Fitzgerald
Colibri Healthcare

Controlled Substance Prescribing: Compliance with the Consolidated Appropriations Act, 2023 for Prescribers of Controlled Substances

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Disclosure

- No real or potential conflict of interest to disclose.
- No off-label, experimental or investigational use of drugs or devices will be presented.

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Objectives

- At the end of this presentation, the participant will be able to:

1. Describe the key steps in pain reception and perception.
2. Compare and contrast mechanisms of opiate and non-opiate pain agents.

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Objectives (continued)

- At the end of this presentation, the participant will be able to:

3. Discuss CDC recommendations and legislative considerations in opioid prescribing.
4. Analyze elements of opioid risk assessment.
5. Evaluate elements of and indications for medically assisted therapy.

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Tips

- References
  - Listed throughout and at the end of the presentation
- To facilitate your learning
  - Specific tables/images can be viewed full page at the end of your handout.

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Physiology of Pain

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Review of Pertinent Physiology

- An understanding of neuronal stimulation, communication and neurotransmitters is the basis of pain physiology.
  - A stimulus is converted to an impulse.
    - That impulse travels to the brain
  - The brain modifies the impulse.
  - End result – Perceived as pain

- Neurotransmitters are the way that the stimulus is conducted from one neuron to the next.
- Some neurotransmitters communicate the message of pain.
  - Substance P

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Review of Pertinent Physiology (continued)

- Others attenuate the message.
  - GABA
  - Serotonin
    - Excitatory in the raphe nuclei
    - Inhibitory in the cerebral cortex
  - Dopamine
    - Primarily inhibitory
- And yet others modify the message of pain.
  - Norepinephrine
  - Serotonin
  - Glutamate
  - Dopamine

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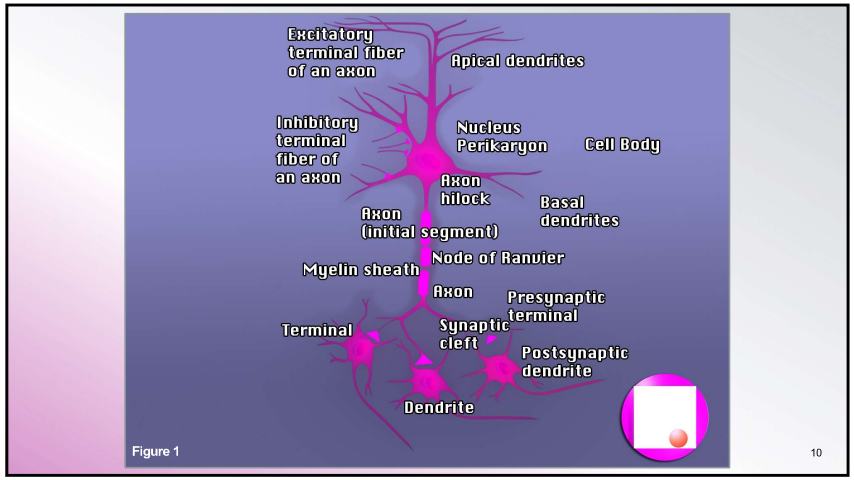

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Review of Pertinent Physiology (continued)

- Dendrites receive stimuli.
  - Both excitatory and inhibitory
- When the net effect of that stimuli reaches threshold, an action potential occurs.
- Release of neurotransmitter promulgates the pain message.
- The neurotransmitter binds to receptors on the post-synaptic neuron.
  - The message moves its way through the spinal cord to the CNS.
  - If at any point the stimuli for inhibition exceeds excitation, the impulse no longer moves forward.

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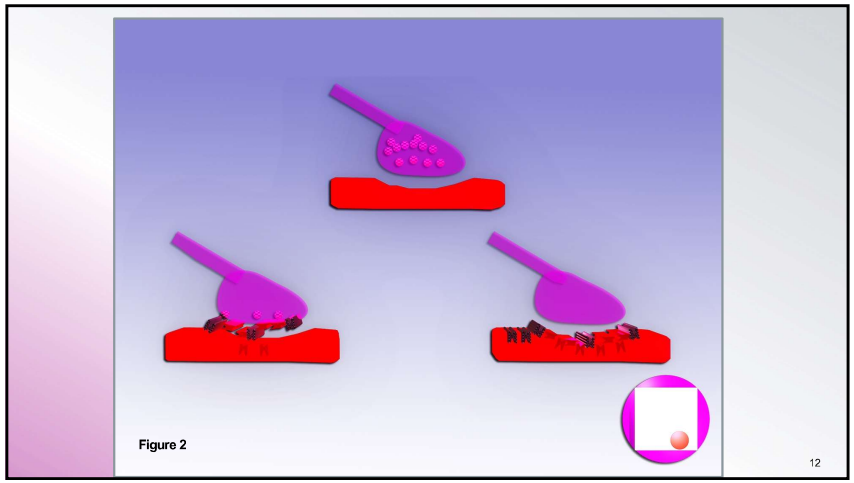

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Review of Pertinent Physiology (continued)

- Most pain medications impact this process in some way.
  - Some will change membrane voltage.
  - Others…
    - Act as inhibitory stimuli
    - Mimic natural pain suppressors

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Acute Versus Chronic Pain

- Acute pain
  - Baseline processes are normal.
  - There is a stimulus that overtly excites neurons and perpetuates excitation up pain pathways.

- Chronic pain can persist long after the acute stimulus is gone.
  - This is a result of neuronal plasticity.
  - Acute pain can alter the resting potential of pain receptors.
    - A lesser-than-normal stimulus will result in release of pain transmitters.
  - Poorly controlled acute pain increases risk.

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Pathophysiology of Pain

- **Transduction**
  - A stimulus is converted into a nerve impulse.
- **Perception**
  - Messages from the periphery are interpreted by the brain.
- **Transmission**
  - The impulse is carried to the brain.
- **Modulation**
  - The brain sends signals that cause the pain signals from the periphery to be suppressed or amplified.

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Physiology of Pain

Types of Pain Receptors

- Fast pain
  - Felt within 0.1 second of stimulus
  - Sharp prickling, acute, electric
  - Not felt in the deeper tissues of the body
  - Associated with tissue destruction

- Slow pain
  - Felt >1 second of stimulus
  - Increases slowly over many seconds
  - Burning, aching, throbbing, nauseous
  - Associated with tissue destruction

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Physiology of Pain (continued)

Pain Receptors and their Stimulation

- All pain receptors are free nerve endings.
  - Widespread in skin, periosteum, arterial walls, joint surfaces
  - Deep tissue is sparsely supplied.
- Types of stimuli
  - Mechanical
  - Thermal
  - Chemical – Especially important in slow, suffering pain

- Bradykinin
- Serotonin
- Histamine
- K+ ions
- Acids
- Prostaglandins
- Substance P

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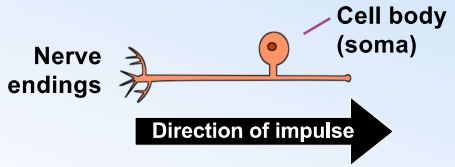
Transduction – Nerve Impulse



- Sensory neurons are unipolar.
- Impulses travel from the nerve endings toward the central nervous system.

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Physiology of Pain (continued)

- Transmission of pain signals to the CNS
  - Although all pain receptors are free nerve endings.
  - Impulses transduced in these nerve endings utilize two separate pathways to transmit the signal to the CNS.
    - Neospinothalamic pathway
    - Paleospinothalamic pathway

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Physiology of Pain (continued)

Transmission of pain signals to the CNS (cont.)

- Neospinothalamic tract
  - Type A delta pain fibers
  - Transmits mechanical and acute thermal pain
  - Pain is transmitted at 6 to 30 m/sec.
  - Most fibers pass all the way to thalamus
  - Pain may be localized precisely

- Paleospinothalamic pathway
  - Type C pain fibers
  - Signal must pass through additional short fibers.
  - Terminates widely in brain stem – Important for suffering
  - Only 10 to 25% terminate in thalamus

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Physiology of Pain (continued)

Transmission of pain signals to the CNS (cont.)

- Reticular formation – Strong arousal on nervous activity in the brain
  - Terminus of some pain fibers located here
  - Person in severe pain is strongly aroused
  - Impossible to sleep when in pain

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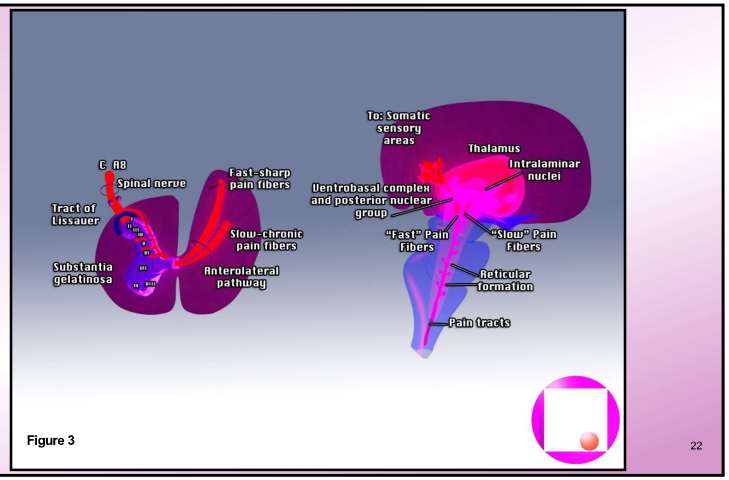

Figure 3

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Pain Conduction

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Perception

Figure 4

- *Pain is perceived in the brain.*
- *Alterations in neural circuitry in the brain can cause change in pain perception.*
- *The experience of pain is also influenced by psychosocial factors.*

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Modulation

- Messages from the brain can suppress the pain signals that would otherwise be sent from the dorsal horn to the spinothalamic tract.

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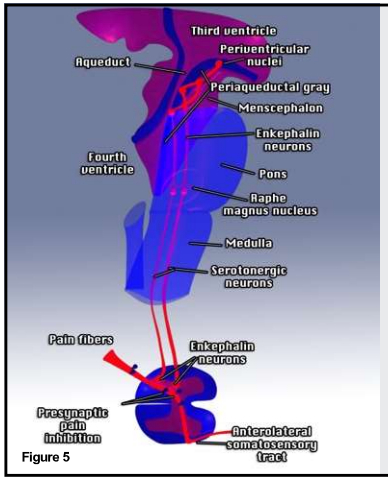

Figure 5

Physiology of Pain **Endogenous Pain Suppression**

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Physiology of Pain (continued)

Endogenous Pain Suppression

- Neurons in the periaqueductal gray and periventricular areas in the upper brain stem and third ventricle send their signals to the raphe magnus nucleus.
- The raphe magnus nucleus (lower pons/upper medulla) transmits signals down the spinal cord to the pain inhibiting complex.

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Physiology of Pain (continued)

Endogenous Pain Suppression (cont.)

- Analgesia signals can block the pain signals arriving from peripheral neurons
- Primary neurotransmitters are enkephalin and serotonin.
  - Enkephalin- Released in the raphe magnus nucleus
  - Serotonin- Released in the dorsal horn

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Physiology of Pain – Summary

Endogenous Pain Suppression (cont.)

- Both C and A delta type pain fibers are inhibited.
- Pain is produced when mechanical, thermal or chemical stimuli excite pain receptors.
- Mechanical/thermal stimuli excite type A delta receptors.
- Chemical stimuli excite type C receptors.
- Chemicals are released during the inflammatory response which follows tissue injury.
- Pain is transmitted to the spinal cord, through the dorsal horn.

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Physiology of Pain – Summary (continued)

Endogenous Pain Suppression (cont.)

- A delta pain fibers terminate in the thalamus.
- C pain fibers terminate in the brain stem.
- Enkephalins and serotonin are important neurotransmitters in the body's endogenous analgesia system.

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Pharmacologic Management of Pain

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Pharmacologic Management of Pain – NSAIDs

- ASA
- Diclofenac
- Diflunisal
- Etodolac
- Fenoprofen
- Ibuprofen
- Celecoxib*
- Ketorolac
- Nabumetone
- Naproxen
- Piroxicam
- Salsalate
- Sulindac
- Tolmetin

*Only COX-2 inhibitor remaining on the market

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Pharmacologic Management of Pain – NSAIDs (continued)

- Mechanism of action
  - Covalently modifies COX-1 and COX-2 pathways
    - COX-1 is constitutive.
      - Found in blood vessels, stomach, kidneys
    - COX-2 is induced by cytokines and mediators in the presence of inflammation.

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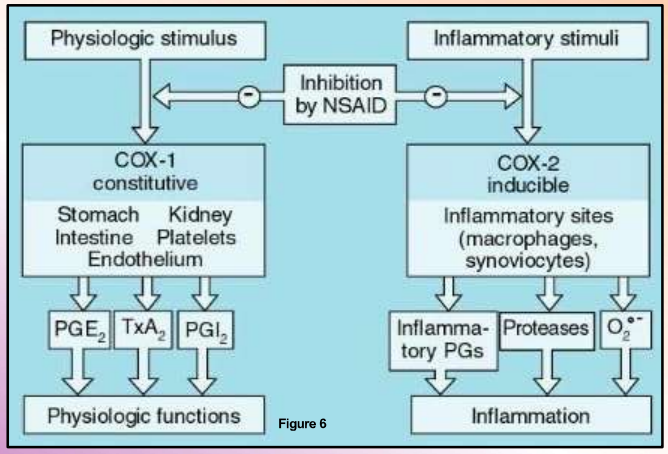

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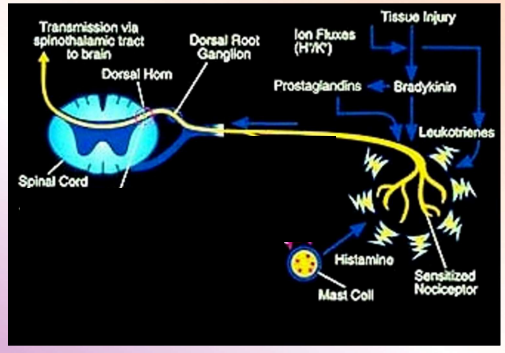
Pharmacodynamics of NSAIDs



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Pharmacologic Management of Pain – NSAIDs (continued)

- Indications
  - Musculoskeletal disorders
  - Chronic postoperative pain due to inflammation
  - Other pain due to inflammation
- Adverse effects
  - GI intolerance and/or ulcers
  - Blockage of platelet aggregation
  - Prolonged gestation
  - Inhibition of prostaglandin-mediated renal function
  - Vasomotor rhinitis

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Pharmacologic Management of Pain – NSAIDs (continued)

- Drug interaction
  - Potentiates anticoagulation
  - Increases lithium and methotrexate toxicity
  - Reduces effectiveness of antihypertensives
- Laboratory
  - Monitor for hyperkalemia.

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Pharmacologic Management of Pain (continued)

Acetaminophen

- Also a COX inhibitor
- Some theorize a COX-3 as acetaminophen does not appreciably reduce inflammation
- More recent data suggest it is highly selective for COX-2.

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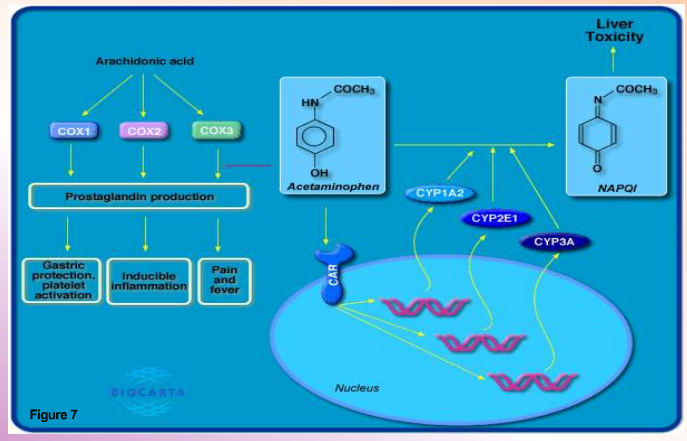

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Pharmacologic Management of Pain (continued)

Opioids – Mechanism of Action

- Bind primarily to μ receptors
- Effective in the management of pain caused by stimulation of nociceptive receptors and transmitted over intact neural pathways
- Inhibits nociceptive reflexes at several sites in the CNS, including the dorsal horn and the raphe magnus nucleus
- Profound analgesia can be produced by instilling morphine into the third ventricle, periaqueductal gray, and raphe magnus nucleus.
- Directly suppresses respiratory centers in the brain stem

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Agonist/Antagonist Combinations

- Pentazocine (Talwin®)
- Nalbuphine (Nubain®)
- Butorphanol
- Morphine/naltrexone (Embeda®)

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Pharmacologic Management of Pain (continued)

Opioids – Mechanism of Action (cont.)

- Depresses the cough center in the medulla
- Stimulates the chemoreceptor trigger zone (CTZ)
  - Nausea and vomiting rarely occur in recumbent patients, suggesting that there is a vestibular component.
- Binding of μ_2 receptors causes
  - Decreased HCl acid secretion in the stomach
  - Decreased biliary, pancreatic, and intestinal secretions
  - Enhancement of non-propulsive contractions in the small intestine
  - Inhibition of propulsive contractions in the small intestine
  - Augments tone of the anal sphincter

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Pharmacologic Management of Pain (continued)

Opioids (cont.)

- Action on the healthy/pain free adult
  - Drowsiness
  - Nausea/vomiting
  - Apathy
  - No significant effects on healthy myocardium
  - In cardiac disease, 8 to 15 mg of morphine decreases oxygen consumption and myocardial workload.
- Adverse effects
  - Nausea/vomiting
  - Constipation
  - Urinary retention
  - Mental clouding
  - Dizziness
  - Hypotension

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Pharmacologic Management of Pain (continued)

Tapentadol (Nucynta® and Nucynta ER®)

- Synthetic mu-agonist
- Norepinephrine reuptake inhibitor
- ER form indicated for diabetic peripheral neuropathy (DPN)

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Pharmacologic Management of Pain (continued)

Tramadol (Ultram®)

- Very selective, weak mu-opioid receptor agonist
- Norepinephrine reuptake inhibition
- Potentiates serotonin release

- Can produce physical addiction
- Recreational use complicated by higher risk of seizure

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Pharmacologic Management of Pain (continued)

Antidepressants

- Mechanism of action not well defined
- Impulses from the paleospinothalamic pathway terminate in mood centers.
  - Raphe nucleus
  - Locus coeruleus

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Pharmacologic Management of Pain (continued)

Antidepressants (cont.)

- SNRI and TCA all used for pain management
- SNRI is the only class in which a drugs has an indication for pain management.
  - Duloxetine- Indicated for depression and diabetic peripheral neuropathy
- SSRIs are not regarded as being as effective for pain as TCA or SNRI drugs.

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Pharmacologic Management of Pain (continued)

Antiepileptics

- Similar chemical structure to TCAs
- Reduces synaptic transmission of pain
- Mechanism of action believed to be related to…
  - Potentiation of GABA receptors
  - Inhibition of glutamate
  - Stabilization of nociceptors

- Pregabalin is indicated for diabetic peripheral neuropathy and postherpetic neuralgia.
- Many older anticonvulsants are used for neuropathic pain.
  - Utility is limited by adverse effects.

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Pharmacologic Management of Pain (continued)

- Adjuvant options
  - Corticosteroids
  - Topical agents
  - Cannabinoids

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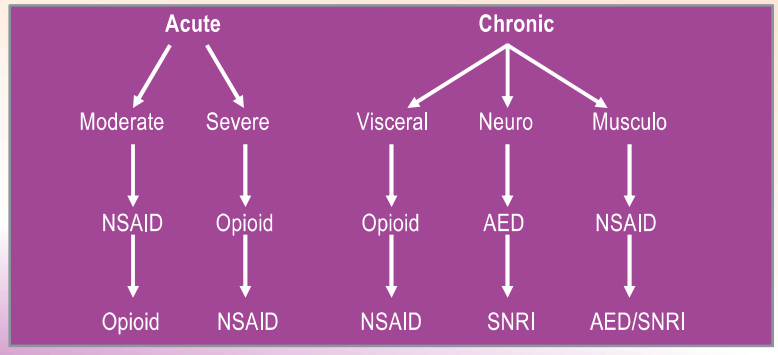
Selection of the Agent



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Legislative Issues and National Guidance

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The Controlled Substances Act (CSA)

- Federal law that was enacted by Congress as Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970.
- Federal U.S. drug policy under which the manufacture, importation, possession, use and distribution of certain substances is regulated.
- Also served as the national implementing legislation for the Single Convention on Narcotic (opiate-derived) Drugs.

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The Controlled Substances Act (CSA) (continued)

- Even though the privilege to prescribe all controlled substances (opioid, stimulant, hallucinogen, etc.) is state mandated, the foundation legislation and classification are federal.
- Created five schedules (classifications) with varying qualifications for a substance to be included in each.
  - Provides a mechanism for adding, deleting or changing drugs between schedules

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The Controlled Substances Act (CSA) (continued)

- May be initiated by…
  - Drug Enforcement Agency (DEA)
  - Department of Health and Human Services (DHHS)
  - Any interested party
- Classification decisions are required to be made on criteria including potential for abuse, currently accepted medical use in treatment in the United States, and international treaties
- Amended numerous times since its initial presentation in 1970

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Scheduling Decisions

- Based upon several factors
  - Actual or relative potential for abuse
  - Scientific evidence of its pharmacological effect, if known
  - The state of current scientific knowledge regarding the drug or other substance
  - History and current pattern of abuse
  - Scope, duration and significance of abuse

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Scheduling Decisions (continued)

- Based upon several factors (cont.)
  - What, if any, risk to public health
  - Psychic or physiological dependence liability
  - Substance is an immediate precursor of a substance already controlled under this subchapter

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Drug Enforcement Administration (DEA)

- A federal law enforcement agency created in 1973 under Dept. of Justice
- Responsibility for enforcing federal law drug policy domestically **and** only agency responsible for coordinating drug investigations out of the country
- The narcotic registry system of the DEA allows healthcare, research and manufacturer professionals with state granted access to manufacture, research, dispense, prescribe and distribute a controlled substance

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Scheduling

- Despite a few exceptions, every schedule requires a finding specifying the "potential for abuse" before a substance can be placed in that schedule.
- The CSA does not define abuse.
- The specific classification of any given drug or other substance is usually a source of controversy, as is the purpose and effectiveness of the entire regulatory scheme.
- The term "controlled substance" means a drug or other substance, or immediate precursor, included in Schedule I, II, III, IV or V.

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Scheduling (continued)

- One of the big criticisms of the scheduling system is that alcohol and tobacco are not controlled substances even though they are the two most widely used drugs of abuse in the United States.
- A similar criticism exists of caffeine.

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Inconsistencies…

- In the classifications as is evident with a review of schedule criteria…
  - Morphine and fentanyl are both Schedule II, while heroin is Schedule I.

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Schedule I Drugs

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Classification Requirements

- The drug or other substance has a high potential for abuse.
- The drug or other substance has **no currently accepted medical use** in treatment in the United States.
- There is a lack of accepted safety for use of the drug or other substance under medical supervision.

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Clinical Utility

- None as we know it!
- Drugs are very selectively available in the research setting.

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Schedule I

- Approximately 78 opiates and opiate derivatives including heroin
- Approximately 33 psychedelics including **marijuana***, psilocin, LSD, mescaline
- Approximately 3 depressants including methaqualone
- Approximately 8 stimulants

*Federal Schedule I drug, but legal for use in many states

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Schedule II

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Classification Requirements

- Substance has a high potential for abuse
- Can cause severe psychological or physical dependence
- Currently accepted medical use

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Therapeutic Categories

- Opiates and opioids
- Stimulants
- Depressants
- Hallucinogens

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Opiates and Opioids

- Four chemical classes that contain 41 opiates including fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone and opium derivatives

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Stimulants

- **6** Schedule II stimulants including…
  - Cocaine
  - Amphetamine
  - Methamphetamine
  - Methylphenidate
  - Phenmetrazine

Depressants

- **3** barbiturates (amobarbital, pentobarbital and secobarbital), glutethimide and phencyclidine
- All strong sedatives of some variety

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Hallucinogen

- There is 1 Schedule II hallucinogen
  - Nabilone (Cesamet®)
  - Used for chemo-induced nausea and vomiting
  - Potentiates natural antiemetic mechanisms

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Schedule III Drugs

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Classification Requirements

- Substance has a potential for abuse less than Schedules I and II.
- The substance has a currently accepted medical use in treatment in the United States.

- Abuse can lead to low or moderate physical dependence.
- Abuse of the drug can lead to high psychological dependence.

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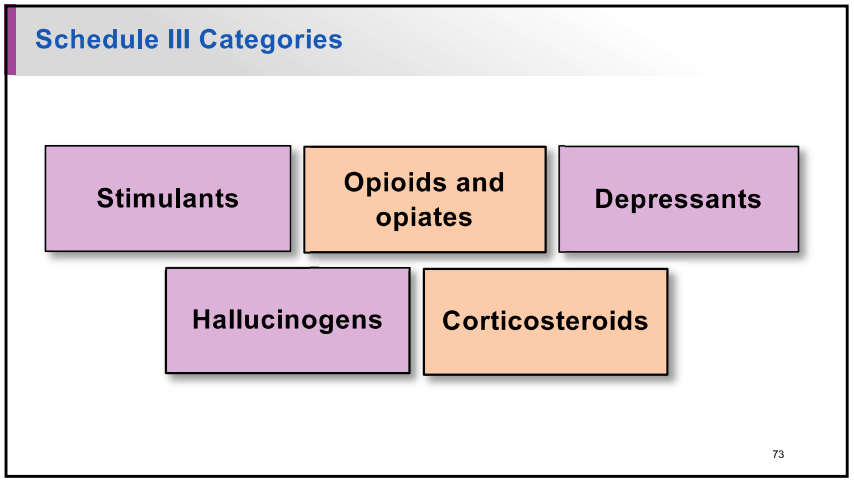

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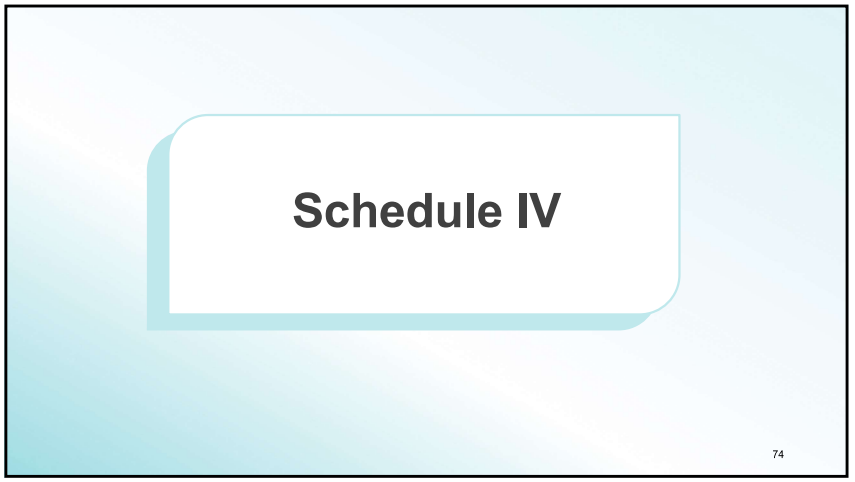

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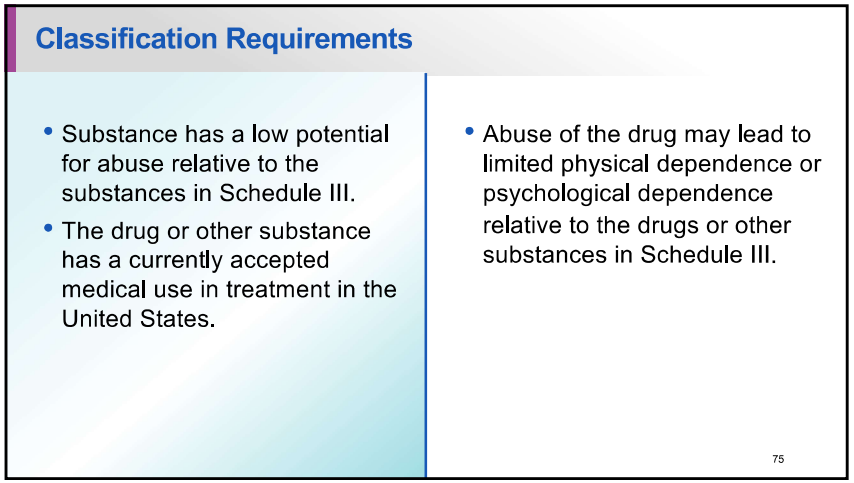

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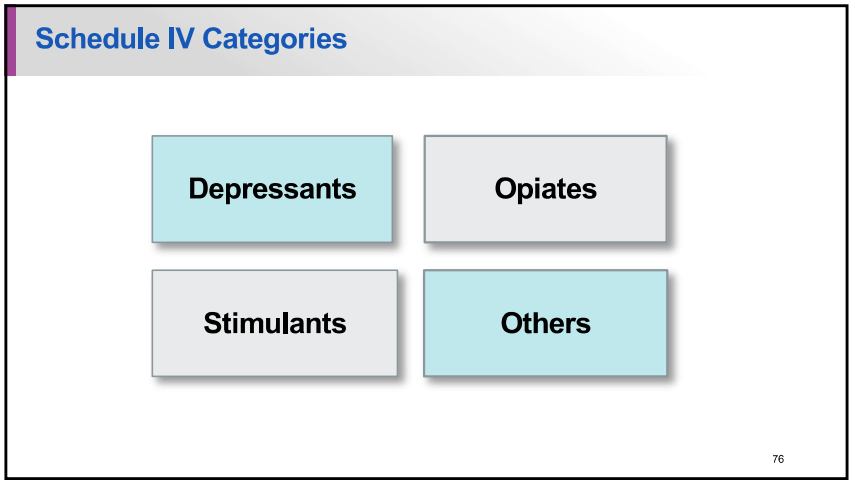

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Schedule IV Depressants

- Benzodiazepines
- Benzodiazepine receptor agonists
  - Zaleplon (Sonata®)
  - Zolpidem (Ambien®)
  - Eszopiclone (Lunesta®)

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Schedule IV Stimulants

- 12 in Schedule IV including mostly appetite suppressants
  - Phentermine
- Also includes armodafinil and modafinil

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Schedule V

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Classification Requirements

- Substance has a low potential for abuse relative to the drugs or other substances in Schedule IV.
- The drug or other substance has a currently accepted medical use in treatment in the United States.
- Abuse of the drug can lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.

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Schedule V Categories

- Opiates and opioids
  - 6 cough preparations not containing more than 200 mg codeine/100 mL
- Stimulant
  - Pyrovalerone used for chronic fatigue syndrome
- Others
  - Two antiepileptic drugs
    - Pregabalin
    - Lacosamide

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State Legislative Mandates

Know Your Nurse Practice Act
and
Any Other Relevant State Statutes

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State-by-state Guidance

- Each state has legislation specific to opiate prescribing in that state.
- Every prescriber should be familiar with the law in his or her practice state.
  - https://www.acep.org/globalassets/sites/acep/media/by-medical-focus/opioids/opioid-guide-state-by-state.pdf

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State-by-state Guidance (continued)

- Specifics will vary.
  - Some laws are…
    - Applicable to all prescribers
    - Specific to APRNs
- Fifteen states limit prescribing to opiate-naïve patients in acute pain to 7 days.
- The majority of states have laws that restrict treatment of acute pain in some way.
- Restrictions placed in variety of ways.

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State-by-state Guidance (continued)

- Examples of restricted prescribing
  - Duration
  - Condition
    - E.g., 4-day limit for post dental procedures, ophthalmic pain
  - Total daily dose
    - Calculated in terms of morphine milligram equivalents (MME)
  - Increased restrictions for minors

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Morphine Milligram Equivalents (MME)

- Total daily dosing is among the parameters monitored to reduce risk of overdose.
  - Several states limit MMEs by statute.
  - Other states direct specific agencies to limit MMEs.
  - Safest dosing <50 MME/day
  - Many states limit dosing to <90 MME/day.

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Morphine Milligram Equivalents (MME) (continued)

- Acute pain
  - Virtually no reason to exceed 90 MME daily

- Chronic pain
  - Doses in excess of 90 MME daily need careful justification.
  - Optimal use of adjuvants and nonpharmacologic agents

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Morphine Milligram Equivalents (MME) (continued)

Drug	Conversion Factor	Dose	MME
Buprenorphine tab	10	16 mg	160
Codeine	0.15	60 mg	9
Fentanyl patch	2.4	25 mcg/hr	60
Hydrocodone	1	60 mg	60
Hydromorphone	4	1 mg	4
Methadone	10	50 mg	500
Oxycodone	1.5	60 mg	90
Oxymorphone	3	50 mg	150
Tapentadol	0.4	200 mg	80
Tramadol	0.1	400 mg	40

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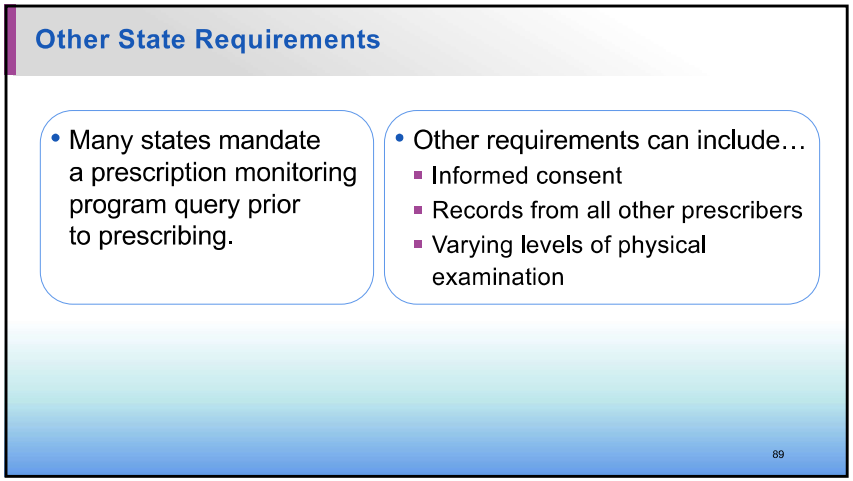

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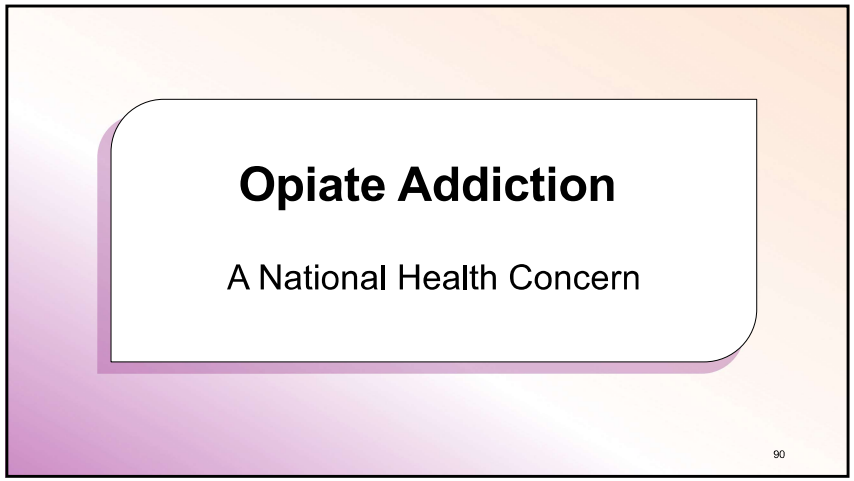

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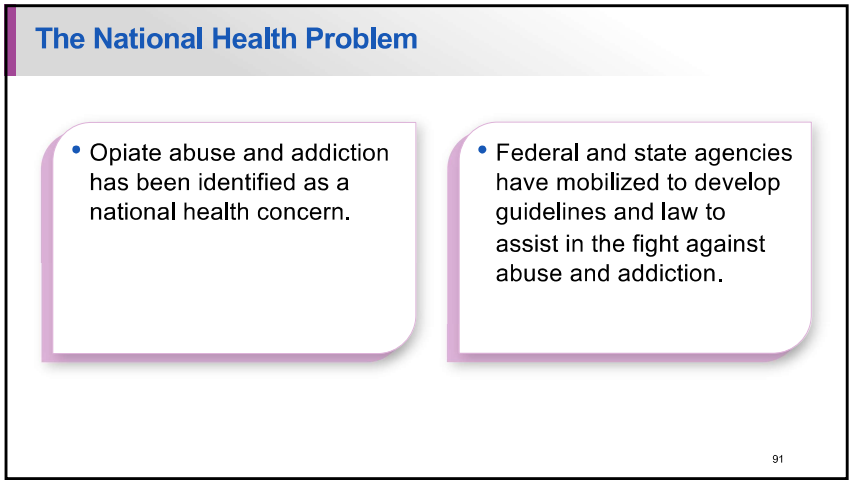

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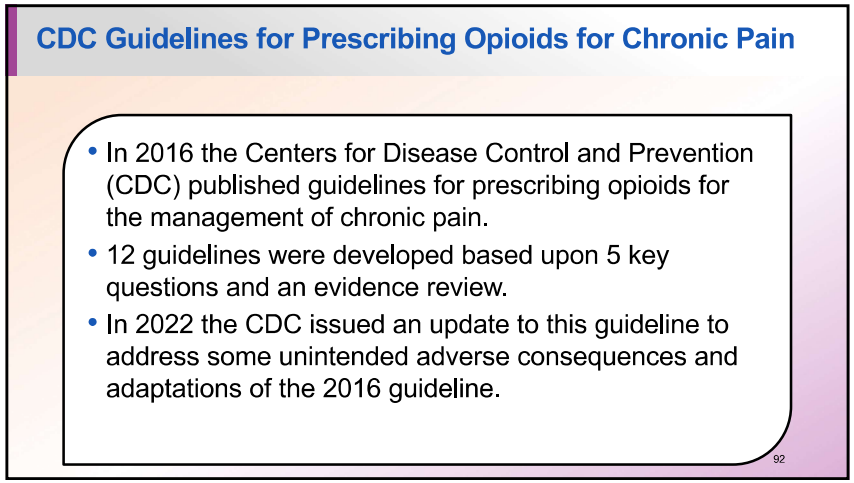

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CDC Guidelines for Prescribing Opioids for Chronic Pain (continued)

- The 2022 update is still characterized by 12 recommendations, now grouped according to 4 actions.
  1. Determining whether to initiate opioids for pain.
  2. Selecting opioids and determining dosages.
  3. Deciding duration of initial opioid prescription and conducting follow-up.
  4. Assessing risks and addressing potential harms of opioid use

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CDC Guidelines for Prescribing Opioids for Chronic Pain (continued)

- New to the 2022 update are 5 guiding principles.
  1. Acute, subacute, and chronic pain needs to be appropriately assessed and treated independent of whether opioids are part of a treatment regimen.
  2. Recommendations are voluntary and are intended to support, not supplant, individualized, person-centered care. Flexibility to meet the care needs and the clinical circumstances of a specific patient is paramount.

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CDC Guidelines for Prescribing Opioids for Chronic Pain (continued)

- New to the 2022 update are 5 guiding principles (cont'd).
  3. A multimodal and multidisciplinary approach to pain management attending to the physical health, behavioral health, long-term services and supports, and expected health outcomes and well-being of each person is critical.
  4. Special attention should be given to avoid misapplying this clinical practice guideline beyond its intended use or implementing policies purportedly derived from it that might lead to unintended and potentially harmful consequences for patients.

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CDC Guidelines for Prescribing Opioids for Chronic Pain (continued)

- New to the 2022 update are 5 guiding principles (cont'd).
  5. Clinicians, practices, health systems, and payers should vigilantly attend to health inequities; provide culturally and linguistically appropriate communication, including communication that is accessible to persons with disabilities; and ensure access to an appropriate, affordable, diversified, coordinated, and effective nonpharmacologic and pharmacologic pain management regimen for all persons.

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CDC Guidelines for Prescribing Opioids for Chronic Pain (continued)

- And finally…the 2022 update specifically excludes:
  1. Pain management related to sickle cell disease.
  2. Cancer-related pain treatment
  3. Palliative care
  4. End-of-life care

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Determine Whether to Initiate Opioids for Pain

1. Nonopioid therapies are at least as effective as opioids for many common types of acute pain.
   - Clinicians should maximize the use of non-pharmacologic and non-opioid pharmacologic therapies as appropriate for the specific condition and patient and only consider opioid therapy if benefits are anticipated that outweigh risks to the patient.
   - Before prescribing opioid therapy for acute pain, clinicians should discuss with the patient the benefits and known risks of opioid therapy

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Determine Whether to Initiate Opioids for Pain (cont'd)

2. Nonopioid therapies are preferred for subacute and chronic pain.
   - Clinicians should maximize the use of non-pharmacologic and non-opioid pharmacologic therapies as appropriate for the specific condition and patient and only consider opioid therapy if benefits are anticipated that outweigh risks. Before prescribing opioid therapy for acute pain, clinicians should discuss with the patient the benefits and known risks.
   - Clinicians should work with patients to establish goals for pain and function and consider how opioids will be discontinued if benefits do now outweigh risks.

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Selecting Opioids and Determining Dosages

3. When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release and long acting (ER/LA) opioids.
   - ER/LA opioids should be reserved for severe, continuous pain. The FDA has noted that some ER/LA agents should be considered only for patients who have received certain dosages of immediate-release opioids daily for at least one week.

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Selecting Opioids and Determining Dosages (cont'd)

4. When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, the lowest effective dosage should be prescribed.
   - If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage
   - Should carefully reevaluate individual benefits and risks when considering increasing dosage
   - Should avoid increasing dosage above levels likely to yield diminishing returns.

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Selecting Opioids and Determining Dosages (cont'd)

5. For patients already receiving opioid therapy, clinicians should carefully weigh benefits and risks and exercise care when changing opioid dosage.
   - If benefits of opioid therapy outweigh risks, work closely to optimize nonopioid therapies; if benefits do not outweigh risks, work closely to gradually taper to lower dosages.
   - Clinicians should not rapidly reduce opioid dosages.
   - Opioid therapy should not be discontinued abruptly unless warning signs of impending overdose are present

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Selecting Opioids and Determining Dosages (cont'd)

6. When opioids are needed for acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids.
   - Nontraumatic nonsurgical pain can often be managed without opioids
   - Opioids are sometimes needed for treatment of acute pain; when warranted, prescribe no greater quantity than expected duration.

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Deciding Duration of Initial Opioid Prescription and Conducting Follow-up

7. Clinicians should evaluate benefits and risks with patients within 1–4 weeks of starting opioid therapy for subacute or chronic pain or of dosage escalation.
   - Clinicians should regularly reevaluate benefits and risks of continued opioid therapy with patients.

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Assessing Risk and Addressing Potential Harms of Opioid Use

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss risk with patients.
   - Clinicians should work with patients to incorporate into the management plan strategies to mitigate risk, including offering naloxone
   - Clinicians should ask patients about their drug and alcohol use and use validated tools or consult with a behavioral health specialist to screen for and assess mental health and substance use disorders

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Assessing Risk and Addressing Potential Harms of Opioid Use (cont'd)

9. When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for chronic pain, clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or combinations that put the patient at high risk for overdose.
   - Ideally PDMP data should be reviewed before every opioid prescription.
   - At a minimum during long-term therapy review every 3 months.

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Assessing Risk and Addressing Potential Harms of Opioid Use (cont'd)

10. When prescribing opioids for subacute or chronic pain, clinicians should consider the benefits and risks of toxicology testing to assess for prescribed medications as well as other prescribed and nonprescribed controlled substances.
    - Toxicology testing should not be used in a punitive manner but used in the context of other clinical information to inform patient care.
    - Before starting opioids and periodically (at least annually) during opioid therapy, clinicians should consider the risks and benefits of toxicology testing.

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Assessing Risk and Addressing Potential Harms of Opioid Use (cont'd)

11. Clinicians should use particular caution when prescribing opioid pain medication and benzodiazepines concurrently.
    - Consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants.
    - In some cases, it may be appropriate to prescribe opioids to a patient on benzodiazepine therapy, but clinicians should use particular caution.
    - Buprenorphine or methadone for opioid use disorder should not be withheld from patients taking benzodiazepines or other CNS depressants.

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Assessing Risk and Addressing Potential Harms of Opioid Use (cont'd)

12. Clinicians should offer or arrange treatment with evidence-based medications to treat patients with opioid use disorder.
    - Detoxification on its own, without medications for opioid use disorder, is not recommended for opioid use disorder because of increased risks for resuming drug use, overdose, and overdose death.

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What to do with all of this information?

Figure 8

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Identifying Opioid Abuse Risk

- Prevention is the best strategy.
- Risk factors for opioid abuse include…
  - History of opioid abuse, misuse, addiction
  - Current or past substance abuse
  - Untreated psychiatric disorders
  - Social or family environments that encourage misuse
- Prevalence is higher in…
  - People of middle age
  - Comorbid non-opioid substance abuse
  - Psychiatric comorbidities

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Risk Assessment

- Opioid Risk Tool (ORT)
  - Brief self-report point scoring system
    - Family history
    - Personal history
    - Age
    - Preadolescent sexual abuse
    - Mental health disorders
  - Score of ≥8 indicates high risk

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Risk Assessment (continued)

- Tool for clinician to determine how much long-term opioid therapy may be required (Screener and Opioid Assessment for Patients with Pain-Revised [SOAPP®-R])
  - Clinician administered 24-item tool
  - Score of ≥18 indicates high risk of abuse
  - Topics similar to ORT although the family history is not well represented

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Risk Assessment (continued)

- The Brief Risk Questionnaire (BRQ)
  - 12-item self-administered screening tool
  - May be better correlated with risk that ORT and SOAPP®-R
  - Some concern about higher false positives
- Utility of screening tools is marginal at best.

- Risk assessment tools are one of many mitigation strategies.
- No studies have evaluated the utility of risk assessment or mitigation strategies with respect to…
  - Overdose
  - Addiction
  - Abuse

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Assessment of Comorbidities

- Patients with mental health comorbidities are at risk for use disorders.
- Mental health comorbidities often produce pain that does not respond to pharmacotherapy.
- Dose escalations lead to chronic use and disorder syndromes.

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Psychiatric Comorbidities

Underlying psychiatric conditions can…

- Produce pain when no organic cause is apparent
  - Psychosomatic
  - Psychogenic
- Exaggerate the pain experience when organic cause is present
  - Psychogenic modification

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Psychosomatic Pain

- Often a consequence of anxiety
- Anxiety results in structural change in muscle.
- A common finding in patients with generalized anxiety disorder
- Can occur acutely during times of high stress

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Psychosomatic Pain – Patient Assessment

- Tense facial expression
- Fidgety and restless
  - Sit on edge of chair, wring hands
- Often feel need to stretch, massage
- Pain often accumulates with day's activities, especially if environment is tense.

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Psychosomatic Pain – Physical Examination

- Good range of motion
- Exam reveals trigger point
- Patient can demonstrate crack

- Localized area of significant pain with palpation
- No evidence of nerve root involvement
- No skin tenderness

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Psychosomatic Pain – Treatment

- Temporary relief
  - Chiropractic or physiotherapy intervention
  - Heat or cold applications

- Definitive treatment centers around relieving the cause

- Pharmacotherapy not typically a first-line approach

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Psychogenic Pain

- The conversion of anxiety into pain without tissue change
- Characterized by underlying mental health disorder
- Usually a history of emotional problems
- No organic cause will be found

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Psychogenic Pain – Assessment

- Patient is convinced of illness.
  - Frequent demands for numerous consultations
- There are periods of symptom improvement.
- Upset body image can produce skin tenderness and dulled sensory appreciation.
- Physical findings are limited and inconsistent.

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Psychogenic Modification of Organic Pain

- Sincere emotional reaction to the organic event modifies the perception of organic pain.
- The organic problem alone would not cause disability; the psychogenic component often does.
- This patient is often the most difficult diagnostic and therapeutic challenge.

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Psychogenic Modification of Organic Pain – Assessment

- The physical findings will be consistent with mild disease.
- Life situation and personality of the patient are important assessment features.
- Psychogenic component interferes with treatment.

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Psychogenic Modification of Organic Pain (continued)

- Minor physical problems result in total disability.
- Treatment failures result in aggressive treatment.
  - Characteristic surgical failure
- In patient with back pain
  - ROM and SLR are normal or minimally impaired.
  - Neuro changes are questionable or inconsistent.

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Short- or Long-acting Agents?

The Current Standard of Care

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Short-acting Agents

- The half-life of common immediate-release (short-acting) opiates is 2.5 to 5 hours.
  - Results in dosing patterns of q 4–6 h
    - Upside – Quick washout
    - Downside – Requires several doses daily
- Short-acting opioids are also often accompanied by post dose euphoria.
  - Differs from the pain relief action
  - Oxycodone among biggest offenders
  - Post dose euphoria contributes heavily to psychologic addiction.

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Long-acting Agents

- Less association with post dose euphoria
- Provides a more steady state of pain control due to less frequent dosing
- Historically was encouraged for patients requiring chronic opioid therapy

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Long-acting Opioids

Compound	Strengths	Typical Starting Dose and Dosing Interval	Name Branding
Morphine controlled-release tablet	15, 30, 60, 100, 200 mg	15–30 mg every 8–12 hours	MS Contin® Oramorph® SR
Morphine controlled-release capsule	20, 30, 50, 60, 100 mg	20 mg every 12 or 24 hours	Kadian®
Morphine extended-release capsule	30, 60, 90, 120 mg	30 mg every day	Avinza®
Oxycodone controlled-release	10, 20, 40, 80 mg	10 mg every 12 hours	OxyContin®
Oxymorphone extended-release	5, 10, 20, 30, 40 mg	5 mg every 12 hours	Opana® ER
Hydromorphone extended-release	8, 12, 16 mg	8 mg once daily	Exalgo® ER
Fentanyl transdermal	25, 50, 75, 100 mcg/hr patch	25 mcg applied every 3 days	Duragesic®
Buprenorphine transdermal	5, 10, 20 mcg/hr patch	5 mcg applied every 7 days	Butrans®

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What is the current approach? Short-acting or Long-acting?

- Short-acting always indicated for acute pain.
  - The risk/benefit analysis universally favors benefit of short-acting agents.
  - Duration of therapy is anticipated to be quite short.

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Short- vs. Long-acting Opioids

- Remember 12 guiding principles for prescribing opioids for chronic pain.
  - #3…when starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.

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When are long-acting agents indicated?

- When it is clear that the patient will be on opioid therapy for an extended duration
  - Cancer care is the classic example.
  - In all clinical circumstances, optimize nonpharmacologic and non-opioid options.

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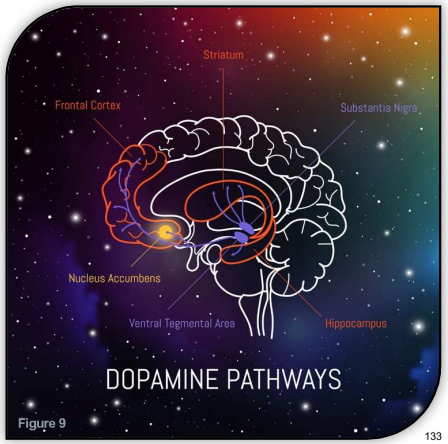
Pharmacologic Management of Substance Use Disorders



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Substance Use Disorders

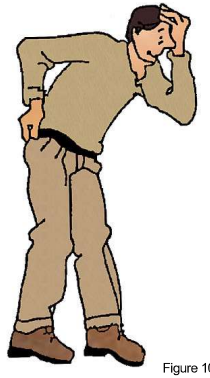
Figure 10

- Opioid use disorder currently most widely discussed.
  - In 1995, pain was identified as the **5th vital sign**.
  - A series of policy changes led to widespread opiate prescribing.
  - Result – Opioid epidemic
  - Stringent legislation emerged to regulate opioid prescribing.
    - Providers abruptly stop prescribing opioids.
    - Deaths occur from both overdose and suicide.

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Opioid Use Disorder (continued)

- ICD-10 terminology
  - Use
  - Abuse
  - Dependence

- DSM-V
  - Substance use disorder
    - Mild, moderate, severe, remission, etc.

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Substance Use Disorder

- A pathological condition reflecting…
  - Compulsive, prolonged, self-administration of opioids with no legitimate medical purpose

    or
  - Using doses greatly in excess of the amount needed
  - Some element of social or occupational dysfunction

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Substance Use Disorder (continued)

1. Taking substance in larger amounts or over longer period than intended
2. Persistent desire or failed efforts to control use
3. Much time spent obtaining, using or recovering from effects
4. Craving, strong desire or urge to use

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Substance Use Disorder (continued)

5. Failure to fulfill major roles at home, work or school
6. Continued use despite social or interpersonal problems related to use
7. Giving up or reducing important social, occupational or recreational activities due to use

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Substance Use Disorder (continued)

8. Recurrent use in physically hazardous situations
9. Continued use despite awareness of a physical or psychological problem due to substance
10. Tolerance
    - Need for larger amount to achieve desired effect or diminished effect with same amount

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Substance Use Disorder (continued)

11. Withdrawal
    - Occurrence of a characteristic withdrawal syndrome or continued use of substance to avoid withdrawal symptoms

SUD	Criteria
Mild	2–3
Moderate	4–5
Severe	>6

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Opioid Use Disorder

- Successful management of opioid use disorder is multimodal.
  - Must include both pharmacologic and nonpharmacologic interventions
- Medication-assisted therapy (MAT)
  - Without MAT abstinence rate
    - <50% at 6 months
    - <15% at 1-year
    - Increased overdose rates following abstinence

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Medication-assisted Therapy

- Opioid treatment programs (OTP) provide MAT for patients with opioid use disorder.
  - Must be accredited by a Substance Abuse and Mental Health Services Administration (SAMHSA)
  - Maintains a "whole person approach"
- **MAT markedly underutilized!**

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Medication-assisted Therapy (continued)

- MAT decreases
  - Opioid use
  - Opioid-related deaths (overdose deaths)
  - Criminal activity
  - Infectious disease transmission
- Heroin overdose deaths fell by 37% in Baltimore after buprenorphine became available
- MAT increases
  - Social functioning
  - Treatment retention
- MAT improves outcomes for pregnant women
  - Decreases incidence of neonatal abstinence syndrome

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Acute Medical Detoxification

- Primary purpose
  - Safe withdrawal from substance use disorder
  - Not necessary for all substance use disorders
  - Commonly performed in an inpatient setting
- Pharmacotherapy and monitoring
  - Foundation of acute medical detoxification

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Acute Medical Detoxification (continued)

- Thiamine replacement
  - 100 mg IM or PO daily or BID for 3 days
    then
  - 100 mg PO daily for length of stay
- Folate
  - 1 mg PO daily for length of stay

- Seizure prophylaxis for length of stay
  - Carbamazepine 200 mg BID
    or
  - Levetiracetam 500 mg BID
    - Consider drug monitoring and weaning.

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Acute Medical Detoxification (continued)

- Benzodiazepine for acute sympathetic nervous system depression
  - Chlordiazepoxide HCl classically used
  - Lorazepam more contemporary
  - Oxazepam with liver disease
    - Intended only for short-term use
    - Contraindicated with many MAT drugs

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Benzodiazepine

- Mechanism of action
  - Potentiates the effects of GABA and other inhibitory neurotransmitters
  - Blocks cortical and limbic arousal

- Very effective for short-term use
  - Particular caution in patients with use disorders

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Acute Medical Detoxification (continued)

- Clonidine
  - Greatest utility in opioid detoxification
  - MOA
    - Stimulates peripheral alpha-antiadrenergic receptors in the CNS
    - Decreases sympathetic activity from the brain down
    - Can produce subjective calming

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Acute Medical Detoxification: Additional Short-term Options

- Hydroxyzine – Anxiety
  - 50 mg q6h PRN
- Trazodone – Insomnia
  - 50 mg orally every bedtime PRN
  - Hyoscyamine – Abdominal cramping
  - 0.125 mg SL (4 × each day PRN)
- Methocarbamol
  - 1500 mg PO TID × 5 days
- Cyclobenzaprine
  - 10 mg PO at bedtime × 5 days
- NSAIDs

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Acute Medical Detoxification (continued)

- Very often given in accordance with guidance from Clinical Opiate Withdrawal Scale (COWS) protocol
  - Intended for short-term use

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Relapse Prevention

- MAT protocols
  - Must be used with counseling and support programs.
  - Patients unlikely to be successful without well-rounded approach.

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MAT Options

- Methadone orally
- Various formulations of buprenorphine, naltrexone, naloxone, alone or in combination are available
- May be used for years in the successful management of opioid use disorder

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Methadone

- Use in opioid use disorder capitalizes on long half-life
  - Activates opioid receptors in the way that opiates of abuse do
- Euphoria of shorter acting agents
  - Eliminated
- Distributed only by SAMHSA-approved centers

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Methadone (continued)

- Risk of abuse
  - Overdose and death still present
- Pharmacokinetic implications
  - Substrate of CYP1A2 isoenzyme
  - Prolongation of QT interval
- Historically, effective but no longer first-line option

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Buprenorphine

- Markedly increased access – can now be prescribed by any provider with state-authorized CIII prescribing authority.
- Available in multiple formulations that promote long-term adherence to treatment.

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Buprenorphine (continued)

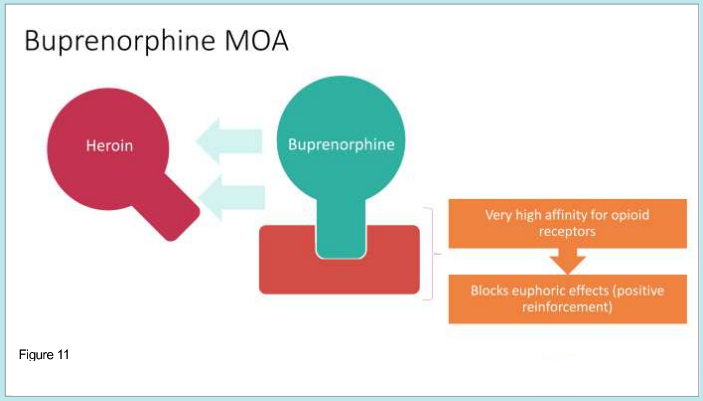

Figure 11

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Buprenorphine MOA

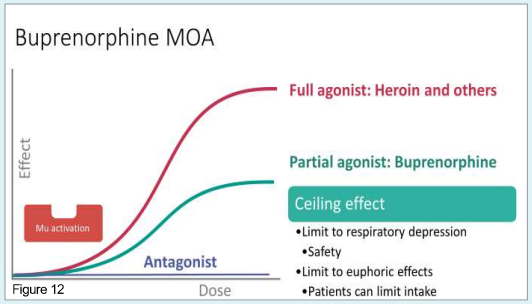

Figure 12

- Partial mu agonist
- Opiate receptors activated to a dose ceiling

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Buprenorphine MOA (continued)

- Very high affinity for mu receptors
  - Will displace heroin when both drugs on board simultaneously
  - Patients on buprenorphine will not experience euphoria if they use heroin

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Buprenorphine MOA (continued)

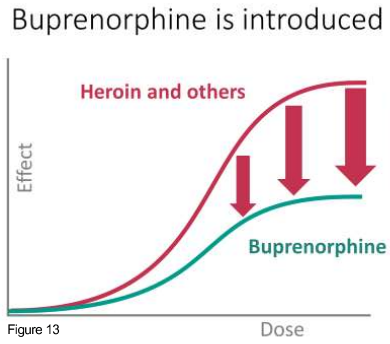

Figure 13

Partial activation
- Experienced as withdrawal
- Antagonist effect

- Patients planning detoxification **should not use** buprenorphine until withdrawal well established.
- Do not begin until COWS score >8.

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Buprenorphine – Available Formulations

- Combo of buprenorphine and naloxone (Suboxone®): Oral
- Buprenorphine sublingual (Subutex SL®)
- Buprenorphine extended-release (Sublocade™): Monthly injection
- Buprenorphine implant (Probuphine®): q6m
- Buprenorphine hydrochloride injectable; injection (Buprenex®)
  - Off-label for inpatient heroin withdrawal

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Buprenorphine – Adverse Effects

- Similar to those of opiates but less profound
  - Can prolong the QT interval
- Precipitates anxiety in some patients
  - Increases risk of relapse

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Buprenorphine/Naloxone Combination

- Bunavail®, Zubsolv®
  - Both formulations add naloxone to decrease ability to crush and abuse
  - Not recommended for induction therapy
    - May be used after patient successfully initiates buprenorphine treatment

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Naltrexone

- Available in oral and injectable forms
  - Functions as an opiate antagonist
- Contraindicated in patients taking opioids

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Naltrexone HCl (ReVia®)

- Opioid antagonist
  - Related to naloxone (Narcan®)
- Markedly attenuates or completely blocks the subjective effect of intravenous opioids
  - Also effective in alcoholism
- Mechanism of action not understood
- Oral form marketed as naltrexone HCl (ReVia®)
  - Titrated to 50 mg at bedtime
- Contraindicated in patients on opioids or those who have failed naloxone challenge test

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Naltrexone Extended-release Injectable Suspension (Vivitrol®)

- Long-acting
- Primary indication
  - Alcoholism
  - One monthly injection
- Need to assess clients for compliance and failure of other therapies
  - Drug supplied to an approved dispenser/provider

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Alcohol Relapse Options

- Acamprosate
  - 666 mg TID
- Naltrexone oral challenge
- Naltrexone
  - 50 mg at bedtime
- Naltrexone extended-release injectable suspension (Vivitrol®)
  - 380 mg once monthly
- Combination of
  - Naltrexone extended-release injectable suspension (Vivitrol®) and acamprosate (Campral®) therapy

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Acamprosate

- Mechanism of action – Unclear
  - Theorized to restore normal or near normal balance of neurotransmitters
  - Modulates hyperglutamatergic function that occurs following withdraw of ETOH after long-term use

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Acamprosate (continued)

- Available as 333 mg tablets
- Standard dose
  - Two tablets TID
- Adherence enhanced by taking with meals
- If dose missed, **do not** double next dose.
  - Resume normal schedule
- Adverse reactions
  - Diarrhea
  - Weakness
  - Nausea
  - Pruritus
  - Typically occur early in therapy

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Summary

- Pain is commonly encountered in clinical practice.
- An understanding of the physiology of pain provides a foundation for best prescribing practices.
  - Opioids are sometimes required.
  - Appropriately chosen non-opioid options can be very effective.

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Summary (continued)

- Opioid use disorder is prevalent and dangerous.
  - Clinicians should always be vigilant to indicators and risk factors for opioid use disorder.
- The CDC guidelines are mean to be a voluntary guide for prescribing – not a mandate that prohibits clinical judgment and good patient care.
- Medication-assisted therapy (MAT) is among the most promising treatment options.

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End of Presentation

Thank you for your time and attention.

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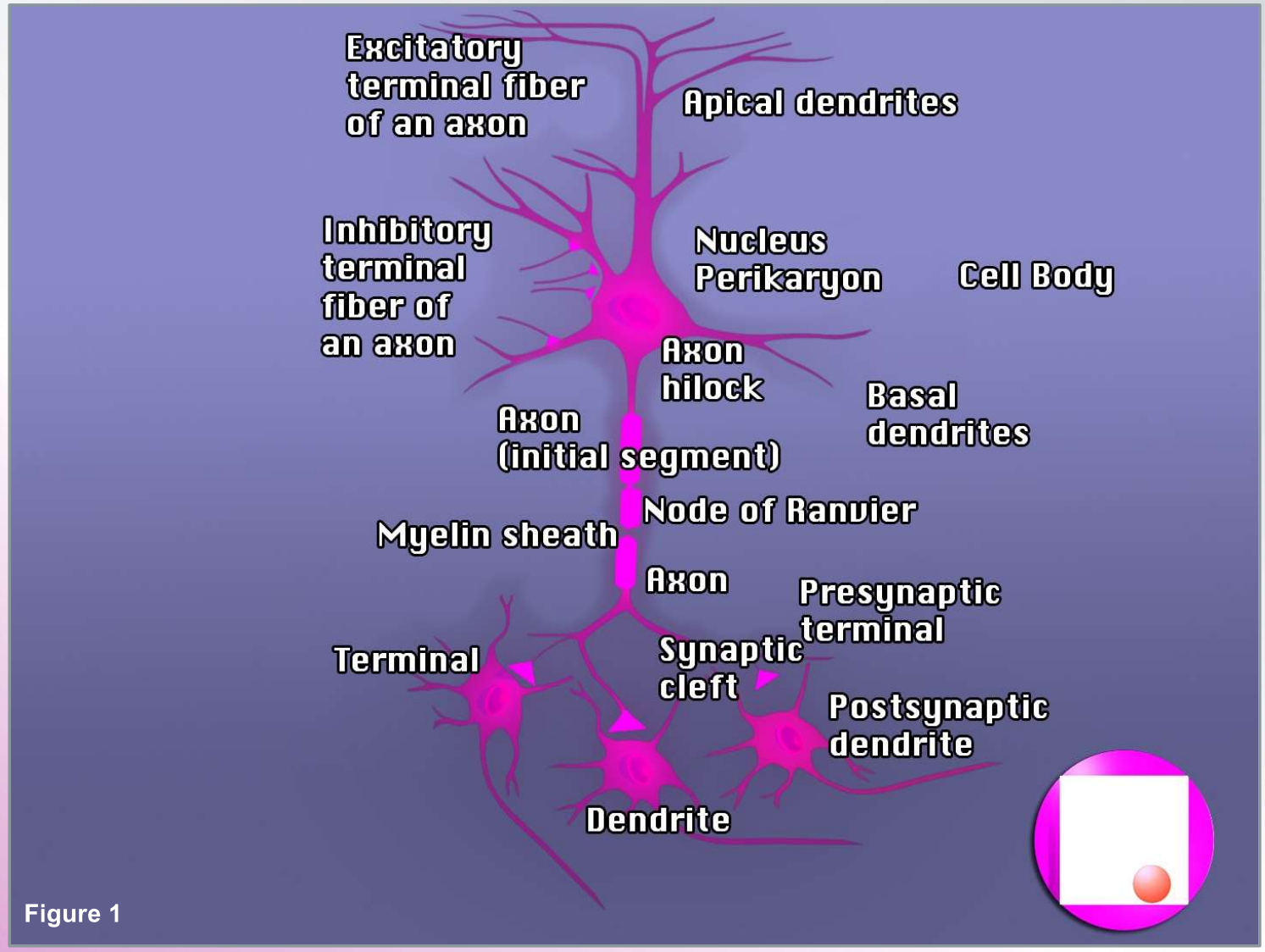

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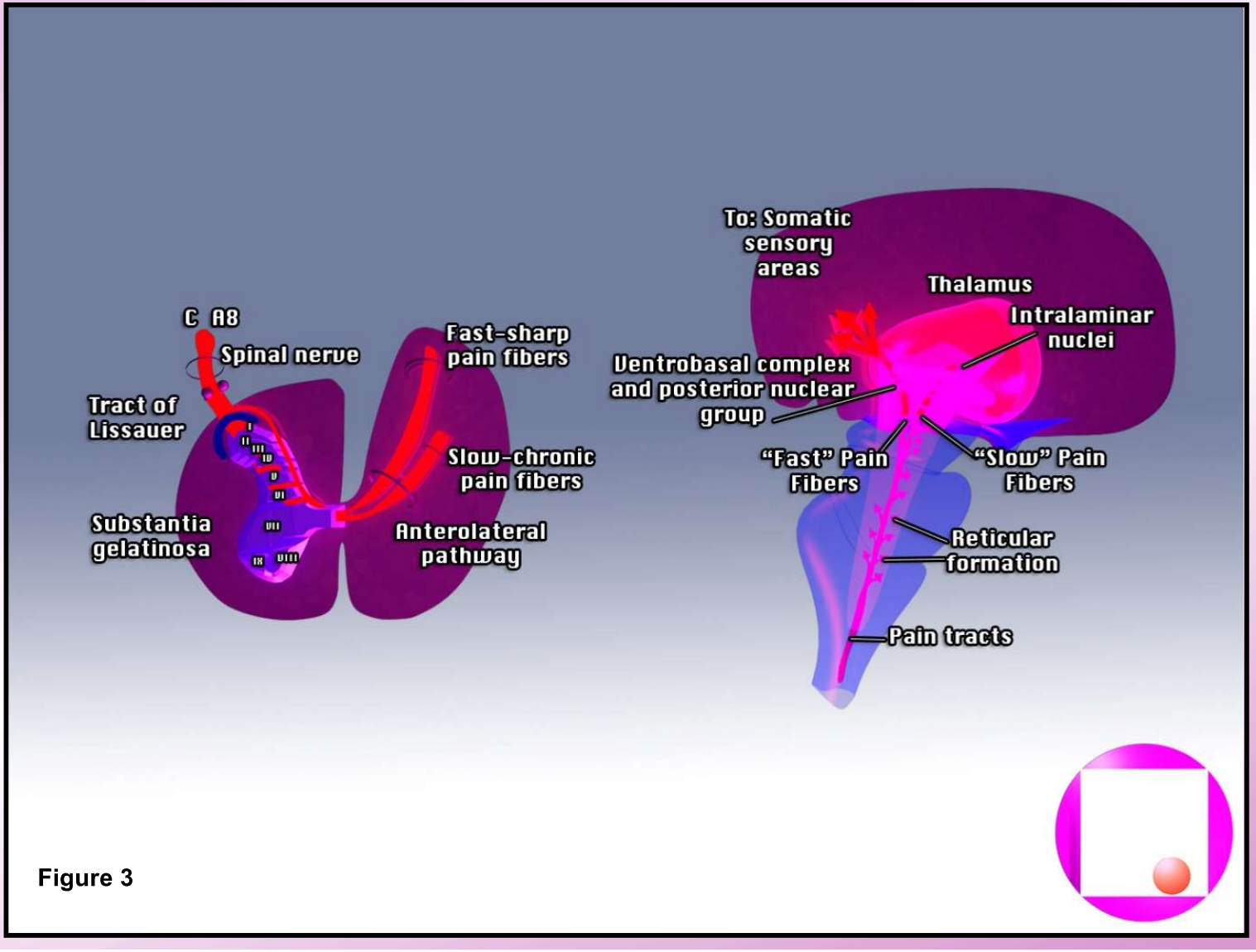

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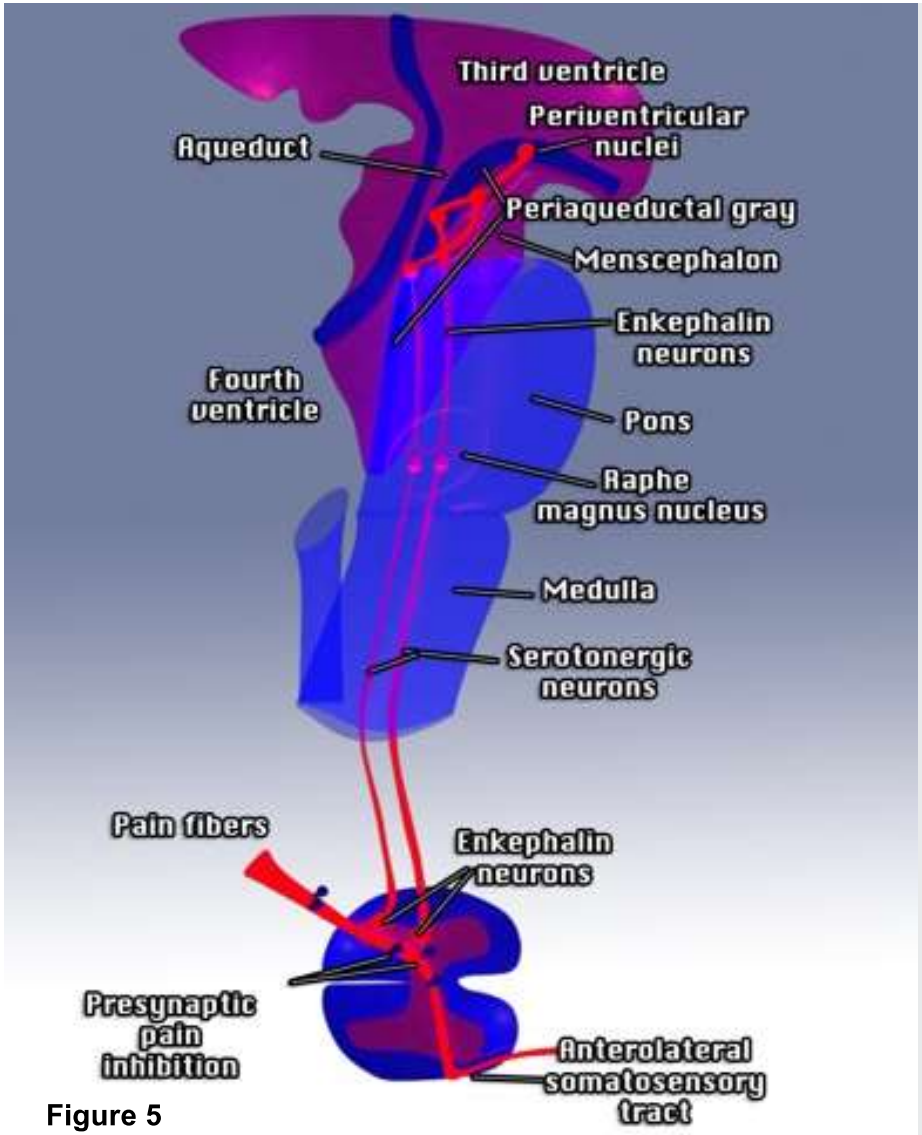


Figure 5

Physiology of Pain
Endogenous Pain Suppression

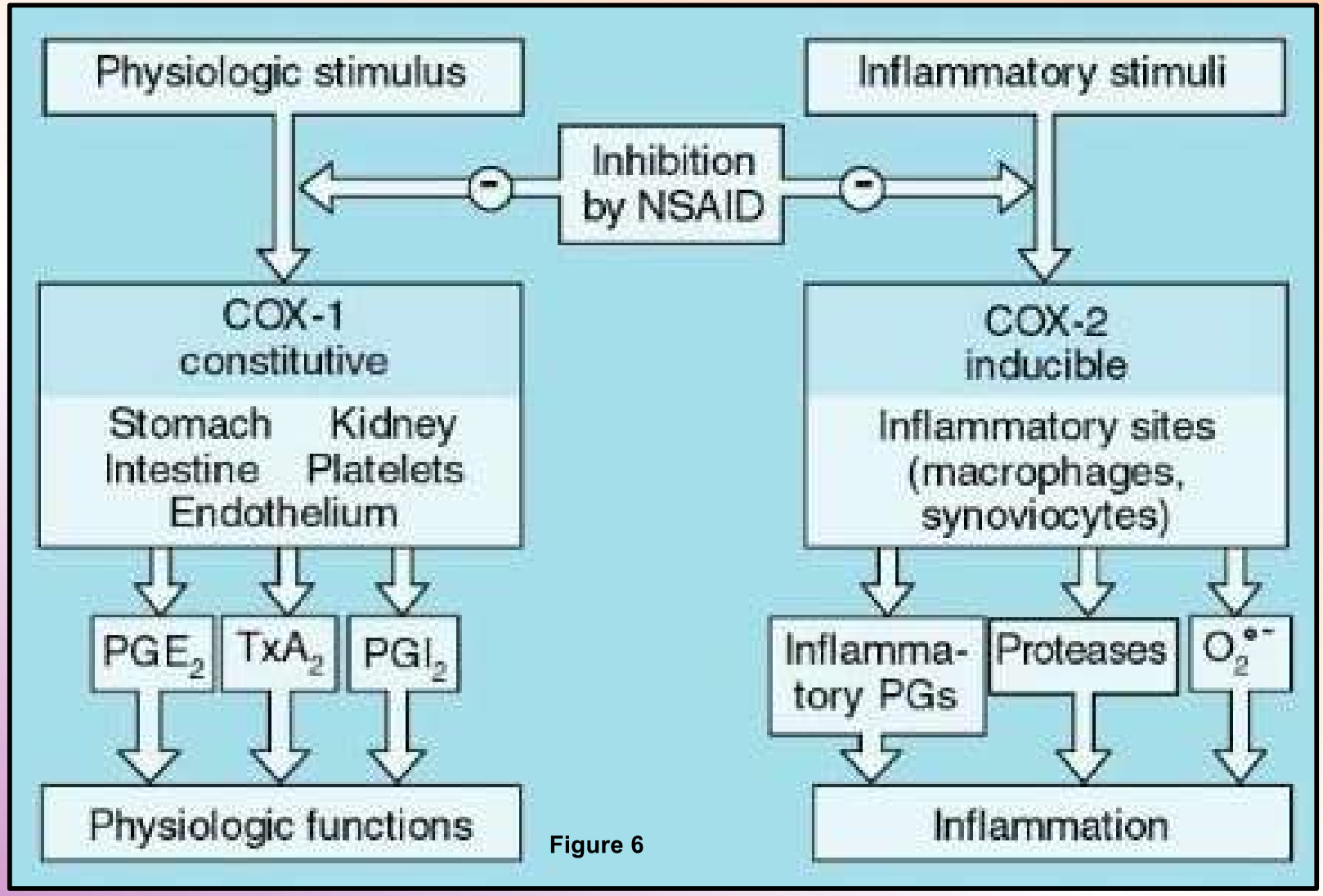
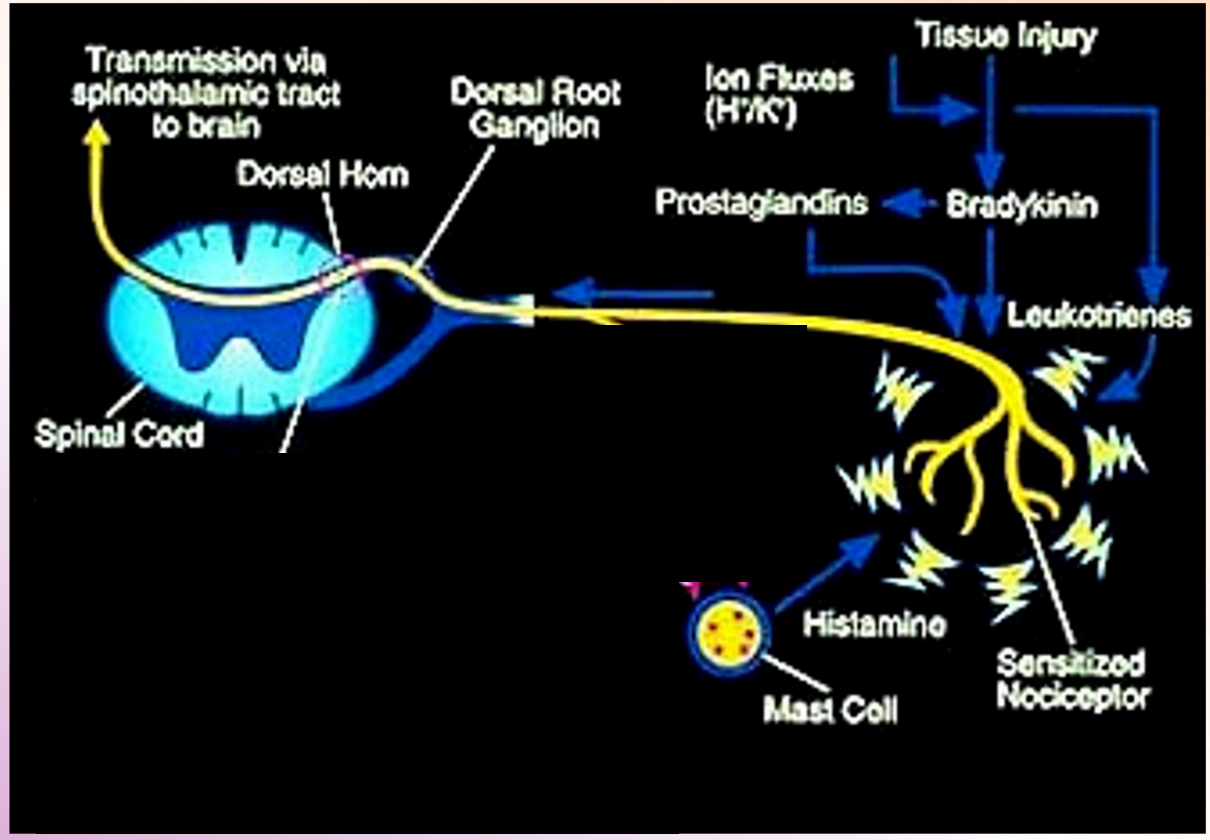


Figure 6

Pharmacodynamics of NSAIDs



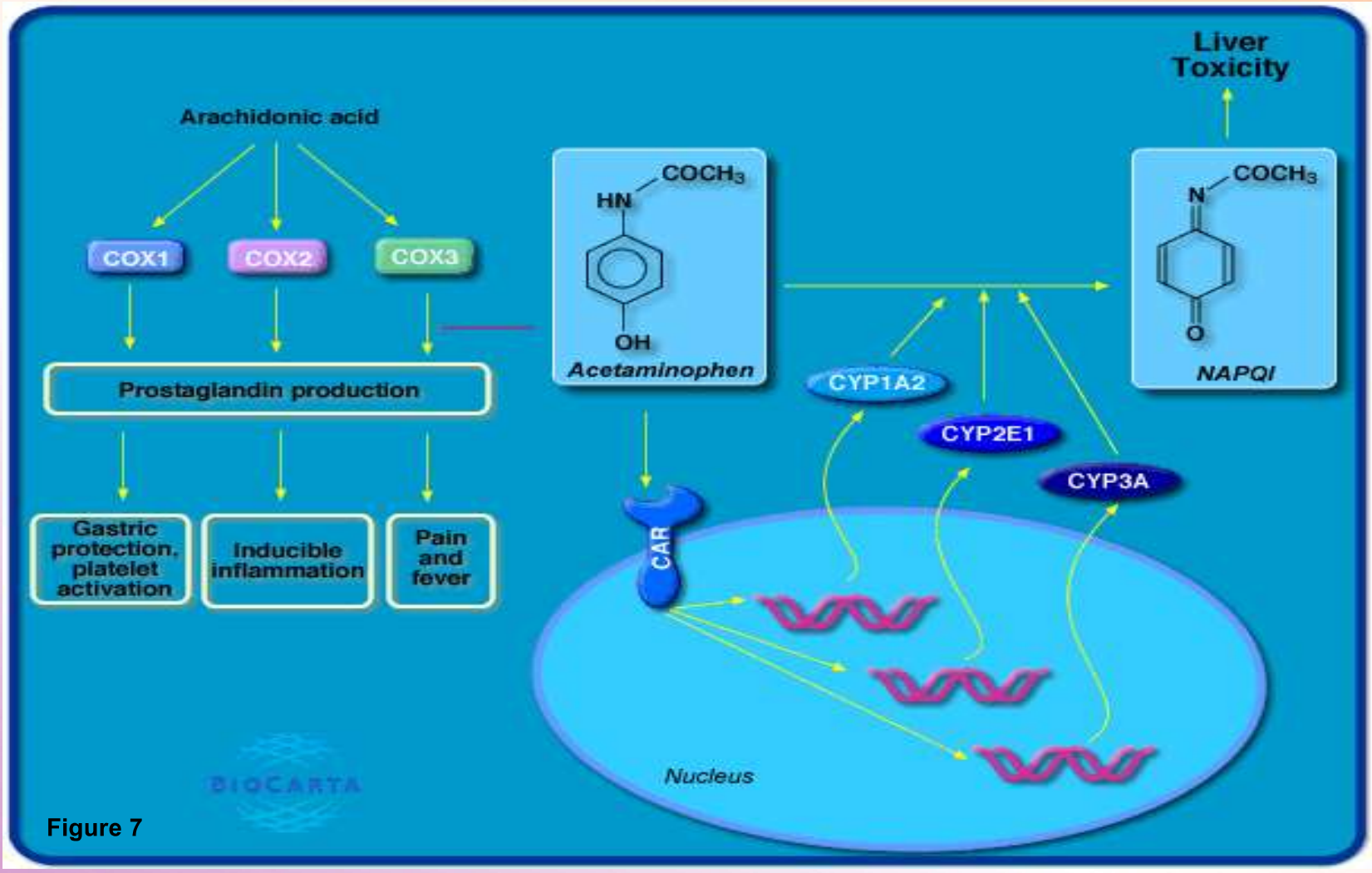
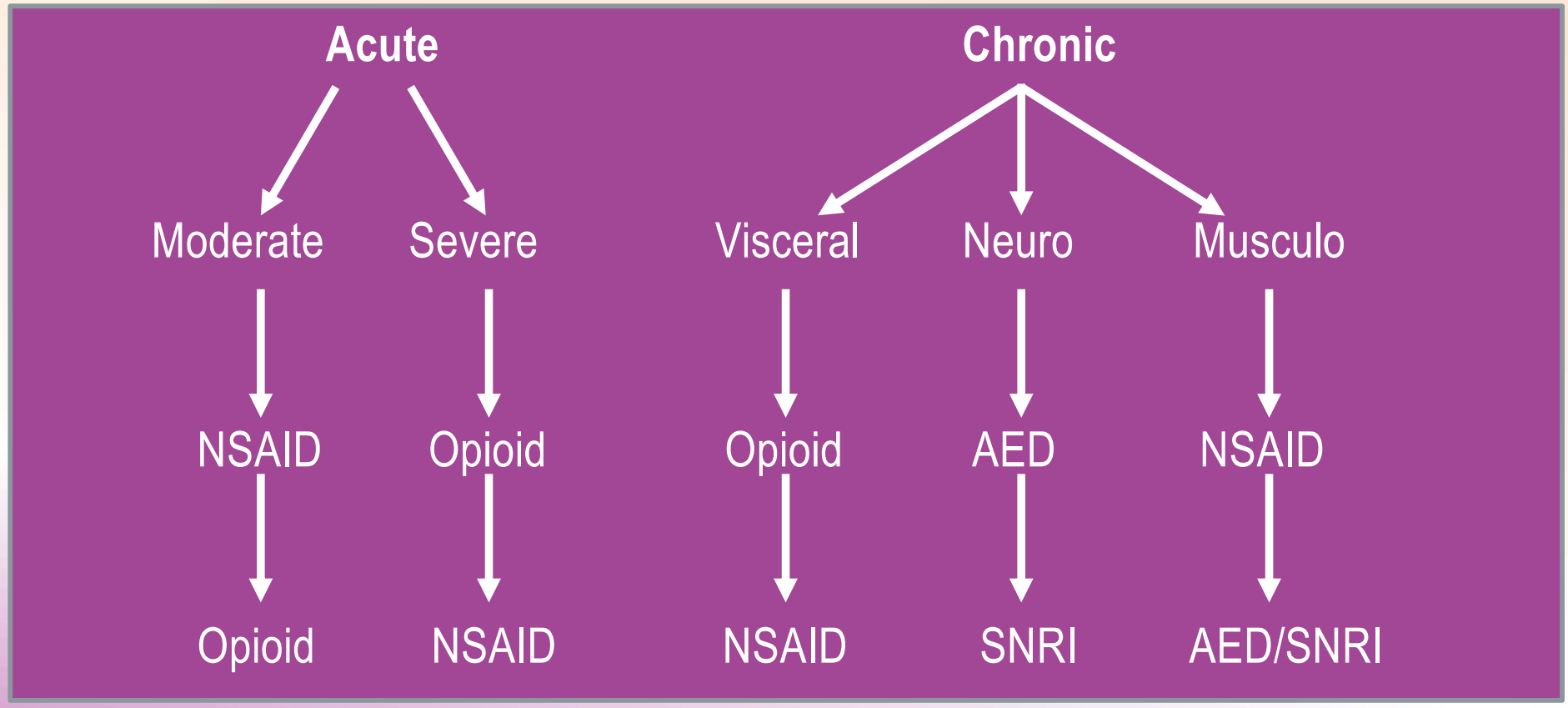


Figure 7

Selection of the Agent



Morphine Milligram Equivalents (MME)
(continued)

Drug	Conversion Factor	Dose	MME
Buprenorphine tab	10	16 mg	160
Codeine	0.15	60 mg	9
Fentanyl patch	2.4	25 mcg/hr	60
Hydrocodone	1	60 mg	60
Hydromorphone	4	1 mg	4
Methadone	**10**	50 mg	500
Oxycodone	1.5	60 mg	90
Oxymorphone	3	50 mg	150
Tapentadol	0.4	200 mg	80
Tramadol	0.1	400 mg	40

Long-acting Opioids

Compound	Strengths	Typical Starting Dose and Dosing Interval	Name Branding
Morphine controlled-release tablet	15, 30, 60, 100, 200 mg	15–30 mg every 8–12 hours	MS Contin® Oramorph® SR
Morphine controlled-release capsule	20, 30, 50, 60, 100 mg	20 mg every 12 or 24 hours	Kadian®
Morphine extended-release capsule	30, 60, 90, 120 mg	30 mg every day	Avinza®
Oxycodone controlled-release	10, 20, 40, 80 mg	10 mg every 12 hours	OxyContin®
Oxymorphone extended-release	5, 10, 20, 30, 40 mg	5 mg every 12 hours	Opana® ER
Hydromorphone extended-release	8, 12, 16 mg	8 mg once daily	Exalgo® ER
Fentanyl transdermal	25, 50, 75, 100 mcg/hr patch	25 mcg applied every 3 days	Duragesic®
Buprenorphine transdermal	5, 10, 20 mcg/hr patch	5 mcg applied every 7 days	Butrans®

Buprenorphine MOA

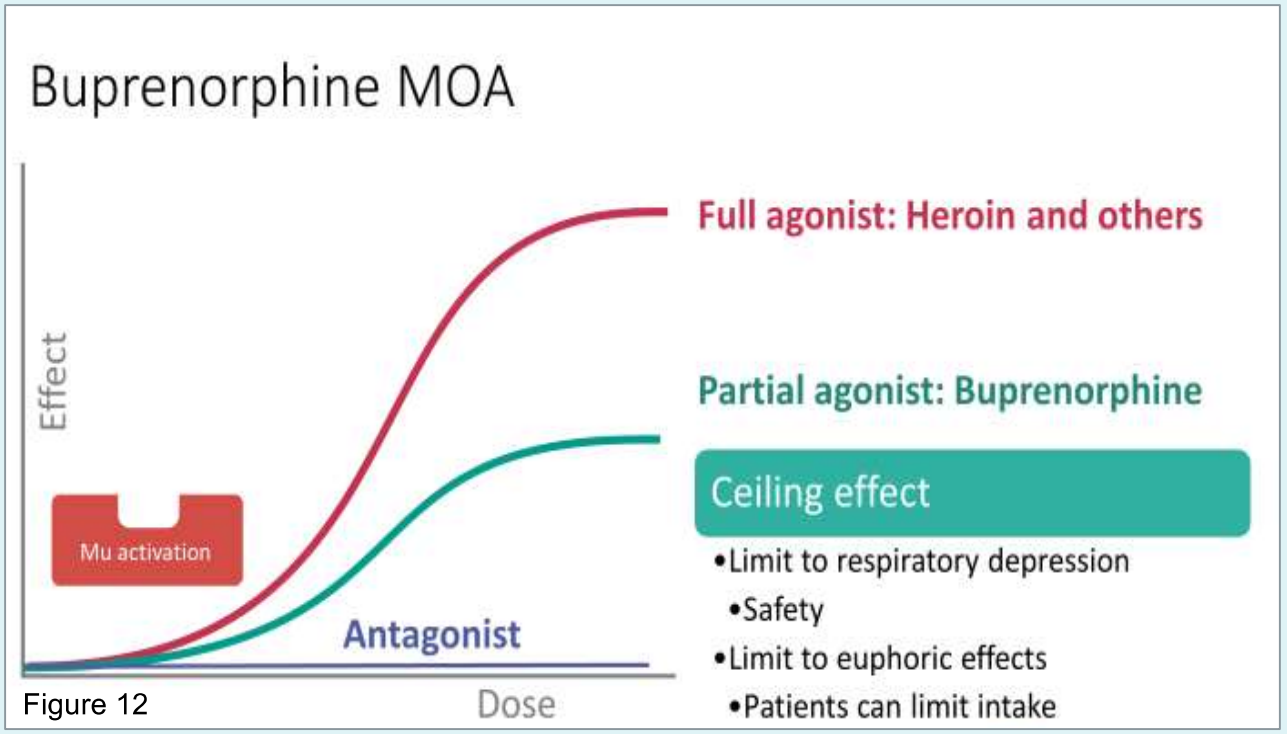


Figure 12

- Partial mu agonist
- Opiate receptors activated to a dose ceiling

Buprenorphine MOA (continued)

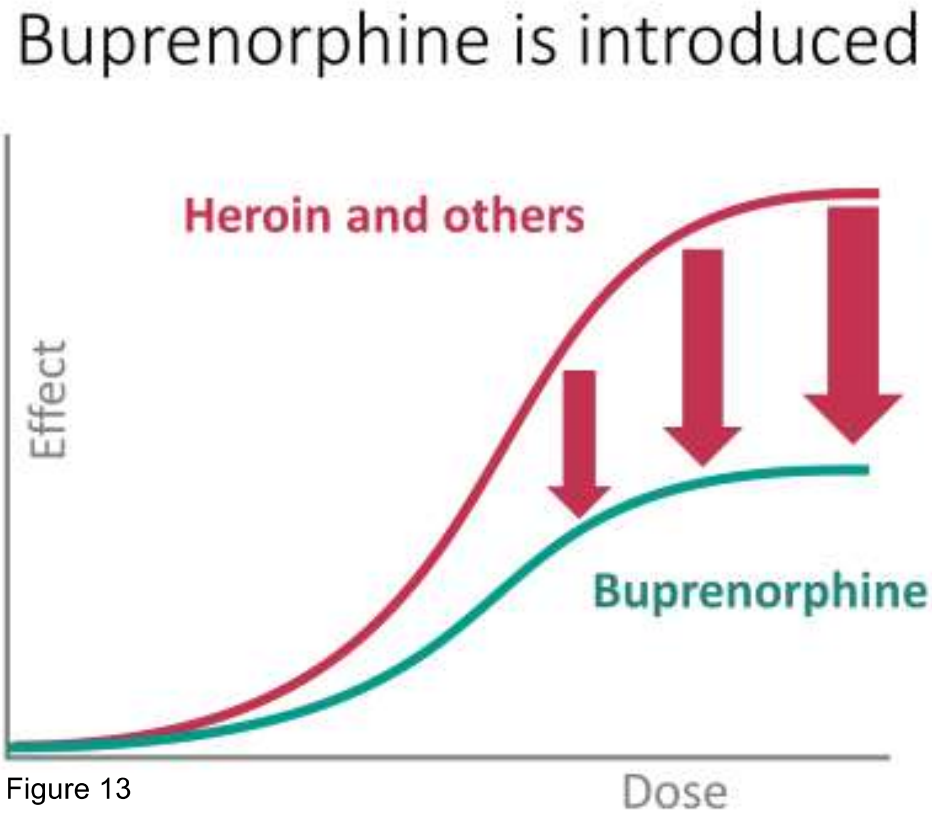


Figure 13

Partial activation

- Experienced as withdrawal
- Antagonist effect

- Patients planning detoxification **should not use** buprenorphine until withdrawal well established.
- Do not begin until COWS score >8.