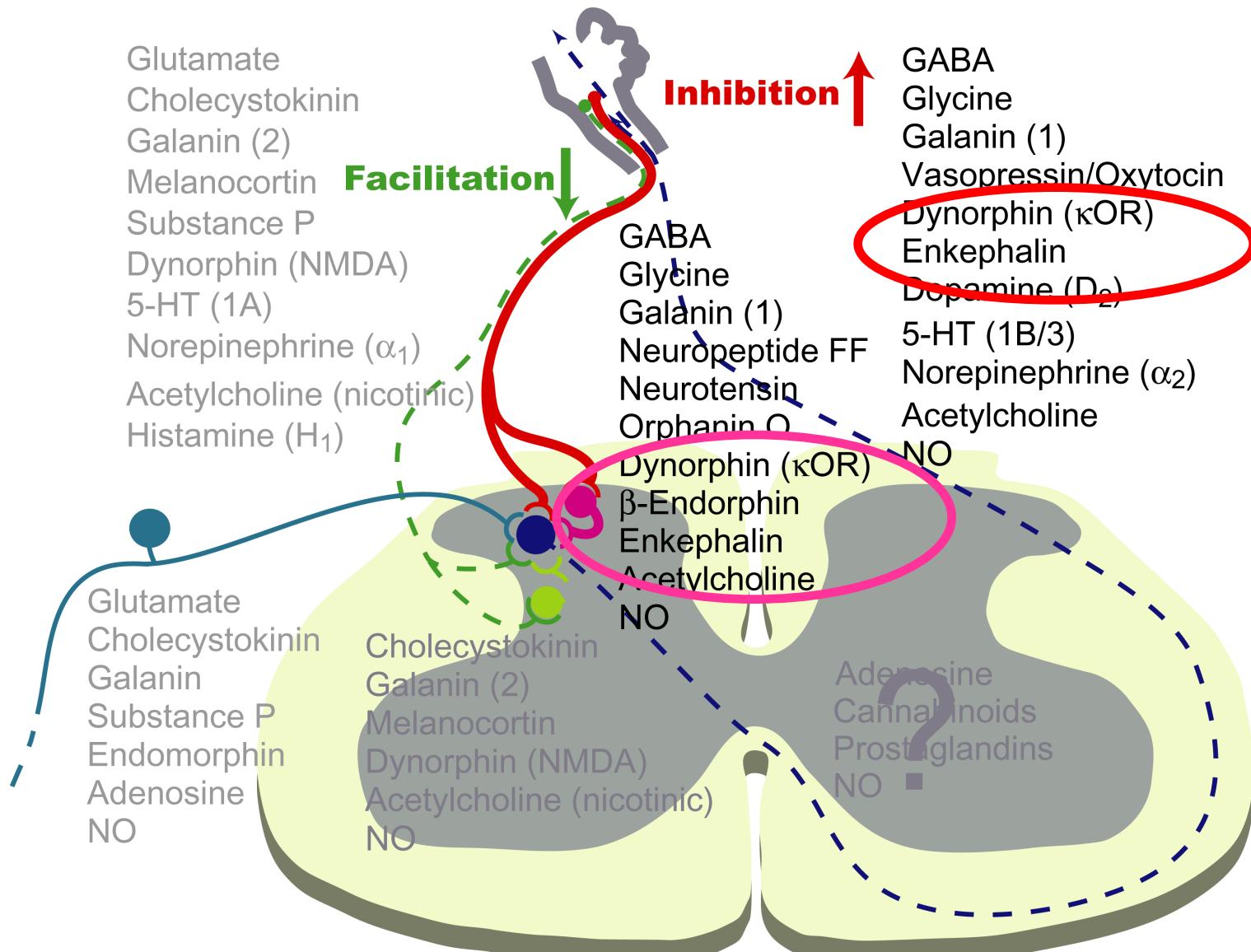


Mechanisms of Postoperative Pain

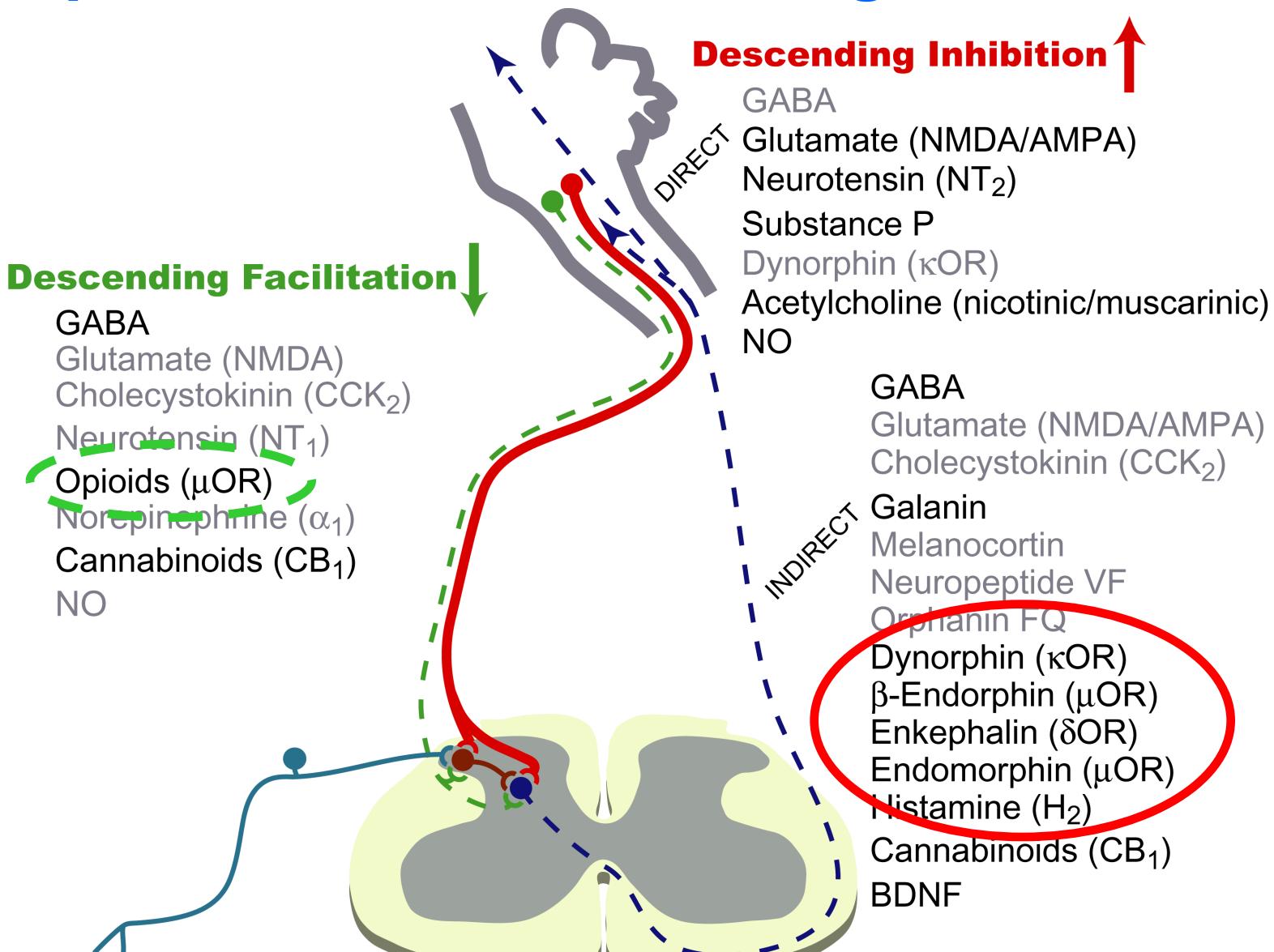
- Nociceptive
 - Somatic
 - Incisional
 - Visceral
 - Ileus
- Neuropathic
 - Direct nerve damage



Opioids Effect Descending Modulation



Opioids Effect Descending Modulation



Perioperative Opioid Analgesia

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

Miaskowski C et al. *Pain* 1999; 80:23-9

Ward SE *Pain* 1994;56:299-306



Perioperative Opioid Use

- Patient on **pre-admission opioid regimen**
 - Prescription vs. illegal
 - Duration of use
 - Stable vs. escalation
 - 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

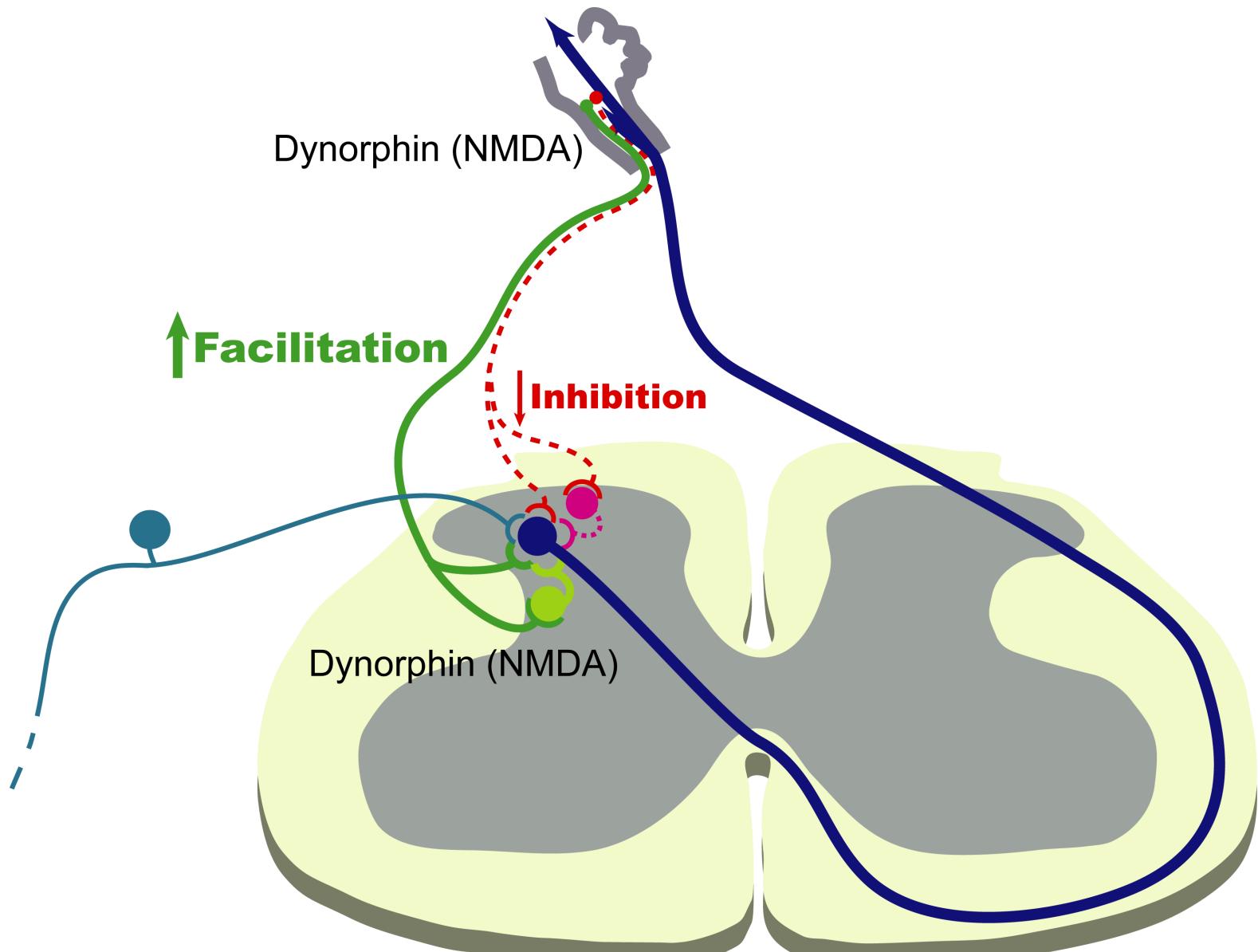
Mitra S, Sinatra RS. *Anesthesiol* 2004; 101:214-27

Martyn JAJ et al. *N Engl J Med* 2019; 380:365-78

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Opioid-Induced Hyperalgesia



Tolerance to Chronically-Administered Opioids

- NMDA antagonists
- AMPA antagonists
- CCK antagonists
- CGRP antagonists
- Ca²⁺ channel blockers
- Dynorphin antiserum
- NOS inhibitors
- PKC inhibitors
- PKA inhibitors
- COX inhibitors
- Glutamate transporter activator
- I₂ 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**

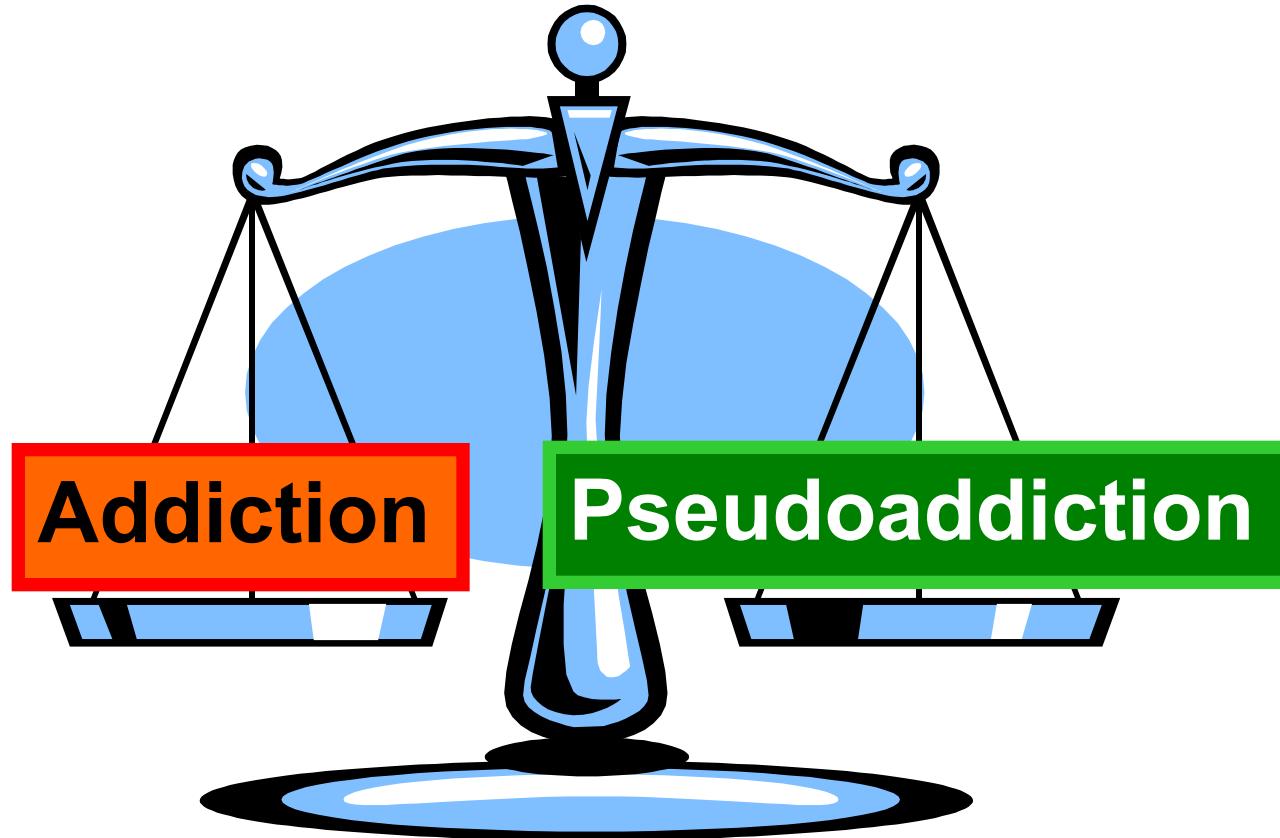


Case - Active Opioid User

- 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



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/narcoticonv.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

Bell RF et al. *Acta Anaesthesiol Scand* 2005;49:1405-28

- **Clonidine / Dexmedetomidine**

Joly V et al. *Anesthesiol* 2005;103:147–5

Fairbanks CA et al. *Anesthesiol* 2009;110:638-47

- **COX-2 inhibitors:**

- **Parecoxib**

Tröster A et al. *Anesthesiol* 2006;105:1016-23



Opioid Tolerance

- **Organ specific:**

Euphoria

Nausea / Vomiting

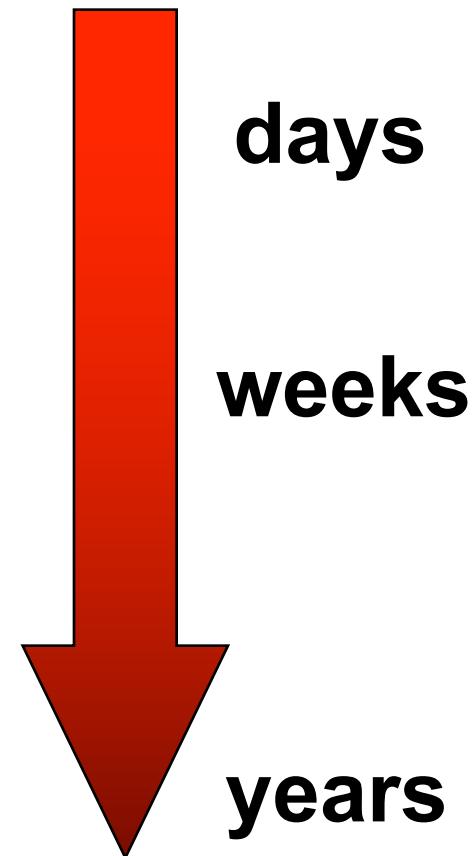
Sedation

Cognitive impairment

Analgesia

Respiratory depression

Constipation



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

Opioid Cautions

- **Meperidine**
 - Normeperidine: neurotoxic
 - Avoid in renal failure or elderly
- **Methadone**
 - Partial NMDA antagonist effects
 - May lead to overdose
- **Mixed agonist / antagonist**
 - May lead to withdrawal



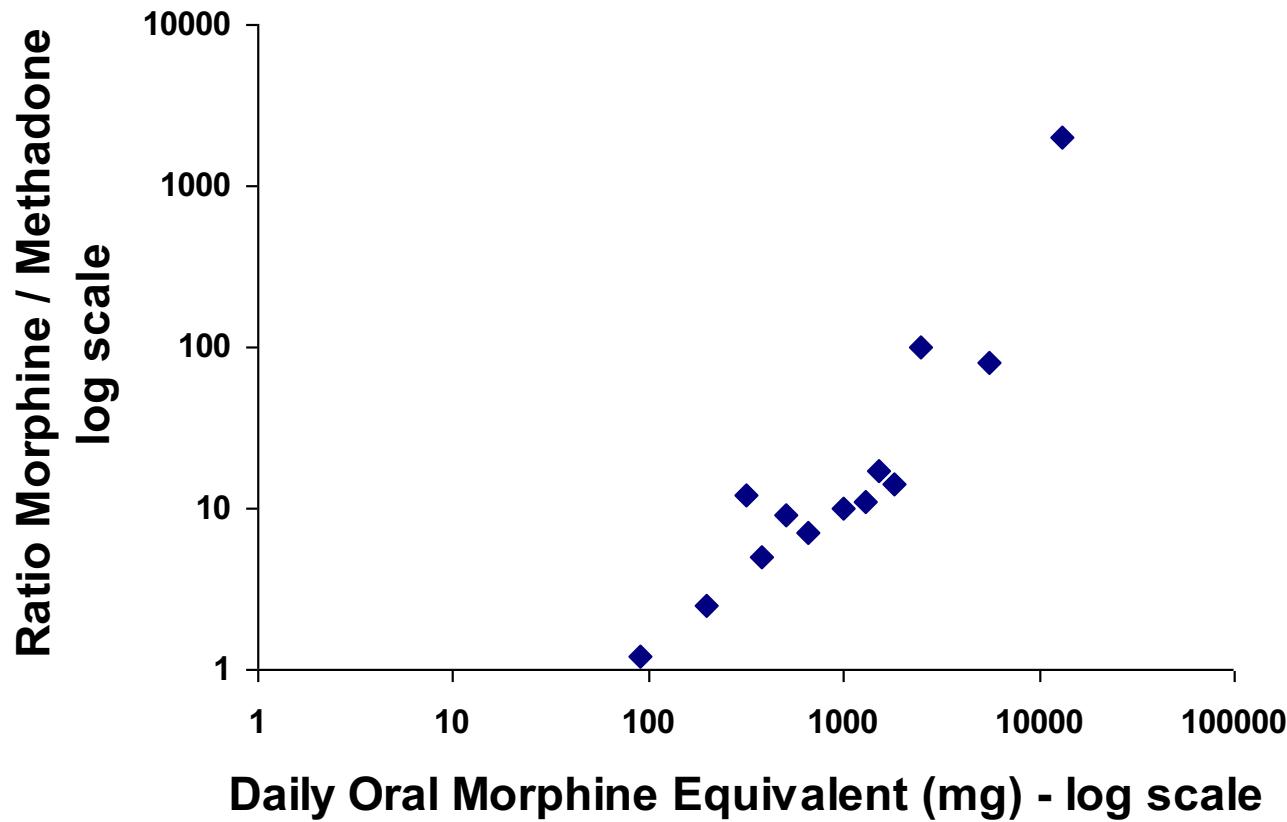
Characteristics of Methadone

- 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

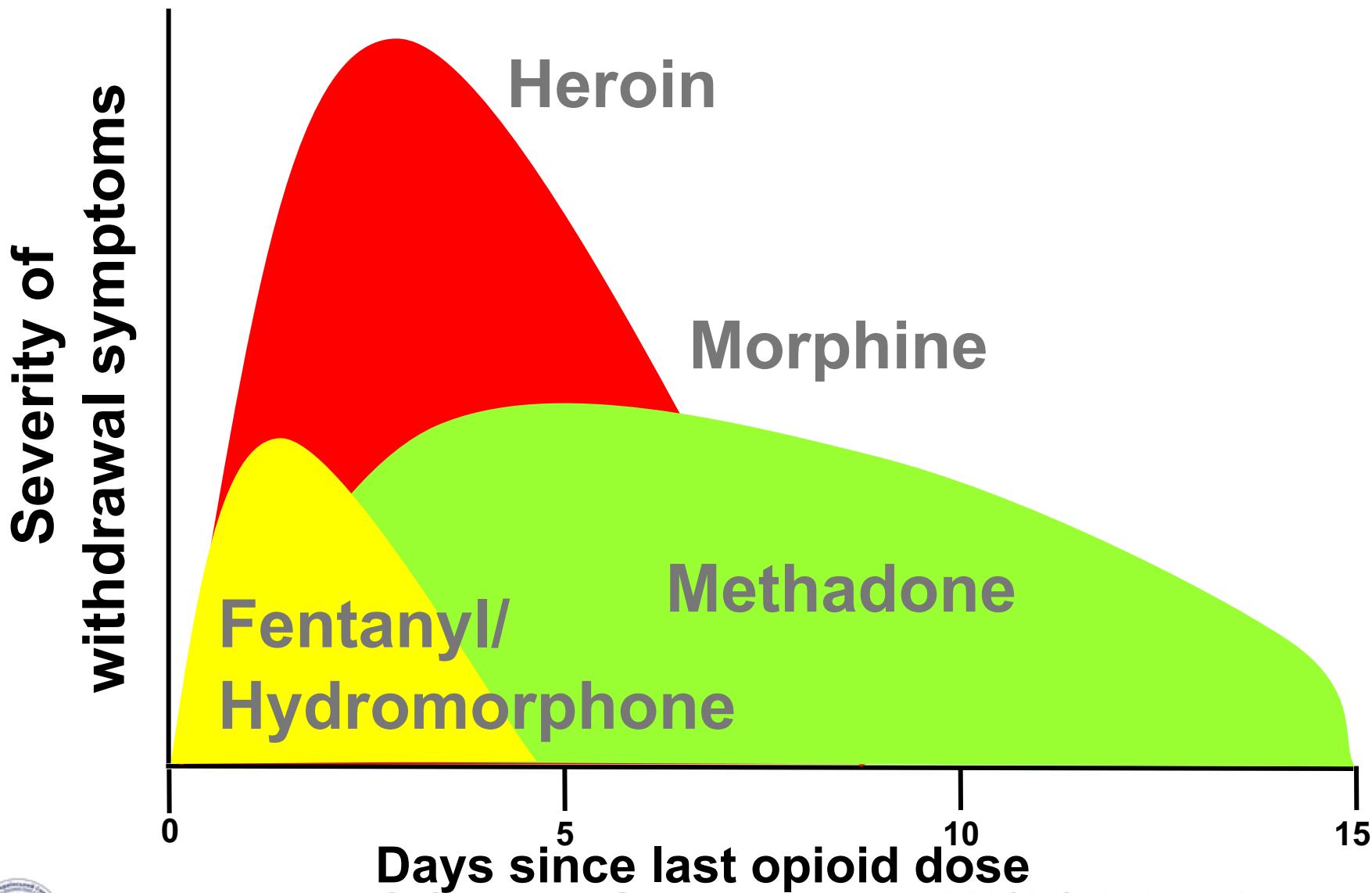
Daily Oral Morphine Equivalent



Lawlor PG et al. *Cancer* 2000; 82:1167-73



Symptoms of Opioid Withdrawal



TR and O'Connor TG. N Engl J Med 348(18):1786, 2003

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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/l6FRSU9vodQ>

