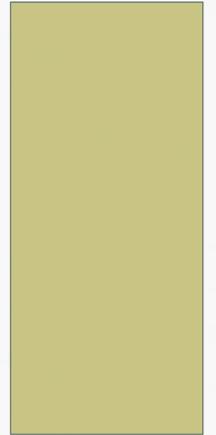


# OPIOIDS:

DEPENDENCE & DETOXIFICATION



# DEPENDENCE

- The term *dependence* is used to describe **two separate phenomena**:
  - Pharmacologically, drug dependence is characterized by the presence of tolerance and a withdrawal symptom.
  - Psychiatrically, drug dependence is characterized by compulsive use, inability to reduce use, preoccupation, drug-seeking behaviors, and a heightened vulnerability to relapse after abstinence.

# PSEUDO-ADDICTION

- Pseudo-addiction describes drug-seeking behaviors iatrogenically produced in pain patients by inadequate pain treatment.
  - This is manifested as **preoccupation with and pursuit of opioid medication driven by a desire for pain relief**, *not* the drug's mood-altering effects.
    - Initially, the patient receives an inadequate level of analgesia → which leads to the patient's escalation of analgesic demands and behavioral changes.
    - This may be exaggerated to convince others of the pain severity and need for more medication → which results in a crisis of mistrust between the patient and the healthcare team.
- Pseudo-addiction is preventable when the patient's report of pain is accepted as valid.

# EPIDEMIOLOGY OF OPIOID ABUSE AND DEPENDENCE

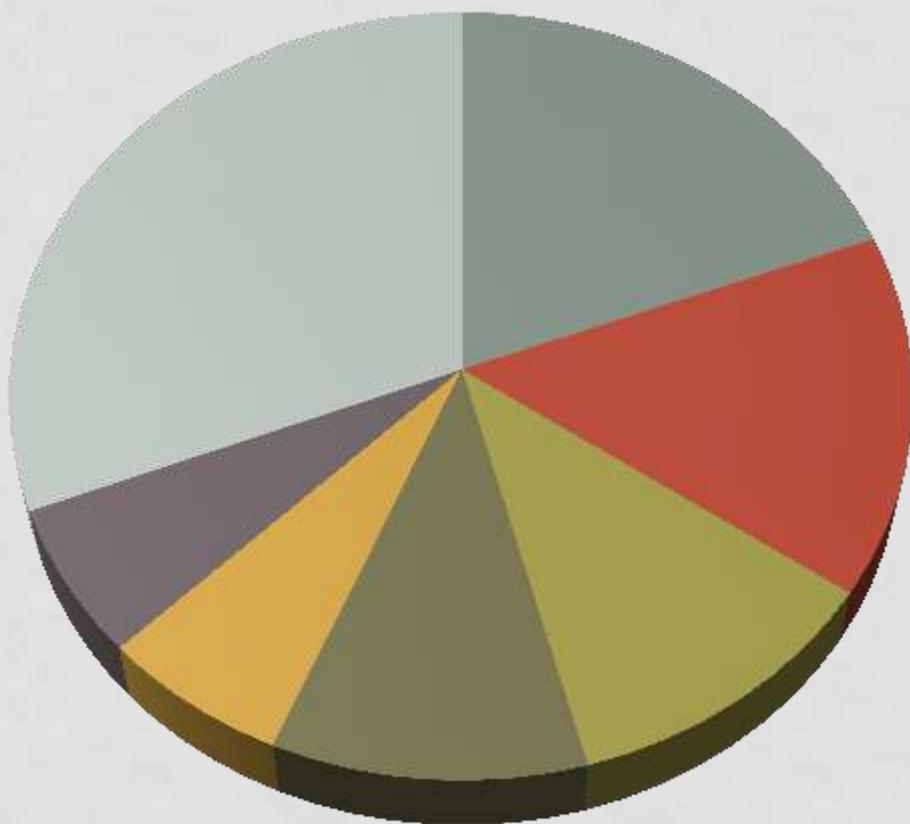
- As of 2009, the estimated worldwide prevalence of current opioid use was between 0.3% and 0.5%, equating to 21 to 35 million people, including nearly 18 million people (5.9% of the population) in the United States. Substantial regional differences in abuse patterns exist.
- An estimated 4.1 million people (1.6%) in the United States have used heroin at least once in their lives, and at least 359,000 are believed to be addicted to the drug.
- Most new users are male and older than 17 years of age.

## CONT'D.

- Nonmedical use of prescription opioids has caused increasing concern among law enforcement officials and regulatory, pain relief advocacy, and drug abuse organizations.
- The prevalence of lifetime nonmedical oxycodone use increased from 11.8 million users (5%) in 2002 to 13.7 million users (5.8%) in 2003.
- Some studies estimate that as many as 20% of individuals in the United States have used a prescription opioid for nonmedical purposes at least once during their lifetime.

# DEMOGRAPHICS OF ILLICIT OPIOID USERS

- The percentages of lifetime nonmedical use of pain relievers among the predominant racial and ethnic groups are:

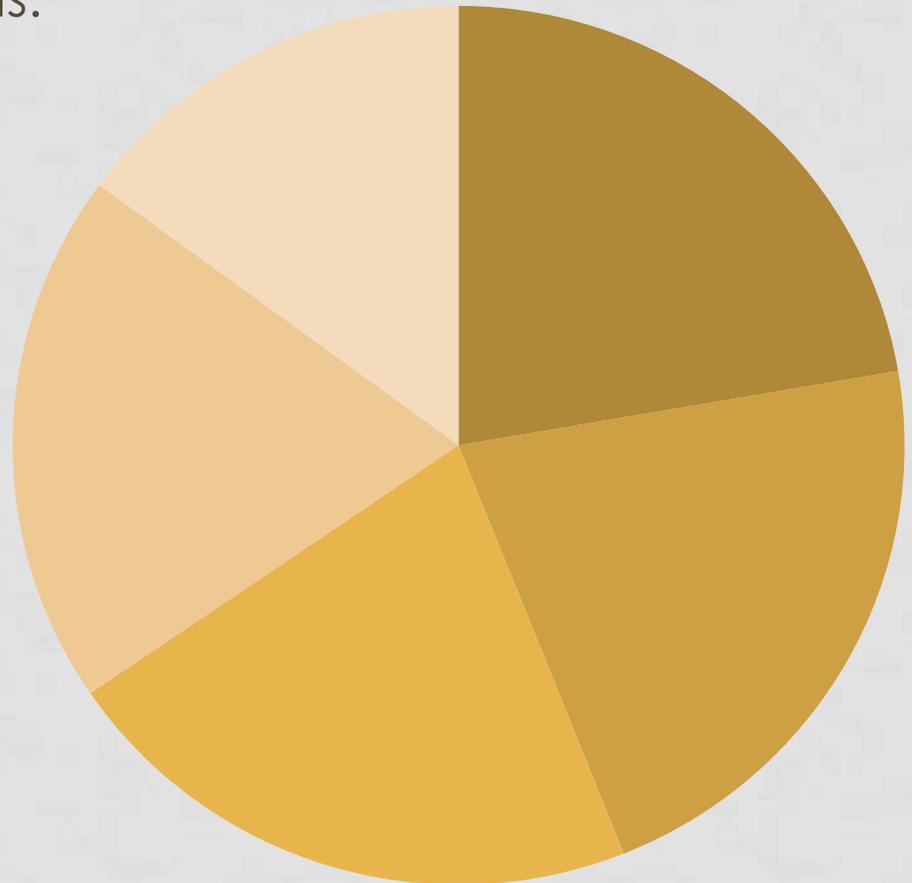


- American Indian/ Alaskan Native 19.3
- White 15.2%
- Hispanic or Latino 11.3%
- Black or African American 10.6%
- Native Hawaiian or Pacific Islander 6.4%
- Asian 6.3%
- Other 30.9%

# GEOGRAPHIC PATTERNS OF MISUSE

- Nonmedical use of opioid analgesics has been observed in both rural and urban areas.

- Small Metro 14.2%
- Large Metro 13.8%
- Urbanized Nonmetro 13.7%
- Less Urbanized 12.5%
- Completely Rural 9.5%



# RISK FACTORS FOR OPIOID ABUSE/DEPENDENCE

- Persons in a heightened risk for heroin experimentation include:
  - Those who abuse alcohol or marijuana.
  - Those with first-degree relatives addicted to alcohol or other drugs.
  - Those with friends and associates addicted to heroin or at high risk of heroin experimentation.
- Individuals who use nonmedical prescriptions before 13 years of age are more likely to become addicts than those who initiated use at 21 years or older.
- The odds of becoming an addict are reduced 5% each year after 13 years of age.

# EPIDEMIOLOGY OF OVERDOSE

- Overdose is a major cause of premature death among opioid drug users.
  - *Nonfatal overdoses* (defined as instances in which loss of consciousness and respiratory depression occur but are not fatal) are highly prevalent among heroin users, occurring in 50% to 70% of this population.
  - According to the CDC, there were 14,800 overdose fatalities attributable to prescription painkillers in 2008.

# RISK FACTORS FOR HEROIN/ OPIOID OVERDOSE

- Identified risk factors for fatal heroin overdose include:
  - Male gender
  - Single status
  - Unemployment
  - History of heroin dependence
  - No current treatment for heroin dependence
  - Intravenous (IV) use
  - Concomitant use of alcohol or benzodiazepines
- An unexplained and consistent finding is that victims of fatal heroin overdose are generally older, experienced users.

# CLASSIFICATION

- The narcotic analgesics can be categorized into **three groups**:
  - The first group includes the natural opium derivatives – heroin, morphine, and codeine – and the semisynthetic derivatives – including hydromorphone, oxymorphone, hydrocodone, oxycodone, dihydrocodeine, and buprenorphine.
  - The two other groups are the synthetic chemicals:
    - The *phenylpiperidines* including meperidine and fentanyl
    - The *pseudopiperidines* including methadone and propoxphene

# OPIOID TOLERANCE

- ***Tolerance refers to a decrease in effectiveness of a drug with repeated administration*** and is encountered in both the clinical use of opioids for pain relief and in recreational use of heroin.
  - *Acute tolerance* stems from transient administration of opioids for pain relief; sustained administration leads to the development of *classical* or *chronic tolerance*.
- Short-term receptor desensitization may underlie the development of tolerance, probably involving phosphorylation of the mu and delta receptors by protein kinase C, protein kinase A, and beta-adrenergic receptor kinase (beta ARK).
- Long-term tolerance is believed to be associated with increases in adenylyl cyclase activity, a counter-regulation to the decrease in cyclic adenosine monophosphate levels.

# OPIOID DEPENDENCE

- Opioid dependence is best described as a central nervous system disorder characterized by neurobiological changes leading to compulsive drug-taking behaviors.
- As a result of chronic use, the cells producing endogenous opioids cease to function and degenerate, causing the user to become physically dependent on exogenous opioids.

# NATURAL HISTORY OF OPIOID DEPENDENCE

- Although the time from initiation to daily use and serious physiological and psychological dependence is highly variable, the different stages of opioid dependence are clearly delineated.
- These stages include:
  - Initiation
  - Continuation
  - Withdrawal
  - Relapse

## CONT'D.

- **INITIATION:** During the initiation phase, acute reinforcement of the initial drug effect is mediated by mu-opioid receptors and dopamine that inhabit the ventral tegmental area and nucleus accumbens → *this results in conditioned responses and drug craving.*
- **CONTINUATION:** The second phase of continued drug use is characterized by diverse neurotransmitter involvement, including dopamine in the nucleus accumbens, corticotrophin-releasing hormone in the amygdala, and glutamate in the frontal-cingulate circuit → *as tolerance develops, the dose and route of administration often change, with progression to IV use a frequent outcome.*

## CONT'D.

- **DETOXIFICATION AND WITHDRAWAL:** During detoxification and withdrawal from opioids and other central nervous system depressants, glutamate and norepinephrine in the locus coeruleus are primarily involved in causing the associated symptoms.
- **RELAPSE FOLLOWING SUSTAINED ABSENCE:** Brain regions implicated in relapse to opioid use include the orbitofrontal cortex, anterior cingulate gyrus, and amygdala.
  - Norepinephrine and corticotrophin-releasing hormones are involved in stress-induced relapse.
  - Gamma-aminobutyric acid (GABA) and glutamate mediate brain systems that are involved in compulsive and habitual behavior and mediate cue-induced relapse.

# MECHANISM OF REINFORCEMENT

- The mesolimbic dopamine system is the likely substrate upon which opioids act to produce their reinforcing effects.

# SIGNS AND SYMPTOMS OF ACUTE OPIOID INTOXICATION

- ❑ Constricted pupils (or dilated pupils with meperidine)
- ❑ Euphoria
- ❑ Apathy
- ❑ Dysphoria
- ❑ Drowsiness
- ❑ Loss of consciousness
- ❑ Coma
- ❑ Psychomotor agitation or retardation
- ❑ Decreased respiration
- ❑ Decreased heart rate
- ❑ Pulmonary edema
- ❑ Impaired social judgment
- ❑ Slurred speech
- ❑ Impaired attention and memory
- ❑ Impaired occupational functioning

# OPIOID OVERDOSE

- Research suggests that the increase in incidence of fatal overdose is not the result of an increase in the number of persons using opioids. Possible mechanisms of fatal overdose include
  - loss of tolerance,
  - synergistic interactions with other CNS depressants,
  - or systemic factors.

# SYMPTOMS OF OPIOID OVERDOSE

- ❑ Mental clouding
- ❑ Stupor or coma
- ❑ Miotic pupils
- ❑ Bradypnea
- ❑ Diminished response to painful stimuli
- ❑ Mottled, cold skin

# SIGNS & SYMPTOMS OF OPIOID WITHDRAWAL

- ❑ Dilated pupils
- ❑ Rhinorrhea
- ❑ Epiphora/lacrimation
- ❑ Piloerection
- ❑ Nausea
- ❑ Vomiting
- ❑ Diarrhea
- ❑ Yawning
- ❑ Muscle cramps
- ❑ Restlessness
- ❑ Elevated vital signs

# PROTRACTED WITHDRAWAL

- Withdrawal symptoms may persist long after elimination of the opioid agent.
- Such persistent behavioral change suggests plastic alternation within the nervous system, some of which may be mediated by the regulation of gene expression.

# DEVELOPMENT OF DEPENDENCE

- The dependence of a patient to a drug initially prescribed for a medical condition is referred to as **iatrogenic dependence**.
- Opioid prescriptions fall into *two major subgroups*:
  - Treatment of acute pain with short-term opioids
  - Treatment of chronic pain with long-term opioids.
- In contrast to the rare association of dependence with short-term use, long-term administration of opioids is estimated to result in opioid abuse or dependence in 2.8% to 18.9% of patients, which typically parallels the rate of abuse or dependence among opioid users in the general population.

# MANAGEMENT OF OPIOID ABUSE AND DEPENDENCE

- Today management of opioid dependence entails methods to achieve different goals, depending on the health situation and treatment history of the patient. These treatment approaches include:
  - **CRISIS INTERVENTION:** Directed at immediate survival by reversing the potentially lethal effects of overdose with an opioid antagonist.
  - **HARM REDUCTION:** Intended to reduce morbidity and mortality associated with use of dirty needles and overdose.
  - **DETOXIFICATION/WITHDRAWAL:** Aims to remove the opioid of abuse from the patient's body, either through gradual taper and substitution of a long-acting opioid or through ultra-rapid opioid detoxification.

## CONT'D.

- **MAINTENANCE TREATMENT OR OPIOID (AGONIST) REPLACEMENT THERAPY:** Aimed at reduction/elimination of illicit opioid use and lifestyle stabilization. Maintenance follows detoxification/withdrawal, whereby the patient is tapered from short-acting opioids and introduced to long-acting opioid agonist, such as methadone or buprenorphine. Patients remain on agonist therapy short-term, long-term, or indefinitely depending on the individual needs.
- **ABSTINENCE-ORIENTED THERAPY:** Treatment directed at cure. The patient is tapered off of short-acting opioids during the detoxification/withdrawal process and may be placed on an opioid antagonist with the goal of minimizing relapse.
- All treatment approaches share the common goal of improving health outcomes and reducing drug-related criminality and public nuisance.

# CRISIS INTERVENTION

- In response to acute overdose, the short-acting opioid antagonist naloxone is considered the gold standard.
  - Naloxone is effective in reversing respiratory depression and coma in overdose patients.
  - There is no evidence that subcutaneous or intramuscular use is inferior to intravenous naloxone.
  - This has prompted discussion of making naloxone available to the general public for administration outside of the healthcare setting to treat acute opioid overdose.

# HARM REDUCTION

- Harm reduction measures are primarily employed to minimize the morbidity and mortality from opioid abuse and to reduce public nuisance.
  - Education
  - Needle-Exchange Programs
  - Injection Rooms
  - Heroin Maintenance

# EDUCATION

- Reducing the risk for harm involves education on polydrug use and needle-exchange programs.
- Heroin users should also be encouraged to switch to *noninjecting* routes of administration to reduce related morbidity and mortality.

# NEEDLE-EXCHANGE PROGRAMS

- Needle-exchange programs have been shown to be effective in:
  - **Reducing drug-related health problems**
  - **Reducing injection frequency,**
  - **Increasing entry and retention in drug treatment.**

# INJECTION ROOMS

- Medically supervised injecting rooms are officially designated areas where injecting opioid users, often persons who use heroin, can inject without fear of arrest and with knowledge that medical assistance is available if overdose occurs.
  - **The goal** of user rooms is to promote health and reduce risk behaviors and public nuisance, with specific focus on overdose reduction and hygiene.

# HEROIN MAINTENANCE

- Heroin maintenance is the implementation of heroin prescriptions under medical supervision.
  - This option *may* improve health and reduce heroin overdoses, illicit opioid use, and crime.
  - However, formidable barriers to heroin exist in the U.S.

# DETOXIFICATION AND WITHDRAWAL

- Detoxification alone should not be considered a treatment and should only be promoted in the context of a well-planned relapse-prevention.
- The three primary treatment modalities used for detoxification are:
  - Opioid agonists,
  - Non-opioid medications,
  - Rapid and ultra-rapid opioid detoxification.
- Many opioid withdrawal symptoms, such as *restlessness, rhinorrhea, lacrimation, diaphoresis, myosis, piloerection, and cardiovascular changes*, are mediated through increased sympathetic activation.

# ULTRA-RAPID OPIOID DETOXIFICATION

- Ultra-rapid opioid detoxification (UROD) has been developed as **a means of avoiding the physical symptoms of withdrawal** from opioids through the use of general anesthesia.
- UROD consists of naltrexone-assisted detoxification under heavy sedation or full anesthesia.
- There are a number of drawbacks to UROD relative to other detoxification methods; Serious adverse events related to the anesthetic procedure have been reported.

# AGONIST REPLACEMENT OR ABSTINENCE THERAPY

- Two principle treatment modalities are offered for opioid dependent patients:
  - Agonist maintenance
  - Detoxification followed by outpatient or residential drug-free treatment
- Both can be effective, with no clear indication for each, although agonist maintenance leads to greater treatment retention.

# AGONIST REPLACEMENT THERAPY

- The theoretical basis of opioid replacement stems from the finding that chronic opioid use results in an endogenous opioid deficiency as a result of down-regulation of opioid production.
  - This creates overwhelming cravings and necessitates interventions that shift the dependent patient's attention and drive from obsessive preoccupation with the next use of opioids to more adaptive areas of focus, such as work, relationships, and non-drug leisure activities.
- Successful maintenance treatment entails stabilization of opioid dependence through opioid receptor occupation.
  - Positron emission tomography studies have revealed that only 25% to 35% of brain opioid receptors are occupied during steady-state methadone maintenance, suggesting that unoccupied opioid receptors disrupted during cycles of opioid abuse could normalize during methadone maintenance.

## CONT'D.

- Roughly 260,000 patients in the U.S. are enrolled in opioid replacement therapy (as of 2008) in more than 1000 opioid treatment programs.
  - However, this represents only an estimated 10% of all opioid-dependent patients.
- Although some have criticized the practice of methadone and buprenorphine therapy on the grounds that one opioid is merely being substituted for another, the clinical benefits strongly support this treatment modality.
  - When compared to active street heroin users, these benefits include:
    - 4-times lower HIV seroprevalence,
    - 70% fewer crime-days per year,
    - and 1-year mortality rate of 1% (versus 8%).

# METHADONE

- The first demonstrated efficacy of methadone treatment for opioid dependence was published in 1965.
- Methadone is now the most inexpensive and empirically-validated agent for use in opioid replacement therapy.
- Methadone is also cost-effective.
  - A 1997 study of Veterans' Affairs patients showed that the estimated 6-month costs are about:
    - \$21,000 for an untreated drug abuser,
    - \$20,000 for an incarcerated drug abuser,
    - \$1750 for a patient enrolled in a methadone maintenance program

# BUPRENORPHINE

- Buprenorphine offers several advantages over methadone:
  - Lower cost
  - Milder withdrawal symptoms following abrupt cessation
  - Lower risk of overdose
  - Longer duration of action, allowing alternate-day dosing
- Mixed agonist/antagonist action entails special considerations;
  - Buprenorphine may precipitate opioid withdrawal.
- **The primary advantage of buprenorphine over methadone is its superior safety profile.**

# AGONIST REPLACEMENT AND PSYCHOSOCIAL THERAPY

- There are **two** general types of psychosocial therapy used for treating addictive disorders.
  - Therapies developed for treating depression and anxiety that were later adapted for treating persons with addictive disorders.
    - Cognitive Behavioral Therapy
    - Supportive Expressive Therapy
    - Interpersonal Therapy
  - Therapies developed specifically for persons with addictive disorders.
    - Motivational Interviewing
    - Motivational Enhancement Therapy

# ABSTINENCE-ORIENTED THERAPIES

- Abstinence is achieved in **two phases**:
  - Detoxification
  - Relapse prevention
- Outcomes in abstinence-oriented programs are generally poor.

# OPIOID ANTAGONIST THERAPY

- Relapse-prevention programs have traditionally involved long-term **residential placement** of 9 months or more, often using therapeutic community format.
- More recently, pharmacotherapeutic agents, such as **naltrexone**, have been added to reduce relapse risk.
  - A drawback with opioid antagonist therapy is the **high dropout rate during detoxification**, which results in highly selective patient samples in most of the naltrexone maintenance studies.

# PSYCHOSOCIAL MONOTHERAPY

- There is no data to support psychosocial interventions as a sole intervention for opioid dependence.

# 12-STEP/SELF-HELP PROGRAMS

- Twelve-step programs for opioid abuse and dependence include:
  - Narcotics Anonymous (NA)
  - Methadone Anonymous (MA)
- These are modeled after Alcoholics Anonymous (AA), an abstinence-based support and self-improvement program that is based on a 12-step model of recovery.

# ACUPUNCTURE

- Auricular acupuncture is the most common acupuncture approach for substance abuse, *including* opioid abuse and dependence.
- Results from well-designed studies indicate that auricular acupuncture treatment is not sufficient in efficacy as a stand-alone treatment for opioid dependence.
  - The placebo response rate is substantial, and the body of evidence does not demonstrate the type of qualitative and quantitative rigor needed to validate acupuncture efficacy.

# CONCLUSION

- Dependence on opioids is associated with serious morbidity and mortality, and advances in the understanding of the dependence have led to the development of effective treatments.
- More recently, the abuse of prescription opioids has become considerably more widespread, fueled in part by the availability of such drugs over the Internet.
  - This has resulted in opioid abuse and dependence in populations seldom afflicted in the past.
  - Thus, medical, mental health, and other healthcare professionals in a variety of settings may encounter patients with an opioid use disorder.
- The knowledge gained from the contents of this course can greatly assist the healthcare professional in *identifying, treating, and providing an appropriate referral* to patients with opioid use disorders.