OPIOID USE DISORDERS MEDICATION ASSISTED TREATMENT

Presentation to the Treatment and Recovery Subcommittee

SUBSTANCE USE RESPONSE GROUP

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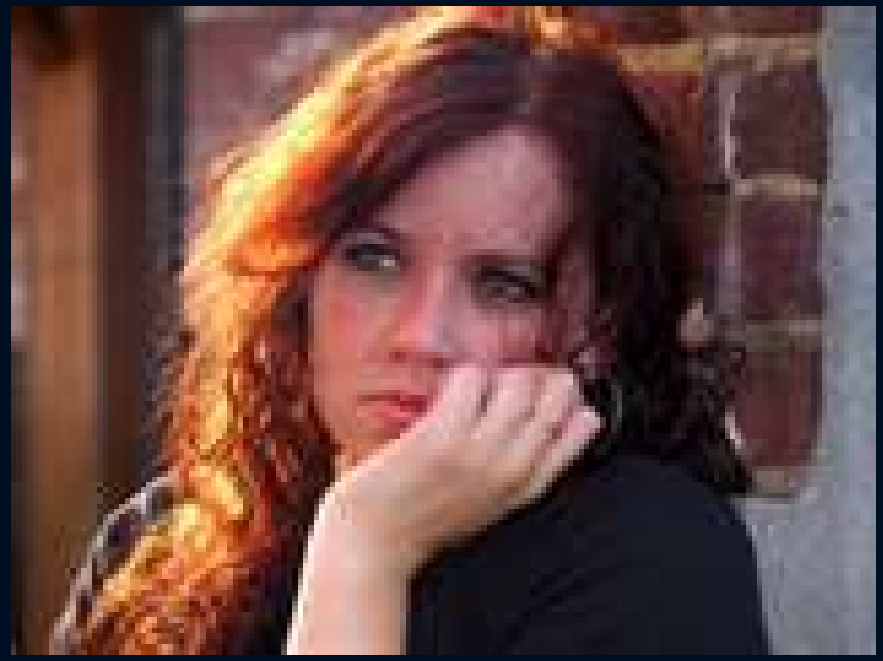
Dr. Dickson has no Financial Arrangements to Disclose

Opioid Use Disorder



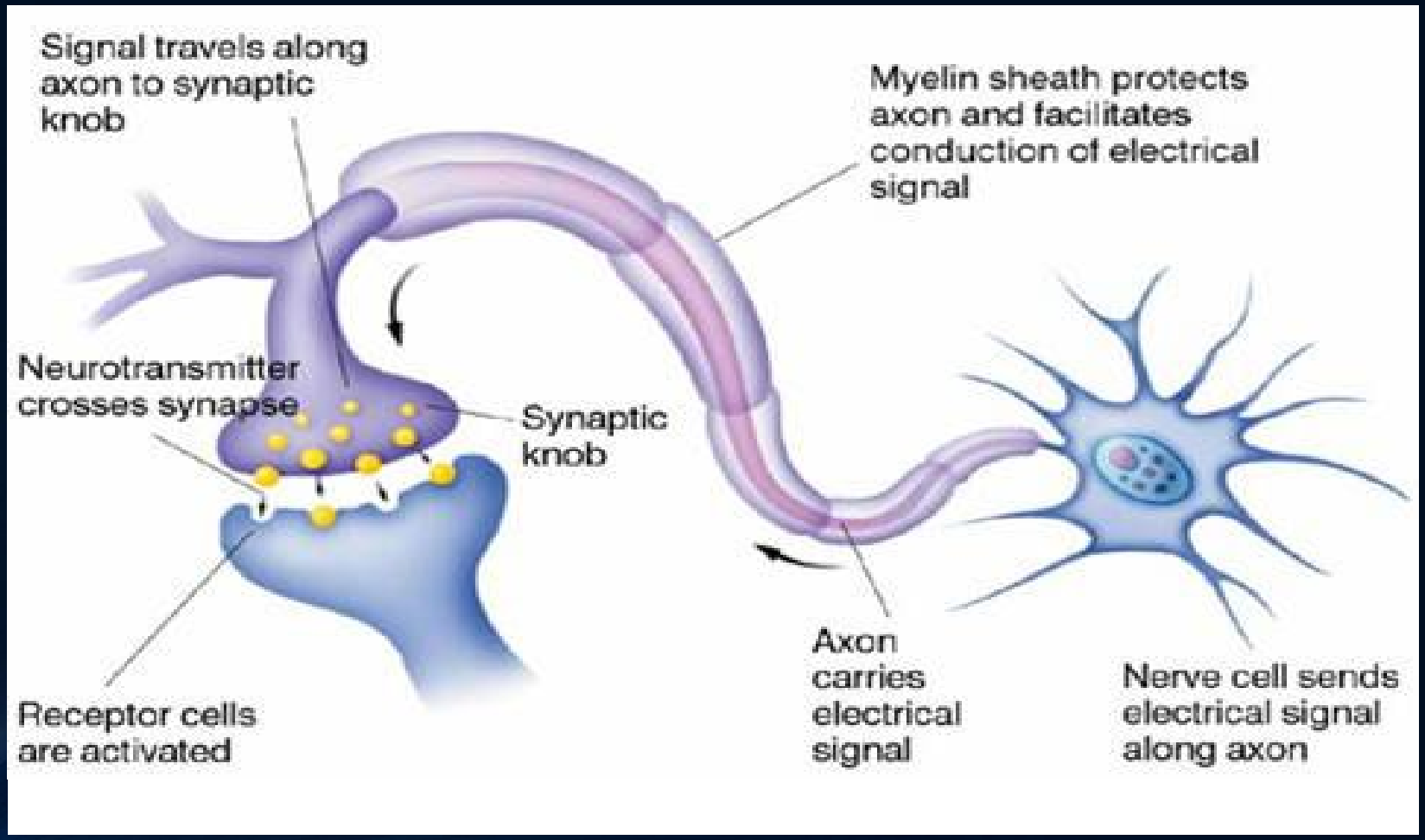
Opioid Use Disorder Pt.2

A. Opioid use leading to impairment or distress, with at least two of the following occurring within a 12-month period:
    1. Opioids used in larger amounts or over longer period than intended
    2. Unsuccessful efforts to cut down or control use
    3. Much time spent obtaining, using or recovering from opioids
    4. Craving or strong desire to use opioids
    5. Failure to fulfill major role obligations at work, school or home
    6. Continued use despite social or interpersonal problems
    7. Important social, occupational or recreational activities are given up or reduced

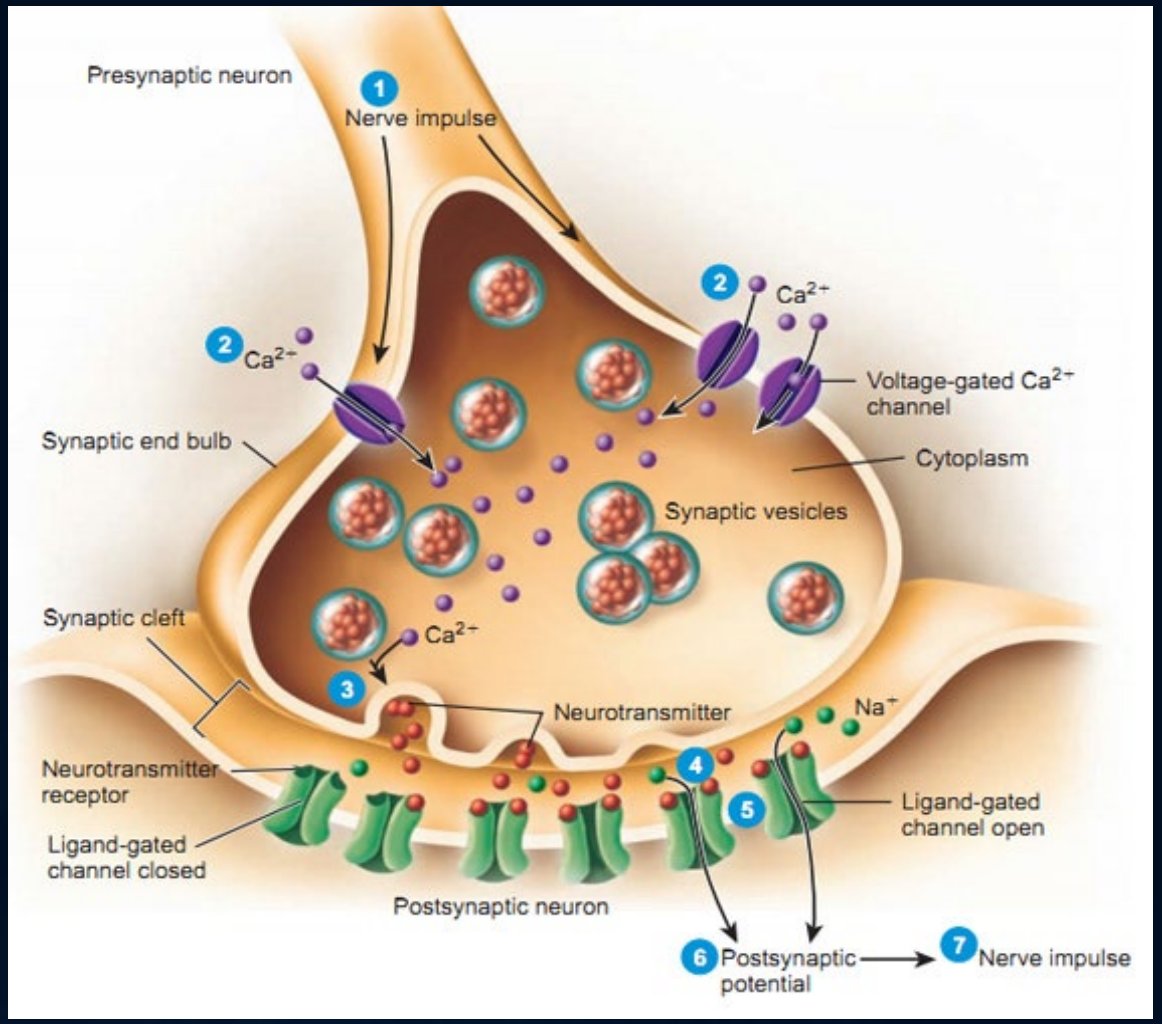
Opioid Use Disorder Pt. 3

8. Recurrent use in situations where it is physically hazardous
9. Continued opioid use in spite of persistent physical or psychological problem
10. Tolerance: the need for increased amounts for the desired effect or diminished effect of same amount
11. Withdrawal: a characteristic syndrome of symptoms with the same or closely related substance taken to avoid or relieve withdrawal symptoms

Neurotransmission



The synapse


Presynaptic neuron
1
Nerve impulse
2
Ca^{2+}
2
Ca^{2+}
Voltage-gated Ca^{2+} channel
Synaptic end bulb
Cytoplasm
Synaptic vesicles
Synaptic cleft
Ca^{2+}
3
Neurotransmitter
Na^{+}
Neurotransmitter receptor
4
5
Ligand-gated channel open
Ligand-gated channel closed
Postsynaptic neuron
6
Postsynaptic potential
7
Nerve impulse

Brief History of Opioids

- Use found as far back as 3400 BC "joy plant" *Papaver somniferum*
- Opioids used to control coughing, diarrhea and pain, primarily oral
- 1600's opium smoking spread around the world, including America
- 1806 isolation of morphine, named after Morpheus, Greek god of dreams and sleep
- By 1820, commercially available around the world
- 1853 syringe perfected allowing parenteral delivery of morphine
- Heroin discovered in 1874 – synthesized from morphine
- Opiates – naturally occurring substances in raw opium and include morphine, codeine, papaverine and thebaine

History of Opioid Use Disorder

- 1830-1899: extracts of opium such as laudanum were common and used to treat food poisoning and GI problems and were valued for their **sedating and calming effects**
- Tended to be white, middle-class females who became addicted while self-medicating – "sickly" or neurasthenic
- Civil War veterans and Chinese immigrants both had problems with overuse
- Dangers of use recognized in late 1800's
- 1900-1914 Morphine Maintenance Clinics
- 1914 Harrison Narcotics Tax Act: established the FDA and a federal system for regulation of drug manufacturing, pharmacies and physician prescribing
- Became illegal to treat OUD with prescribed opioids – 3000 physicians were jailed!

History of OUD Treatment

- With the Harrison Act, OUD problems were shifted to criminal justice system
- Introduction of heroin worsened the situation and there were several heroin epidemics after the wars of the 20th century
- 1960 Vincent Dole and wife Marie Nyswander published on efficacy of methadone maintenance
- 1972 FDA issued federal methadone regulations, thereby legalizing methadone maintenance treatment
- Never caught on with most users and the medical community
- Heroin misuse remained the predominant opioid problem until the mid 1990's when pain pill misuse increased

Opioid Mechanisms

- Opioids are molecules which circulate in the blood and enter the central nervous system (primarily brain and spinal cord)
- All opioids bind to three receptors, μ, δ and κ
- Most clinical effects come from binding at the μ (mu) receptor in the brain
- Endogenous (self-made) opioids include the β-endorphins, enkephalins and dynorphins
- Opiates are compounds derived or synthesized from the natural product thebaine and its derivatives isolated from the opium poppy plant

- Exogenous (from outside) opioids lead to rapid receptor desensitization and tolerance and withdrawal
- Tolerance is the need for increasing amounts to get the same effect
- Withdrawal is an array of unpleasant symptoms when the drug is reduced or stopped
- Opioids are medically used for relief of pain and cough suppression and all have an abuse potential

Fentanyl

- Very potent synthetic opioid
- Huge threat and linked to many recent accidental deaths
- Produced in Mexico and China – often mixed with heroin
- Analogs such acetyl fentanyl, furanyl fentanyl and carfentanil (veterinary use) also out there, Schedule I drugs
- Fentanyl, Schedule II, used in anesthesia and for post-op pain
- Also used for severe cancer pain when other opioids no longer effective – available as a long-acting transdermal (skin) patch and in lozenges or lollipops
- It is being added to amphetamines, opioid pills and benzodiazepines

Opioid Agonist Effects

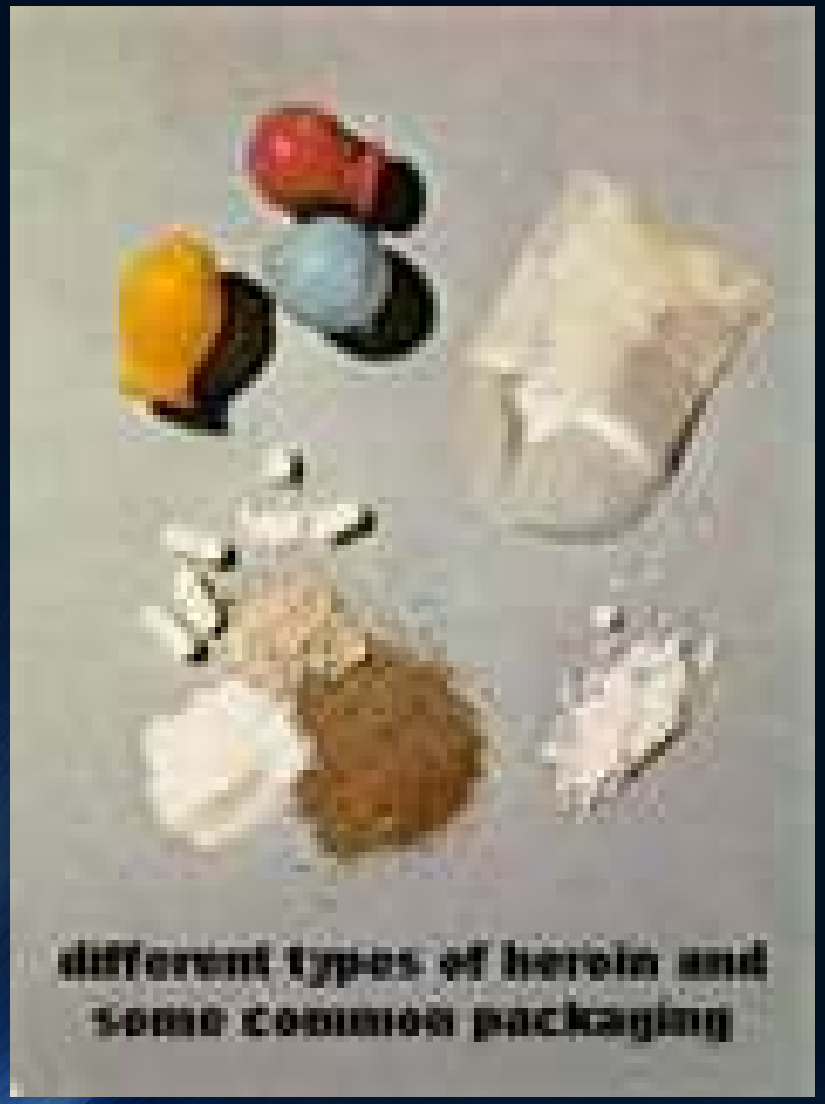
- Acute Use Effects: **Euphoria**, Vomiting, Constricted Pupils, Slowed respirations, Drowsiness, Analgesia, Decreased awareness, Altered consciousness
- Chronic Use Effects: Physical dependence, Psychological dependence, Variable energy changes, Constipation
- Overdose Effects: Nonresponsive, Pinpoint pupils or "blown" pupils, Bradycardia, Hypotension, Skin cyanotic (blue-gray), Muscles flaccid, Pulmonary edema, Slowed respirations

Opioid Withdrawal

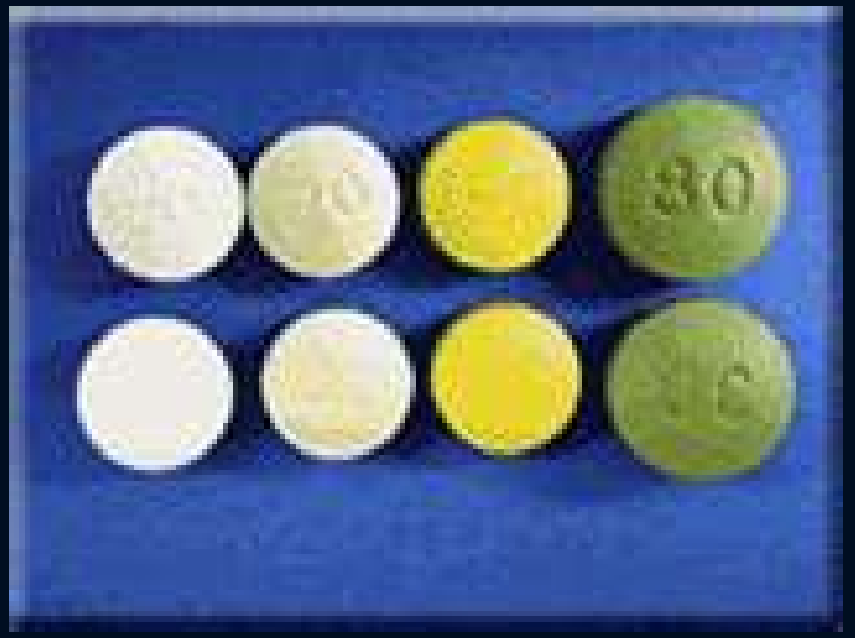
- Cessation or reduction in opioid use or administration of an opioid antagonist after a period of opioid use
- Three or more of the following:

Dysphoric mood	Diarrhea
Nausea or vomiting	Yawning
Muscle aches	Fever
Lacrimation (tears)	Rhinorrhea (drippy nose)
Pupillary dilation	Piloerection (goose bumps)
Sweating	Insomnia

- Symptoms cause significant distress or impairment
- Symptoms not due to a medical or other mental condition



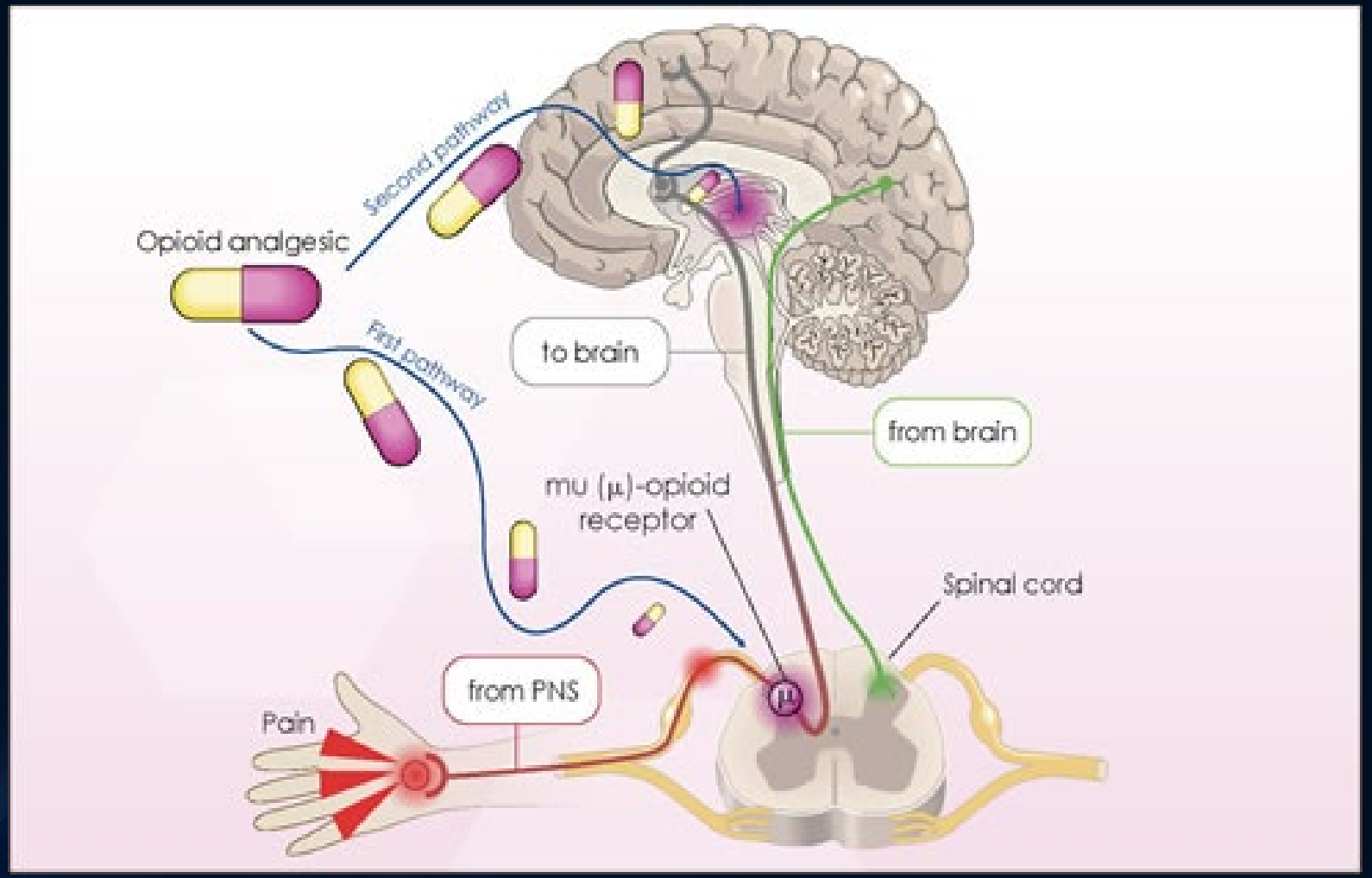
different types of heroin and some common packaging



The μ Receptor in Normal Physiology

- Neuroendocrine function including the HPA axis and Reproductive
- Immunological function
- Gastrointestinal function
- Cardiovascular function
- Pulmonary function and respiratory drive
- Endogenous response to pain
- Mood, affect, cognition

Pain and the Mu Receptor



Medical Complications of Opioid Dependence

- Infections, primarily from injecting
  - Hepatitis B, C and delta
  - Cellulitis and abscesses
  - HIV and STD's
- Endocrine, primarily reproductive
- Gastrointestinal, primarily constipation
- Liver disease, primarily from viral infections
- Respiratory depression and accidental overdose death
- Trauma from accidents, violence, sexual abuse
- Depression and suicide

Reversal of Overdose: Naloxone

- Pure mu receptor short-acting antagonist – brand name is Narcan
- Used for overdoses but timing is essential
- Brain death starts in 4-8 minutes after breathing stopped
- Not available for oral use
- Injectable solution, nasal spray and one-dose administered injection
- Now available for families, friends and rescue personnel
- Laws now protect those who call to report overdose

Pain in the United States

- Approximately 30% of Americans have pain
- Older adults: 40%
- Opioids are most prescribed class of medications in the U.S.
- About 80% of world opioid use is in USA
- 2014: 245 million prescriptions for opioids
  - 65% for short term (less than 3 weeks use)
  - 3-4% of population (9-11.5 million) receive chronic opioid therapy

Misuse and Diversion

- Opioids are important analgesics for acute pain
- Less evidence for effectiveness in chronic pain
- Increases in misuse and diversion have tracked with increased prescribing
- Mu receptors are widespread in the brain: pain perception, emotional response to pain, pleasure, respiratory depression
- Safety issues and adverse events including overdose, death, and addiction

Abstinence Based and Psychosocial Treatments

- Inpatient detox and rehabilitation
- Intensive Outpatient Treatment (IOP)
- 12 Step Programs
- Counseling, particularly Cognitive Behavior based
- Mindfulness becoming popular
- Family therapy
- Sober Living Residences
- Nowhere near enough!

Medication Assisted Treatments (MAT) for Opioid Use Disorder

- Short-Term:
  - Medical Withdrawal (Detoxification)
    - Opioid and non-opioid
- Long-Term
  - Opioid antagonist
  - Opioid agonist or partial agonist

Opiate Withdrawal

- Time to onset depends on how long the opioid is present
- When used for pain for a period of time, withdraw gradually by tapering dose – difficult for patient to do
- Most signs and symptoms abate in 48-96 hours after stopping opioids but some persist for months
- Withdrawal is so unpleasant for many that they relapse to use, thus referral to MAT is an important option
- Methadone and buprenorphine work well for detoxing with supervision

Opiate Substitution = Medication Assisted Treatment (MAT)

- Methadone and Buprenorphine
- Goals are to reduce or prevent the adverse effects of drug use and improve functioning, quality of life and overall functioning
- Continual, regular use prevents periods of intoxication alternating with withdrawal and the need to be looking for the next dose
- Should be partnered with rehabilitation services and supportive counseling, individual or group

Methadone

- A synthetic, long acting, orally available μ and δ agonist – approved in 1964
- Rapidly and nearly completely absorbed in GI tract
- Peak plasma levels in 2-6 hours
- Gives some euphoria
- Plasma half-life about 24 hours so can dose daily
- Can cause respiratory depression
- Many overdoses and deaths due to methadone so closely monitored
- Done in Federally certified programs with frequent inspections

Methadone: Program Management

- Effective dosages between 60 and 120mg a day
- Initially daily dosing in clinic, comes in liquid form
- Start about 30mg and increase to lack of withdrawal and cravings
- Programs need policies for illicit use
- Expect relapses and support return to program
- Programs should have counseling components
- Reward clean urines and other positive behaviors
- Earn privilege of take-home doses

Methadone: Chronic Use

- Demonstrated safety and efficacy when used in a monitored program
- No long-term damage to organ systems
- Constipation common - treat actively
- Relatively inexpensive and most programs take Medicaid
- Non-Medicaid patients pay cash
- Methadone is not reported on PDMP
- Daily dosing is difficult for some patients

Buprenorphine: Unique in Opioid Use Disorders MAT

- Buprenorphine first drug approved for office-based treatment of opioid addiction
- Available by prescription – Schedule III
- Up to 30-day prescription may be given – avoid refills
- Physicians with specific training and DEA waiver can prescribe
- Number of patients originally limited to 100 but recently increased to 275

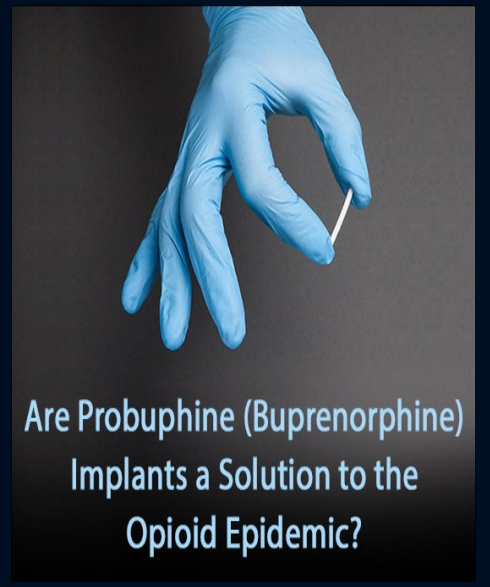
Buprenorphine continued

- Most insurance no longer requires a prior authorization but usually granted, expensive if cash pay
- May need to become a Medicaid provider
- Avoid sedatives such as benzodiazepines - check PDMP
- Methadone clinics now prescribing or dispensing
- APRN's and Physician Assistants can now get "waivered" after a 24-hour course
- DEA tracks prescribing and visits offices to assess compliance with regulations

Buprenorphine

- Buprenorphine is a mixed μ receptor agonist / antagonist
- Binds tightly to the μ receptor
- Antagonist properties displace other opioids
- Effectively blocks the effects of other opiates and therefore the reward qualities
- Like methadone, is long-acting and safe
- Can precipitate withdrawal reaction if given too soon after use of an opioid agonist
- Must be in withdrawal or detoxed to start
- Patients report little cravings or relapses, no “high”

Buprenorphine Preparations

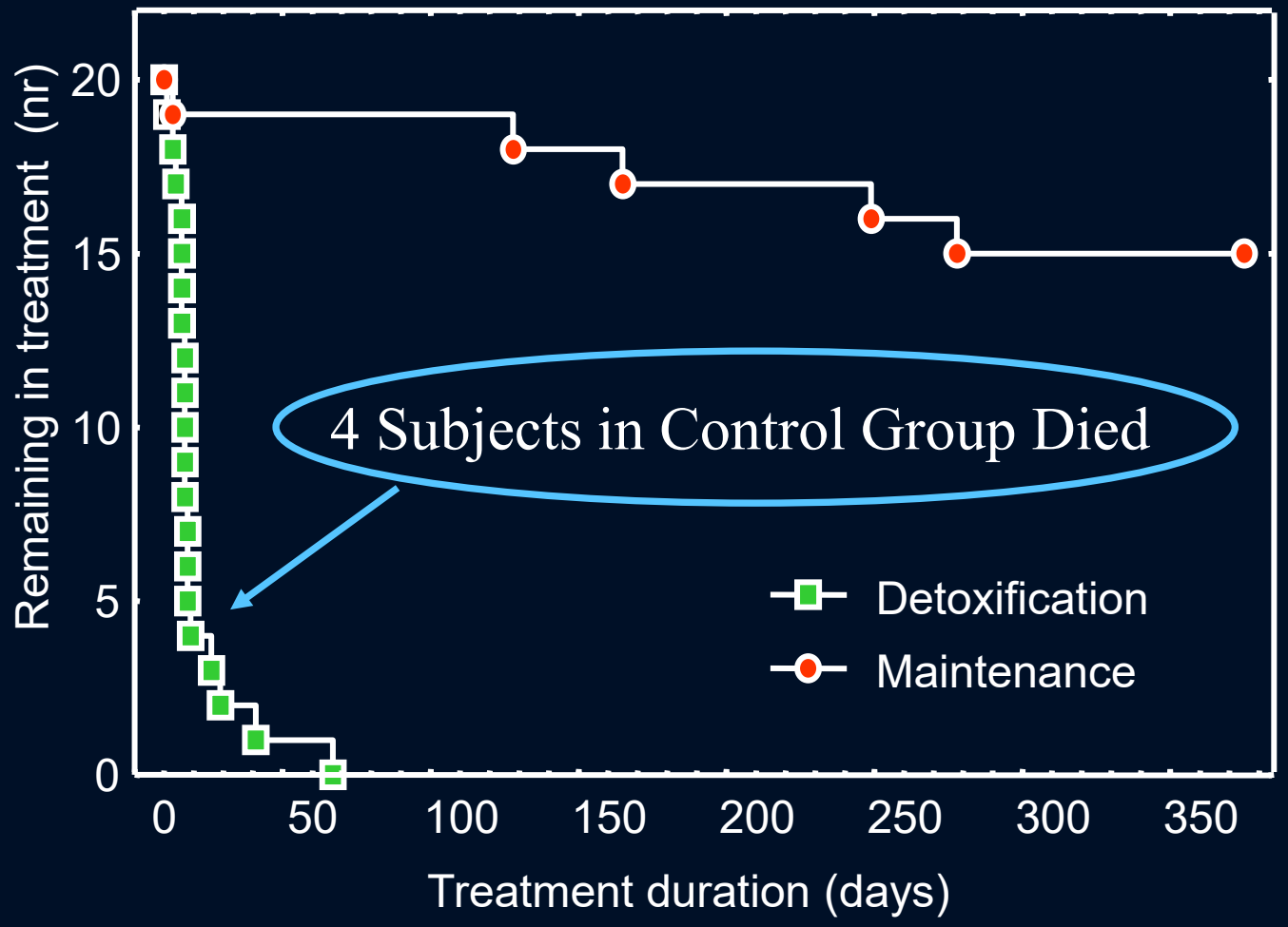


Buprenorphine Preparations Cont.

- Available now in sublingual tablet and rapidly dissolving film, now 5 generic films
- Used for detox and maintenance
- Starting dose usually 8 to 16mg SL daily, can divide dose
- Tablets and film can also contain naloxone in 4:1 ratio to reduce risk of abuse by injection (Suboxone, Zubsolv)
- 6-month implant available
- Long-acting, 30-day, injection recently approved (Sublocade)
- Tablet with only buprenorphine (Subutex) available for pregnant women
- Must use sublingually – inactivated by acid in stomach

Buprenorphine vs. Withdrawal and Drug-Free Treatment for Heroin Dependence

Kakko, Lancet 2003

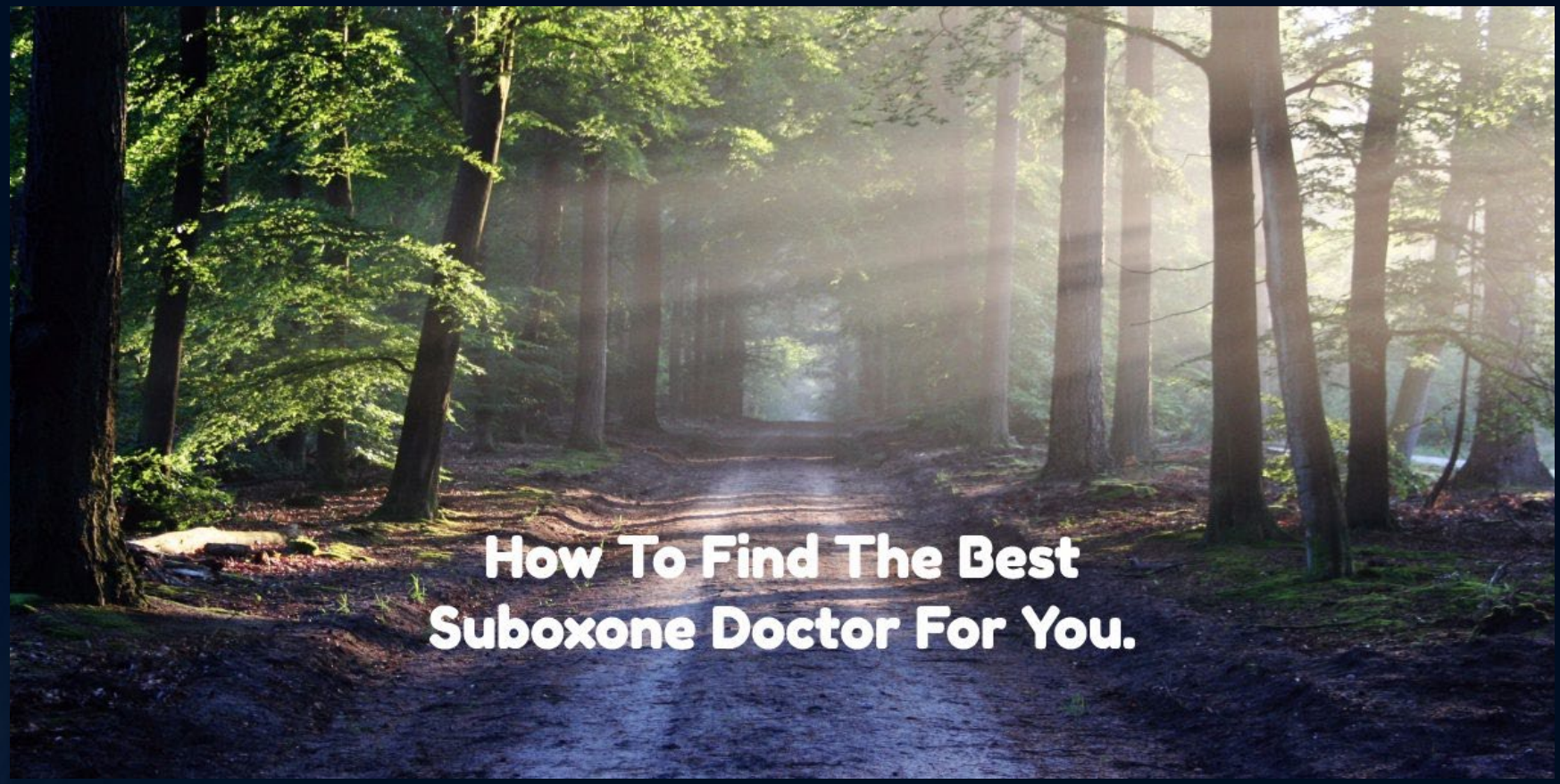


Opioid Antagonist: Naltrexone

- Binds tightly to the μ (mu) receptor
- Prevents other opioids from binding
- Patients lose interest in using and no craving
- Naltrexone tablet 50 mg/day (Revia) approved in 1994
- Efficacy is best among motivated patients
- Nausea, headache, anxiety or sedation are uncommon side effects
- Cannot be prescribed in patients with severe liver disease

Naltrexone continued

- Depot (IM shot) Naltrexone (Vivitrol), 380 mg once a month, originally approved for alcohol use disorder
- Recently approved for opioid use disorder and may enhance compliance
- Depot shot expensive but some insurance and Medicaid covers
- Efforts being made for use in those leaving a detox program, jail or prison to decrease risk of relapse
- Important to warn a recently detoxed person that tolerance has decreased and to use a smaller dose if relapses



www.samhsa.gov/medication-assisted-treatment/physicianlocator
www.suboxone.com/treatment-plan/find-a-doctor

Bridge Program

- Modeled on California and Connecticut (Yale)* programs
- To encourage emergency room staff to start buprenorphine in the ER and then refer to outpatient treatment
- Requires ER staff to recognize and counsel patient
- Will include a peer support recovery specialist or community health worker to be available to do the initial counseling and referral
- ER docs will need to be waivered or at least educated in the dosing of buprenorphine
- Working on eliminating the waiver requirement
- Need hospitals to get on board and have buprenorphine on the formulary

* *Emergency Department-Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence: A Randomized Clinical Trial,* G. D'Onofrio et al, JAMA. 2015;313(16): 1636-1644.

Candidates for Naltrexone

- Patients who are not interested or able to be on agonist maintenance
  - Highly motivated for abstinence from all opioids (e.g., active in 12-step programs)
  - In professions where treatment with agonist is still controversial (e.g., healthcare professionals, pilots)
- Patients who are detoxified and abstinent but at risk for relapse
  - Released from a controlled setting (prison, residential program)
  - Moving back to old neighborhood
  - With increased stress or worsening of psychiatric problems

Patients who may be better candidates for agonists

- Patients with history of overdoses, particularly following detoxification
- Patients with serious psychiatric or medical problems
- Patients with limited social supports (unstable lives, homeless)
- Patients who have been opiate-free but never felt "normal"
  - Patients in whom psychiatric illness emerged/worsened after previous detoxifications (with or w/o naltrexone)
- Patients with chronic pain requiring chronic opioid treatment
- Patients with severe GI disorders exacerbating during withdrawal/abstinence

Prescription Monitoring Program - PMP

- Register or check a patient at https://Nevada.pmpaware.net
- Nevada established in 1997 – one of the first states
- All states now have them
- States with stronger mandates for use of PMP have decreased prescribing of opioids and overdose deaths
- Can register a delegate in office to pull the reports
- Can look at own prescribing history to check for fraudulent prescribing
- Network between states – Nevada can check 23 other states, unfortunately not California

Governor's Opioid Bill
AB474

- Overdoses from controlled substances must be reported
- PMP must be consulted
- Patient must be evaluated for history or risk of addiction
- Must use consent form
- 2 hours of CME relating to the misuse and abuse of controlled substances, the prescribing of opioids or addiction during each relicensure period.
- Good history and physical must be performed and entered into medical record along with diagnosis and treatment plan

PRESCRIBING OPIOIDS for PAIN

- Painkillers are prescribed for no more than 14 days for acute pain.
- After 30 days of consecutive prescriptions, the doctor and patient must enter into a narcotic contract that lays out goals for treatment and gives consent to drug testing if necessary.
- At 90 days, a doctor must offer up an "evidence-based diagnosis" — not something generic like a diagnosis of "lower back pain" — and must recheck the state's Prescription Monitoring Program database
- For any prescription exceeding 365 days, doctors must document their rationale for prescribing opioids for so long.

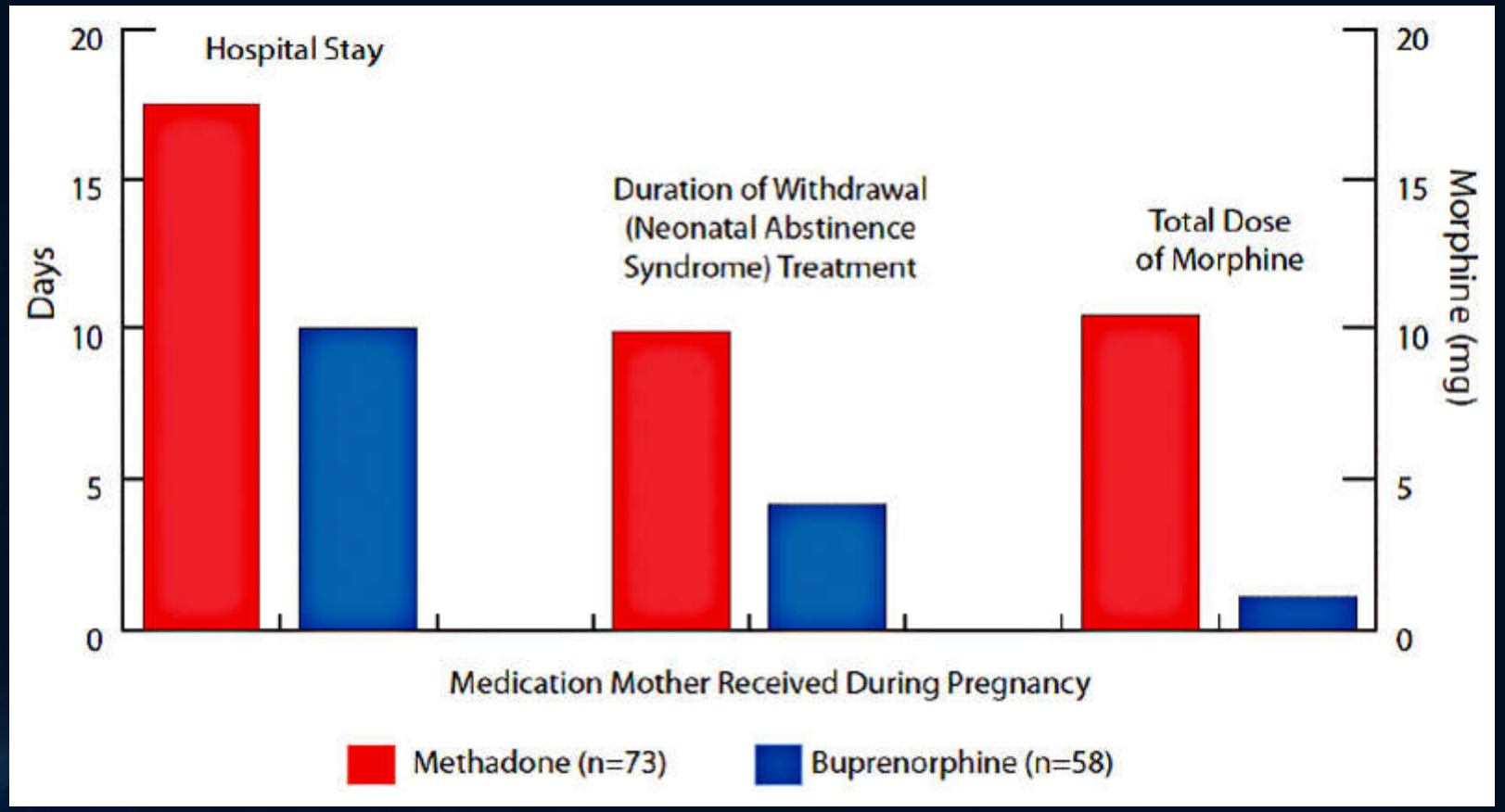
MAT and Pregnancy

- Methadone has been the "Gold Standard"
- Want to stabilize patient and prevent using and withdrawals – hard on the fetus
- Provides for supervised prenatal care
- May need to increase dose toward end of pregnancy
- Buprenorphine now shown to be safe and effective although not FDA approved
- Recent study used buprenorphine for Neonatal Abstinence Syndrome
- Mother can breastfeed on either drug but watch timing of dosing and feeding

Neonatal Abstinence Syndrome - NAS

- Opioids not good for baby: fetal growth restriction, Intrauterine withdrawal, depressed breathing, preterm delivery, premature rupture of membranes, perinatal death, NAS
- NAS in 30% to 80% infants born to women taking opioids, including those in MAT programs
- Disruption of mother-infant relationship, sleep-wake abnormalities, feeding difficulties, weight loss and seizures
- Withdrawal symptoms include tremors, diarrhea, fever, irritability, jitteriness, sweating, vomiting, generalized convulsions
- Opioids first-line therapy – methadone, buprenorphine and morphine

Methadone vs Buprenorphine in Pregnancy: Effects on Newborn

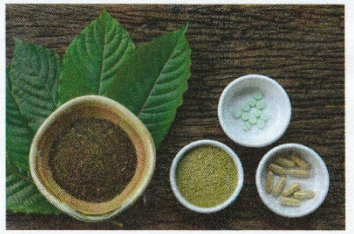


Kratom

Leaves of Mitragyna Speciosa

Kratom Products

- Leaves, dried or crushed.
- Extracts, powders, capsules.
- Tablets, liquids, and gum/resin.
- Readily available at shops or online.
- Dramatic increase in importation in 2016.
- Amounts accounted for millions of doses for recreational use.
- Often declared and falsely labeled similar to other newer drugs of abuse.



Kratom II

- Recreational drug in SE Asia and the West
- 55% of regular users become dependent
- Implicated in some overdose deaths
- Used in self-management of opioid withdrawal
- Users tend to be middle-aged, male, white and employed
- Small doses are stimulatory while larger doses have sedative-narcotic effect

Kratom III

- Active drugs are mitragynine and 7-hydroxymitragynine
- Binds to opioid receptors and several others (serotonin, noradrenaline and dopamine)
- Mu partial agonist
- Withdrawal similar to opioid withdrawal
- Cravings and relapse
- Presently unregulated or limited to over 18 or 21 in most states but banned in some
- Working on changing to a Schedule I drug but push back from billion-dollar industry

Local resources

- Inpatient/Detox Programs
  - WestCare 383-4044
  - Crossroads 702-433-4357
  - Seven Hills Behavioral Inst / Henderson 646-5000
  - Las Vegas Recovery Center (Landmark) 800-790-0091
  - Desert Hope Treatment Center 888-211-6274
- Outpatient
  - Community Counseling 369-8700
  - Bridge Associates 474-6450
  - WestCare 702-385-2020
  - BHG Recovery (formerly Center for Behavioral Health) 702-796-0660
  - AA 598-1888
  - High Risk Pregnancy Center 702-940-3266
  - Several Methadone Programs – www.samhsa.gov/treatment