

A Review of Opioids and Treatment of Opioid Dependence

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Opioid Dependence – Goals of Review

- Epidemiology
- Neurobiology
- Types of opioids and their effects
- Pharmacology of opioids
- Treatment modalities
- Pregnancy and other special groups

Opioids

- Opioids: opium and opium-derived compounds as well as semisynthetic and synthetic compounds that resemble the structure and/or function of the naturally occurring forms
- Opioids are medically used for relief of pain and cough suppression, and many have an abuse potential

Historical Perspective of Opioid Abuse

- Late 19th and early 20th century:
- Civil war: introduction of hypodermic needle and morphine analgesia
- Many women/higher income Americans: high rates of morphine use leading to addiction. Most introduced to the drugs by their physicians for menstrual pain and menopausal symptoms.
- 20th century: U.S. adopted severe policies toward addiction; criminalized addiction
- Harrison Act (1914): prohibition on prescription of narcotics (opiates) to addicts.
 - Many physicians prosecuted
 - Physicians fear opioid prescribing
 - Increased drug trafficking and crime associated with opiate and cocaine abuse

Historical Perspective

- 1974: first methadone maintenance programs for opioid addiction; serve approximately 260,000 patients
- Large increases in prescription opioid addiction starting in late 1990s to present
- DATA 2000: Office-based treatment of opioid dependence

Opioid Abuse: Epidemiology

- Prevalence: Heroin
- 2009: 180,000 new users
- 900,000 addicted
 - NSDUH, 2010, NIDA Research Report Series, 2004
- 0.7-0.9% (125,000) 8th, 10th, 12th graders endorse trying heroin at least once in the year prior to interview (2005-2009)
 - Monitoring the Future, 2010

Abuse of Prescription Opioids

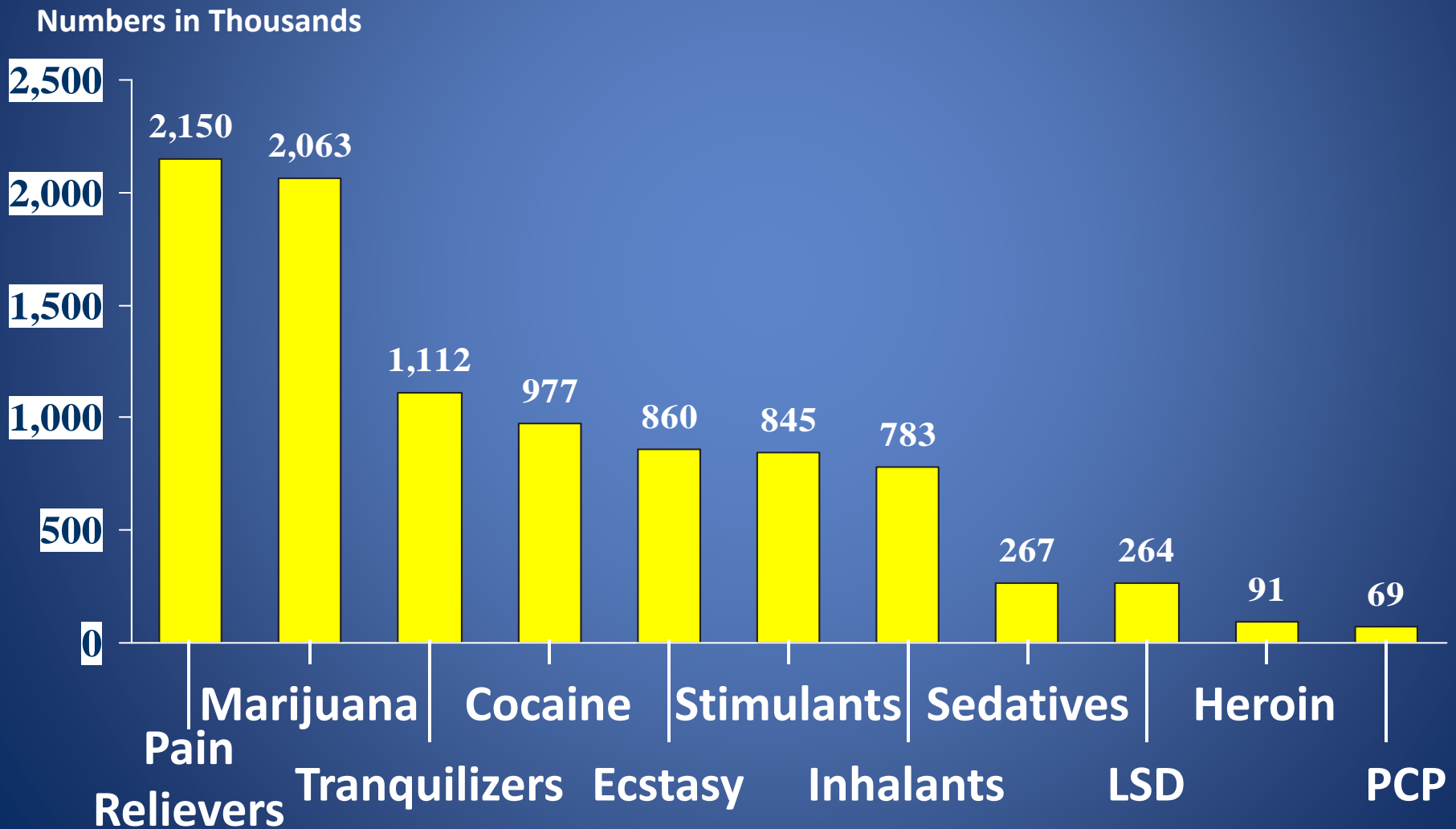
Nonmedical use of prescription pain medications (2009):

- Previous month misuse: 5.2 million over age 12
- 4.8% of those aged 18-25
- 1.9 million prescription narcotic users meet diagnostic criteria for opioid abuse or dependence (second only to marijuana (4.3 million))
- In 2006, deaths involving opioid analgesics surpassed those for other illicit drugs:
 - 1.63 times number cocaine-associated deaths
 - 5.88 times the number heroin-related deaths

Source: NSDUH, 2006, 2010

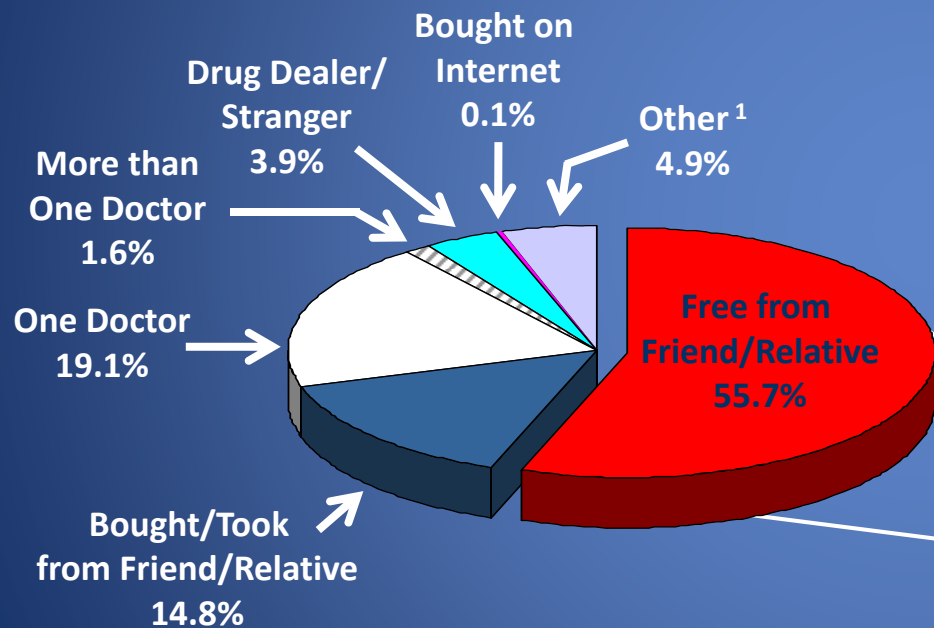
<http://www.cdc.gov/HomeandRecreationalSafety/pdf/poision-issue-brief.pdf>

Past Year Initiates for Specific Illicit Drugs Among Persons Aged 12 or Older: 2006

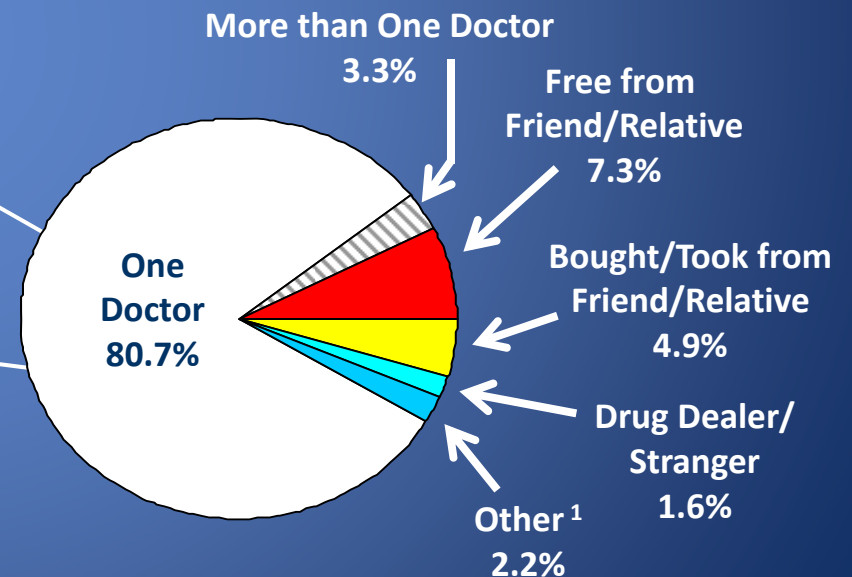


Source Where Pain Relievers Were Obtained for Most Recent Nonmedical Use Among Past Year Users Aged 12 or Older: 2006

Source Where Respondent Obtained



Source Where Friend/Relative Obtained



Note: Totals may not sum to 100% because of rounding or because suppressed estimates are not shown.

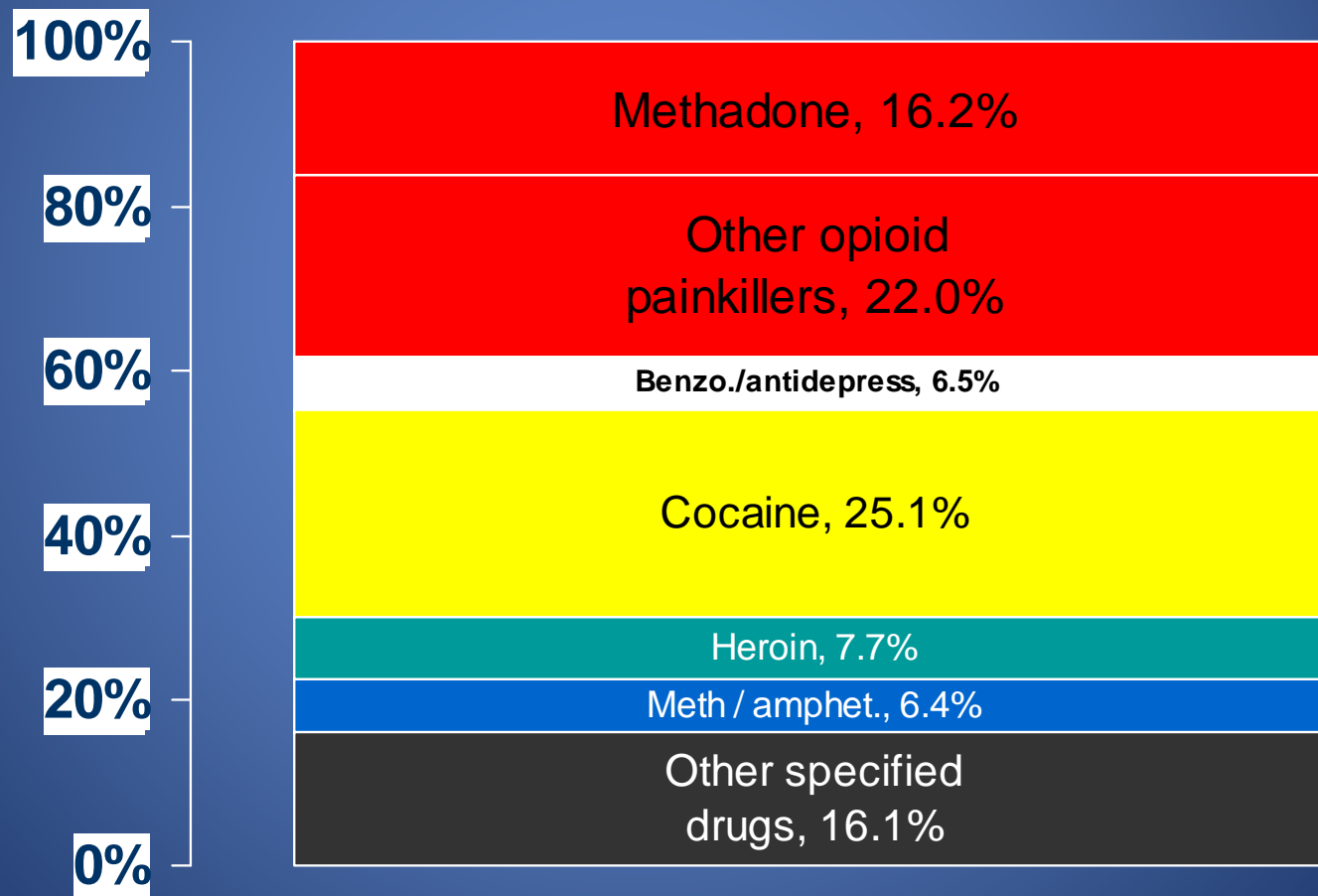
¹ The Other category includes the sources: "Wrote Fake Prescription," "Stole from Doctor's Office/Clinic/Hospital/Pharmacy," and "Some Other Way."

DAWN 2009

- Heroin 213,118 visits
- Narcotic Pain Relievers: 397,160 visits
- Oxycodone/combinations – 175,949 visits
- Hydrocodone/combinations – 104,490 visits
- Fentanyl/combinations – 22,143 visits
- Buprenorphine/combinations – 12,544
- Alcohol involvement: 32% of visits

Source: Drug Abuse Warning Network, National Estimate, 2009

Distribution of First-Listed Specified Drugs Among Unintentional Drug Overdose Deaths, US, 2005



Opioid Pharmacology

- Types of opioid receptors:
 - Mu
 - Kappa
 - Delta
- Addictive effects of opioids occur through activation of mu receptors
- Role of kappa and delta receptors in addictive process not well defined

Opioid Receptors

Drugs and medications that activate mu receptors:

- Morphine
- Methadone
- Hydromorphone
- Codeine
- Fentanyl
- Heroin
- LAAM
- Buprenorphine
- Oxycodone
- Hydrocodone

Function at Receptors: Full Opioid Agonists

Mu
receptor

Full agonist binding ...

- ① activates the mu receptor
- ② is highly reinforcing
- ③ is the most abused opioid type
- ④ includes heroin, oxycodone, methadone, & others

Function at Receptors: Partial Agonists

Mu
receptor

Partial agonist binding ...

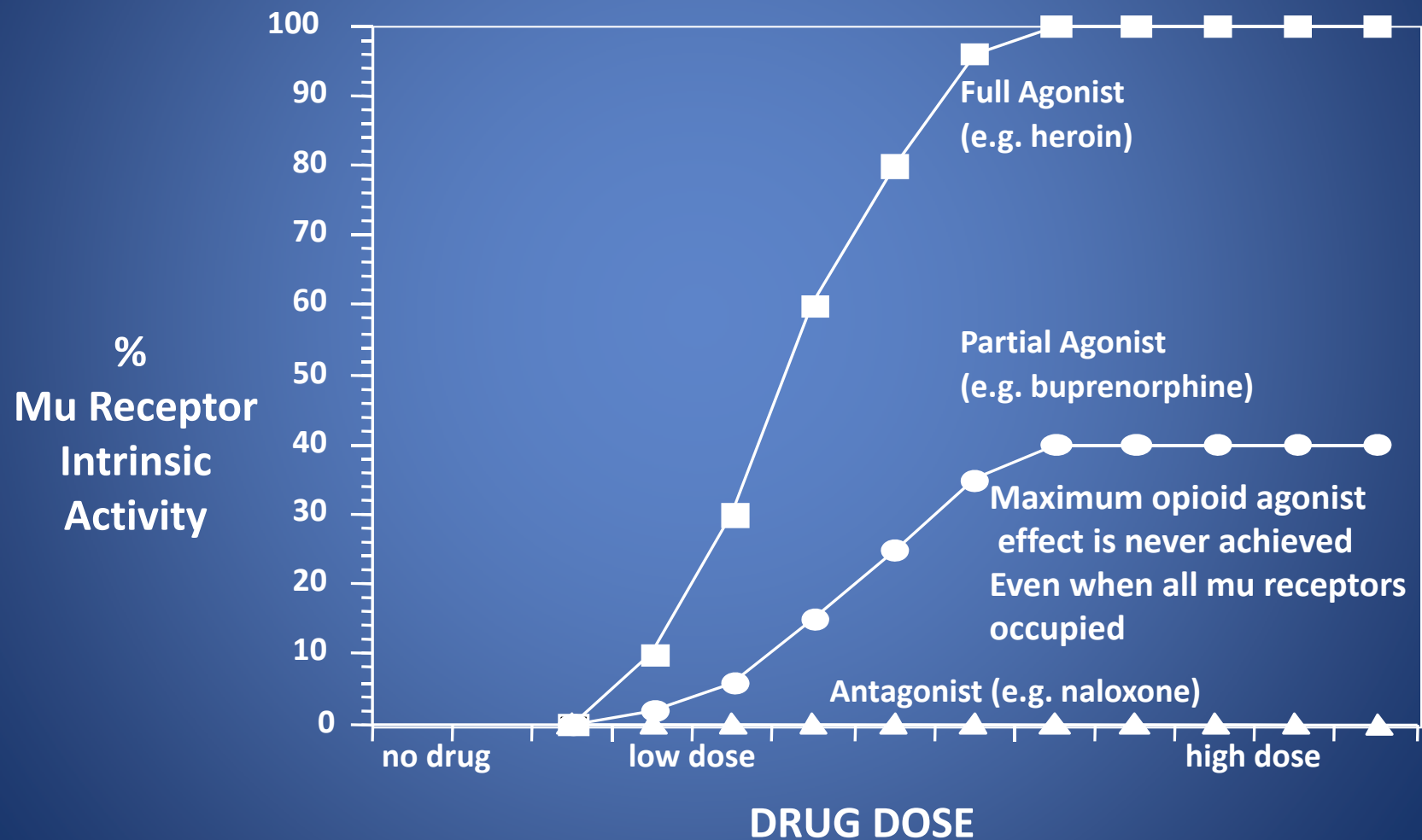
- ① activates the receptor at lower levels
- ② is relatively less reinforcing
- ③ is a less abused opioid type
- ④ includes buprenorphine

Function at Receptors: Opioid Antagonists



- ① occupies without activating
- ② is not reinforcing
- ③ blocks abused agonist opioid types
- ④ includes naloxone and naltrexone

Comparison of Activity Levels



Pharmacology of Opioids

- First pass after oral ingestion varies: morphine only 15% orally available but methadone 80-90%
- Duration of analgesia 3-6 hours but constipation or respiratory depression may last longer in drugs such as methadone
- Metabolized by liver (glucuronidation or P450 CYP 2D6, 2B6, 3A4)
- Opioids are excreted in urine and bile
- Impaired hepatic function could increase bioavailability and impaired renal function could cause accumulation of metabolites

Repeated Dosing: Opioid Tolerance and Withdrawal

- Tolerance:
 - Need more for same effect
 - Less effect with same amount
 - Occurs for euphoria, sedation, respiratory depression, vomiting, analgesia
 - Minimal tolerance to constipation, miosis, sweating
 - Can attain high levels of tolerance with gradual increases to doses that would otherwise be lethal
- Withdrawal
 - Upon reduction or cessation of opioid use/administration

Opiate Withdrawal

Physical dependence is typically shown through the signs and symptoms of opioid withdrawal

- Dysphoric mood
- Nausea or vomiting
- Muscle aches/cramps
- Lacrimation
- Diarrhea
- Insomnia
- Hypertension
- Pupillary dilation
- Sweating
- Gooseflesh
- Rhinorrhea
- Yawning
- Tachycardia

Can use standardized scales to measure:

- e.g.: COWS, OOWS

Repeated Administration and Withdrawal

- Physical dependence and syndrome of dependence (as in DSM-IV) are importantly different:
 - Physical dependence indicates physiological change or adaptation in an organism in response to repeated administration of a drug
 - A “syndrome of dependence” is a group of signs and symptoms indicating a pattern of pathologic use or “addiction”

Repeated Administration and Withdrawal

- Spontaneous Withdrawal
 - Occurs when a person physically dependent on mu agonist opioids suddenly stops or markedly decreases the amount of use
 - For short-acting opioids (e.g., heroin, hydrocodone, oxycodone): usually begins 6-12 hours after last dose, peaks at 36-72 hours, and lasts about 5 days (with possible protracted withdrawal?)

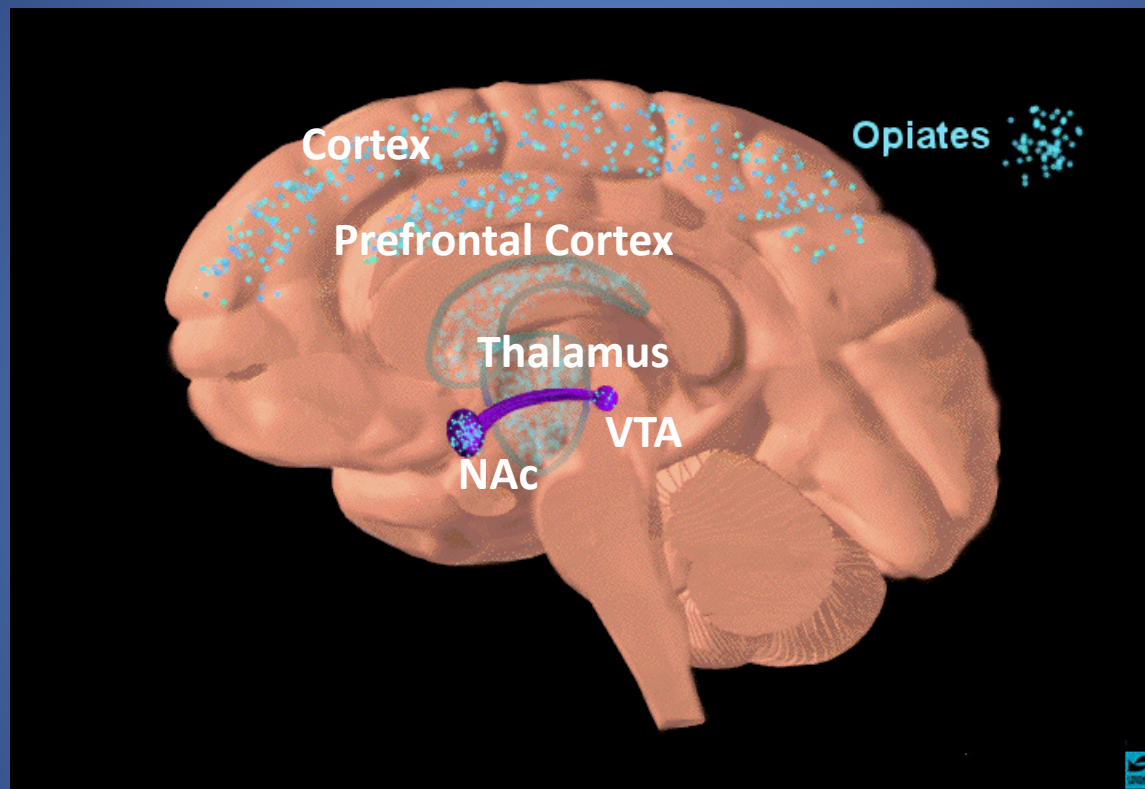
Repeated Administration and Withdrawal

- Spontaneous Withdrawal (*continued*)
 - For opioids with longer half-lives (e.g., methadone), there is a longer period before onset (methadone: 36-72 hours), longer period before peak effects occur
 - Medications with longer half-lives generally have less severe spontaneous withdrawal syndrome-but longer withdrawal syndrome

Opioid Overdose

- Respiratory depression - usual cause of death
- Coma, hypotension, pinpoint pupils (may dilate with hypoxia)
- Noncardiogenic pulmonary edema
- High-dose meperidine (Demerol) or propoxyphene (Darvon) can cause seizures
 - Note: FDA Advisory Panel recently voted to recommend removal of propoxyphene from market
- Antidote for heroin overdose: naloxone (i.m. or i.n. work equally well); note: naloxone does not work well for buprenorphine

Etiology of Opioid Abuse: Neurobiology of Addiction



Mu opioid receptors are distributed widely in the brain. While binding in the thalamus produces analgesia, binding in the cortex produces impaired thinking/balance; binding in prefrontal cortex contributes to an individual's decision about how important use of the drug is (salient value of the cue) and ventral tegmental area (VTA)/nucleus accumbens (NAc) is associated with euphoria that some experience (i.e. the "high").

Clinical Treatment of Opioid Use Disorders

DSM-IV Criteria for Opioid Abuse

A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following occurring within a 12-month period:

- Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home
- Recurrent substance use in situations in which it is physically hazardous
- Recurrent substance-related legal problems
- Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects

DSM-IV Criteria for Opioid Dependence

- Three (or more) of the following occurring at any time in the same 12-month period:
- Tolerance, as defined by either of the following:
 - *A need for markedly increased amounts of the substance to achieve intoxication or the desired effect, or*
 - *Markedly diminished effect with continued use of the same amount of the substance*
- Withdrawal, as manifested by either of the following:
 - *The characteristic withdrawal syndrome for the substance, or*
 - *The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms*
- The substance is often taken in larger amounts or over a longer period than was intended

DSM-IV Criteria for Opioid Dependence

- There is a persistent desire or unsuccessful efforts to cut down or control substance use
- A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
- Important social, occupational, or recreational activities are given up or reduced because of substance use
- The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

Pharmacological Treatments for Opioid Dependence

Short-Term:

- Medical Withdrawal (Detoxification)
 - Opioid and non-opioid

Long-Term

- Opioid antagonist
- Opioid agonist or partial agonist

Medical Withdrawal- Efficacy

- Ball (1988): methadone taper: 82% relapsed within 12 months
 - 45% in first 3 months
- Ling (2009): Buprenorphine: no difference in 7 vs. 28 d taper; at 1 mo opioid neg urines: 18% and 12%; at 3 mos: 18% and 13%; no advantage of 28 d taper over 7 d taper
- Minimal follow-up data for ultra-rapid detox
- Overall, HIGH RELAPSE RATE for medical withdrawal procedures
- Risk of overdose

Medical Withdrawal Using Opioids

- Stabilize on methadone (e.g.: 40 mg/d) and taper
- Stabilize on buprenorphine (variable doses have been reported to be effective) and taper
 - May have less withdrawal
 - Short vs. prolonged taper

Non-Opioid Detoxification

- Clonidine: Alpha-2 adrenergic agonists suppress increased noradrenergic activity from locus cereuleus caused by withdrawal of opioid
- Clonidine
 - FDA approved for hypertension; limiting side effect is hypotension
 - Helps autonomic symptoms
 - Reduces withdrawal symptoms better than placebo
 - Most commonly used non-opioid approach over past 20 years
- Sedation, dry mouth, hypotension
- Sometimes accelerated with naltrexone

Opioid Dependence Maintenance Therapy

Naltrexone (antagonist therapy) Why antagonist therapy?

- Block effects of a dose of opiate
- Prevent impulsive use of drug
- Relapse rates high (90%) following detoxification with no medication treatment
- Dose (oral): 50 mg daily, 100 mg every 2 days, 150 mg every third day
- Blocks agonist effects
- Side effects: hepatotoxicity, monitor liver function tests every 3-6 months
- Biggest issue is lack of compliance –works well in motivated patients
- Injectable naltrexone (380 mg/month) recently approved for opioid dependence; once a month administration may assist with adherence

Long-Acting Opioid Treatment Options

- Methadone
 - Schedule II
 - Highly regulated
 - Narcotic Treatment Program settings
 - Approved for pregnancy
- LAAM (l-alpha acetyl methadol) – taken off market after problems with arrhythmias
- Buprenorphine
 - Schedule III
 - Can be prescribed from physician offices
 - Safer in overdose
 - MOTHER study: recommends BUP be considered as first-line drug for opioid dependent pregnant women; less severe NAS

Opioid Dependence Maintenance Therapy: Agonist Treatment

- What is agonist therapy?
- Use of a ***long acting*** medication in the same class as the abused drug (once daily dosing)
 - Prevention of Withdrawal Syndrome
 - Induction of Tolerance
- What agonist therapy is not:
 - Substitution of “one addiction for another”
- Who is appropriate for opioid agonist therapy?
 - ≥ 18 years (for methadone; exceptions for 16-17 y.o. with parental consent and special methadone treatment programs)
 - Greater than 1 year of opioid dependence
 - Medical compromise
 - Infectious disease
 - Pregnant, opioid-addicted, women

Opioid Dependence Maintenance Therapy

Determine opiate dependence

- History (including previous records)
- Signs of dependence (withdrawal symptoms, tracks)
- Urine toxicology
- Naloxone challenge can be given if unsure of opioid dependence
- Prior to starting methadone: ECG: determine if pre-existing prolonged QT interval, ECG after 30 days to compare to baseline; methadone prolongs QT in approx. 2%; 500 msec or greater—reduce dose

*Risk appears greater with doses over 100 mg/d

Methadone Dosing

- Once daily
- Start low, go slow
- Look for signs of withdrawal prior to Dose 1
- Regulation: 1st dose ≤ 30 mg; 1st day NTE 40 mg; for person with low tolerance: 10-15 mg Day 1
- If no evidence of opiate withdrawal; give no more than 10-15 mg Day 1
- Usual starting dose 20-30 mg
- Watch in clinic after first dose approximately 2 h
- Dose increases: every 5-7 days
- If in withdrawal at peak; increase dose by 5-10 mg
- If comfortable at peak; maintain dose
- If intoxicated at peak; reduce next day dose by 5-10 mg and evaluate at time of peak daily to determine if intoxication continues/increases

Methadone Dosing

- Target range 60-100 mg
 - Stop withdrawal, avoid sedation/euphoria
 - Doses should be individualized but higher doses generally more effective
- Beware accumulation in first 5-10 days; do not make rapid dose changes
- Methadone 40 mg will block withdrawal in everyone—won't address craving, but will block withdrawal; therefore no need to rapidly increase the dose

Methadone Side Effects

- Minimal sedation once tolerance achieved
- Constipation - talk to patients about a bowel program
- Increased Appetite/Weight Gain
- Lowered Libido; May decrease gonadal hormone levels
- Exhaustively studied in all other organ systems with no evidence of harm with long-term use

Opioid Dependence Maintenance Therapy

Methadone Benefits:

- Lifestyle stabilization
- Improved health and nutritional status
- Decrease in criminal behavior
- Employment
- Decrease in injection drug use/shared needles

Drug Interactions: Methadone

Decreased methadone concentrations:

- Pentazocine
- Phenytoin
- Carbamazepine
- Rifampin
- Efavirenz
- Nevirapine
- Lopinavir (Kaletra)
- Above may be associated with opiate withdrawal syndrome

Increased methadone concentrations:

- Ciprofloxacin
- Fluvoxamine
- Drugs that inhibit 2D6, 3A4, 2B6 (some SSRIs)
- Or Discontinuation of inducing drugs
 - Cognitive impairment
 - Respiratory depression
 - Possible QTc prolongation; Torsade de Pointes

Opioid Dependence Maintenance Therapy

Buprenorphine

- Partial agonist
- Binds opioid receptors; slow to dissociate
- Dosing may be daily, every other day or three times weekly
- Tablets and rapidly dissolving strip now available
- Average dose 8-16 mg daily
- Use buprenorphine/naloxone (4:1) combination for opioid dependence (exception: pregnancy; use mono product)
- Little effect on respiration or cardiovascular responses at high doses

Opioid Dependence Maintenance Therapy

Buprenorphine

- Mild withdrawal syndrome
- Primary care physicians are expected to be providers of this treatment as well as addiction specialists
- Abuse by injection may be problem (addition of naloxone helps to diminish the risk)
- Drug Interactions: Atazanavir/ritonavir: increases buprenorphine concentrations
- Rifampin: decreases buprenorphine concentrations; opiate withdrawal possible
- Buprenorphine certification (CSAT/DEA) required to prescribe

Buprenorphine Induction

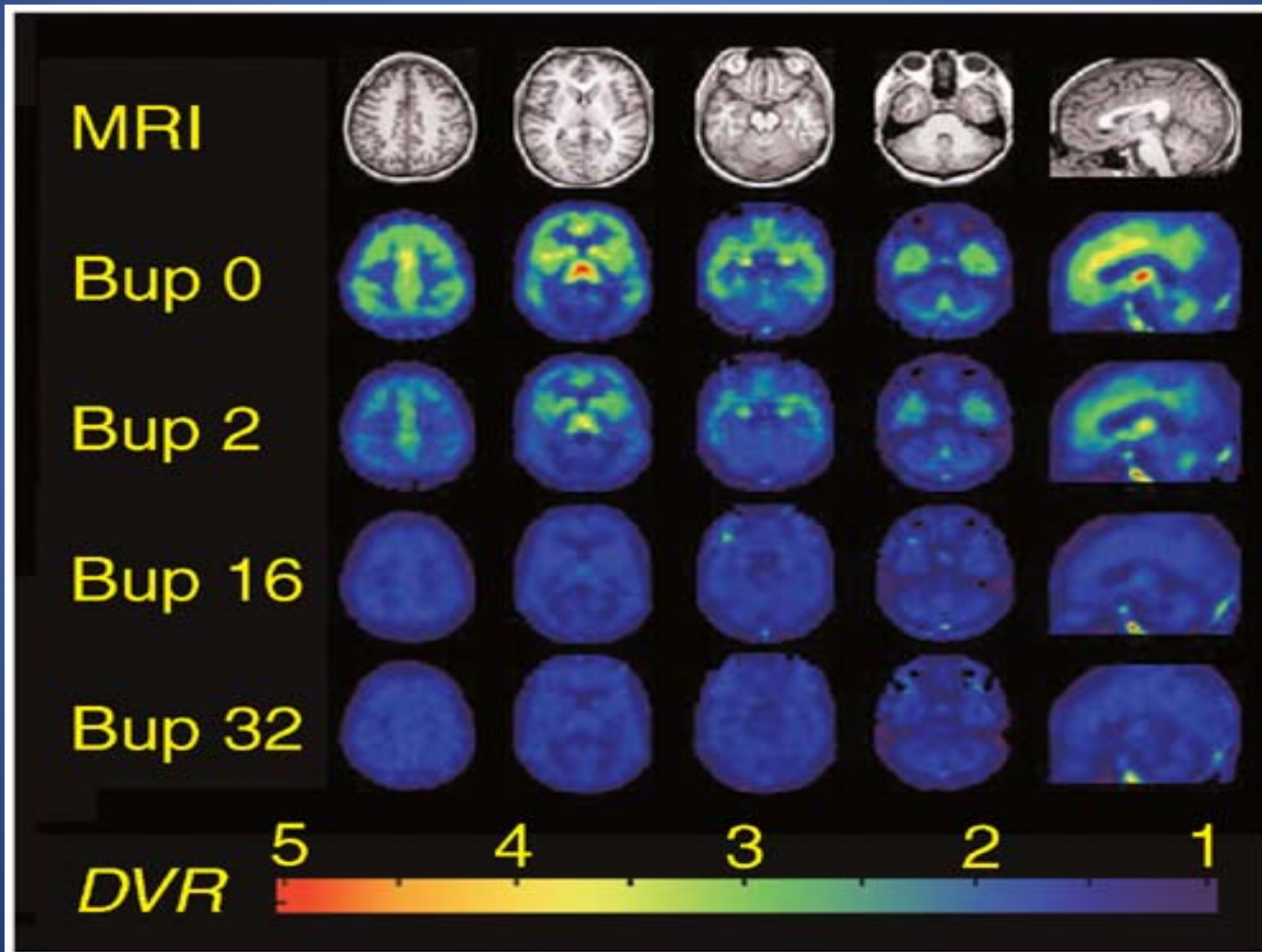
To begin buprenorphine treatment:

- Patient must show signs of mild-moderate opiate withdrawal
- Use Clinical Opiate Withdrawal Scale or Objective Opiate Withdrawal Scale to quantify
- Begin with 2/0.5-4.1 mg buprenorphine/naloxone
- Can re-dose in 2 hours if opiate withdrawal diminished by first dose
- 8/2 mg first day dose
- Return to clinic to re-evaluate next day; increase dose if indicated
- Most stabilize on 8/2-16/4 mg daily
- FDA approved dose range is up to 24/6 mg daily

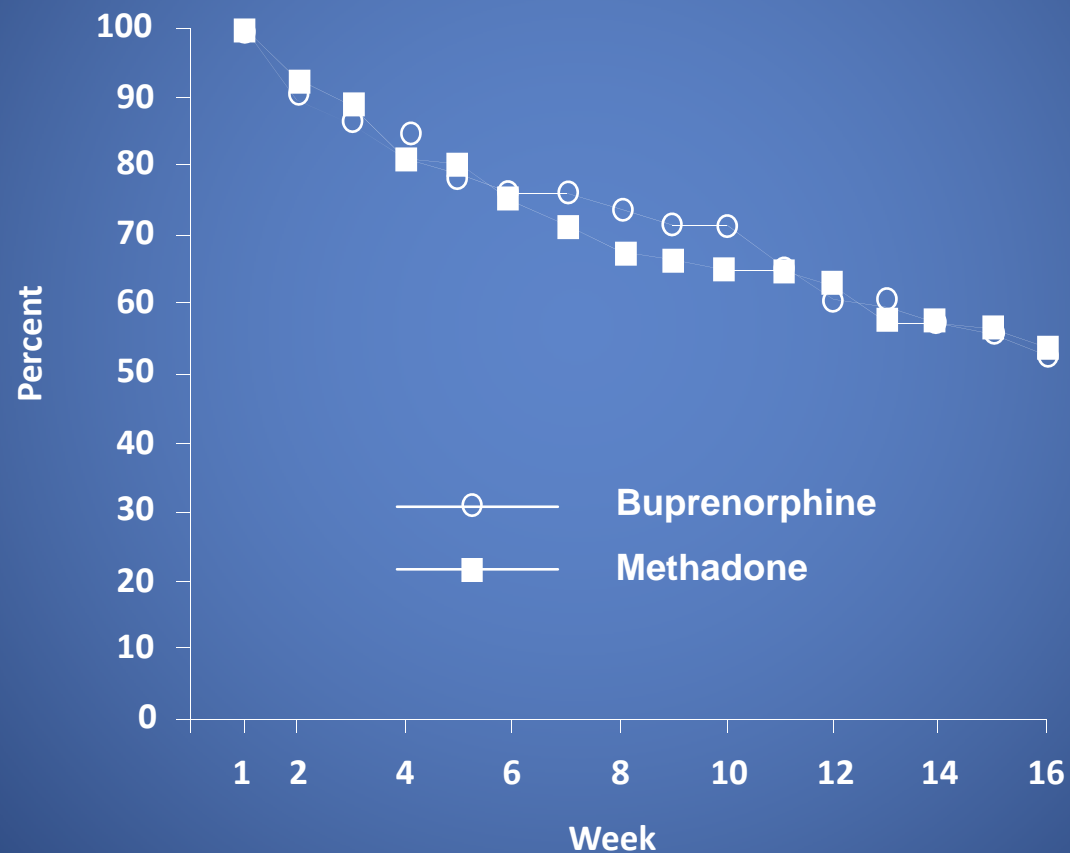
Doses of Buprenorphine

PET/11 Carfentanil Label of Mu Receptors

Greenwald et al. 2003 Nearly all mu receptors are occupied by BUP 16 mg



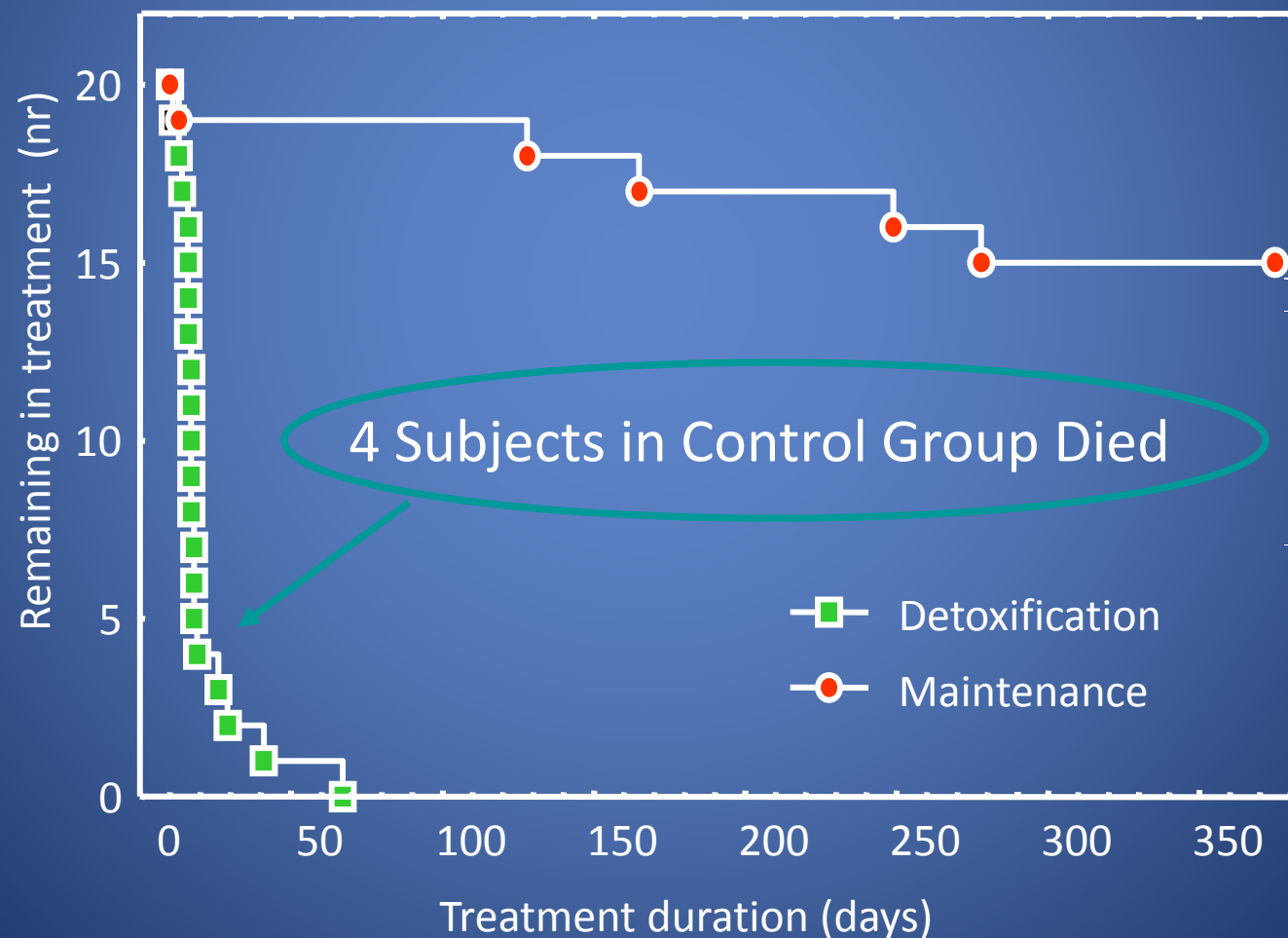
Buprenorphine – Methadone: Treatment Retention is Similar for Both Medications



(Strain et al., 1994)

Buprenorphine vs. Withdrawal and Drug-Free Treatment for Heroin Dependence: Maintenance is Associated With Longer Duration of Treatment

Kakko, Lancet 2003



Opioid Dependence: Additional Treatment Components

- Psychosocial Services
 - Individual and group therapy
 - Family therapy
 - 12 Step
 - Higher psychiatric severity patients more responsive to increased services
- Contingency treatments very useful
 - E.g.: Take-home medication

Opioid Dependence: Additional Treatment Components

- Opioids detected in blood, urine, saliva, and hair
- Random Urine Toxicology Screening: Gold standard
- Heroin is excreted in urine as morphine
- 6-monoacetyl morphine (6-MAM) detected for 12 hours – evidence of recent heroin use
- Routine screens may not detect meperidine, oxycodone, fentanyl, tramadol, buprenorphine
- Poppy seeds contain trace amounts of codeine and morphine. Even small amounts of poppy seeds can give positive morphine in urine

Opioid Replacement Therapy In Pregnancy And In The Neonatal Period

- Methadone maintenance is considered the gold standard and strongly advised; BUP shown to be effective as well (Jones et al. 2010)
 - Removes mother from drug-using environment
 - More likely to get prenatal obstetrical care
 - Reduces obstetrical complications
 - Improves maternal/fetal nutrition
 - Increases birth weight
- Need structure and psychosocial support
- Opioids not teratogenic

Opioid Dependence and Pregnancy

- Methadone Dosing during Pregnancy
 - High enough dose to stop use and block craving
 - Detoxification safest weeks 14-32
 - Withdrawal may precipitate miscarriage in 1st trimester or premature labor in 3rd
 - Methadone: may need split dose or higher dose as pregnancy progresses
- Convert buprenorphine/naloxone to buprenorphine if woman wants to continue buprenorphine treatment
- Higher dropout with BUP (33%) v. methadone (18%)

Opioid Dependence and Pregnancy

- Neonatal Abstinence Syndrome often occurs (in up to 90% and 50% will need treatment):
 - Irritability, fever, diarrhea, hyperreflexia, seizure
 - Treatment: Tincture of opium, morphine
 - Methadone: NAS associated with significantly longer hospital stay than for infants of BUP treated women (9.9 vs. 4.1 d) ($p=0.003$)
- Methadone and buprenorphine are excreted into breastmilk
- Breastfeeding should be encouraged unless there are other conditions that would be a contraindication
- Methadone in breast milk may help with NAS
- Buprenorphine in breast milk not well absorbed; not likely to help with NAS

HIV and Opioid Dependence

- Opioid replacement therapy obvious harm reduction
 - Reduced high risk behavior: reduced needle use, less chaotic life style
- Treatment of HIV pain may become issue: neuropathy: anticonvulsants, avoid CBZ
- Buprenorphine interactions with antiretroviral medications have not been clinically significant, except for significant increase in buprenorphine and metabolite with atazanavir/ritonavir, may be associated with sedation, possibly cognitive impairment

See www.PCSSB.org Guideline on Opioid Therapies, HIV disease, and Drug Interactions by McCance-Katz

Opioid Dependence and Acute Pain

- Acute pain in methadone patients
 - Usual methadone dose will not provide analgesia
 - Increasing methadone dose acts too slowly
 - Give regular dose of methadone for addiction plus short-acting medication for pain
- Acute pain in buprenorphine patients
 - Blocks most mu agonists - may depend on dose
 - Challenge to provide adequate analgesia
 - Consider non opioid alternatives first line
 - For severe pain: regional anesthetic, high potency opioid such as fentanyl, or switching to full agonist and then re-induce when pain condition stops
- Watch for relapse risk. Use short term prescriptions and coordination of care

Opioid Dependence and Chronic Pain

- Limited evidence of usefulness of long term opioid therapy for chronic, non-malignant pain
- Treatment Agreement /Informed Consent (documentation of risk/benefit) advised
- Treatment Agreement to stipulate:
 - One physician/one pharmacy
 - UDS when requested
 - Agreement to return for pill count when asked to do so
 - Medication Levels
 - Number/frequency of all refills
 - Reason for discontinuation (violation of agreement, misuse of medication, abuse of other substances)
- Chronic pain with opioid addiction may do better with methadone maintenance

Opioid Dependence and Adolescents

- Increasing problem, but limited data
- Experiment with prescription analgesics but may progress to heroin
- Usual treatment is non-pharmacologic following medical withdrawal
- Office buprenorphine may be better than methadone clinic
- Extended medication-assisted (buprenorphine/naloxone) treatment shown to be better than detoxification

Another Source of Assistance: Physicians' Clinical Support System-Buprenorphine

Sponsored by Center for Substance Abuse Treatment/SAMHSA



Ask a clinical question...

- Get a response from an expert PCSS mentor
- 888-5pcss-b-4u (Buprenorphine)

From *www.PCSSB.org*...

- Download clinical tools, helpful forms, and concise guidances (like FAQs) on specific questions regarding opioid dependence, use of buprenorphine, information on training and mentoring

Conclusions

- Opioid addiction is a growing problem in the US mainly due to large increases in prescription opioid dependence
- Chronic opioid abuse produces physical dependence
 - Medication treatment needed
 - Medical withdrawal
 - Maintenance therapy
 - Psychosocial treatments

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Upon completion of the Post Test:

- You will receive an email detailing correct answers, explanations and references for each question.
- You will be directed to a module evaluation, upon completion of which you will be emailed your module Certificate of Completion.

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