Medication Assisted Therapy in the Treatment of Opioid Dependence

John H. Evans, DO, MA, DABAM, CAADC

Victory Clinical Services – Saginaw

508 Shattuck Road

Saginaw, MI 48604

989-752-7867 (T)

989-752-6830 (F)

vcsjevans@yahoo.com

Disclosures of Conflict of Interest

The speaker discloses that he has no relevant financial relationships with any commercial interests.

Objectives

- Gain understanding of addictions.
- Gain knowledge of methadone, buprenorphine, and naltrexone and the medication selection process.
- Gain understanding of the purpose of treatment.
- Develop understanding of treatment considerations in the treatment of opiate addiction, especially in the pregnant patient.

DEA: Five schedules

- **I**: no accepted medical use (heroin, LSD, MDMA, marijuana, PCP)
- **II**: limited use/high abuse (opioid analgesics, cocaine, amphetamine, secobarbital, pentobarbital, methadone) restrictions on prescribing & no refills
- **III**: decreased abuse potential, anabolic steroids and buprenorphine
- **IV**: tramadol, butorphanol, benzodiazepines for anxiety or sleep
- **V**: codeine cough syrup & Lyrica

Opioid Use Disorders

- A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.

Opioid Use Disorders (cont)

3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.

Opioid Use Disorders (cont)

6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.

Opioid Use Disorders (cont)

9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

Opioid Use Disorders (cont)

10. Tolerance as defined by either of the following:

    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.

    b. A markedly diminished effect with continued use of the same amount of an opioid.

Opioid Use Disorders (cont)

11. Withdrawal as manifested by either of the following:

    a. The characteristic opioid withdrawal syndrome.

    b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

Opioid Use Disorders (cont)

Severity:

a. Mild: Presence of 2-3 symptoms.

b. Moderate: Presence of 4-5 symptoms.

c. Severe: Presence of 6 or more symptoms.

Opioid Use Disorders (cont)

- Early remission: no criteria are met, except cravings, between 3 months and 12 months.
- Sustained remission: no criteria are met, except cravings, for a period of 12 months or longer

Dependence vs. Addiction

- Addiction is not considered to be a clinical term.
- Proper diagnostic phraseology is Opioid Use Disorder.
- Disordered thought process differentiates addiction from physical dependence.
- Cravings.
- With opioids, physical dependence *usually* precedes addiction.

Epidemiology

- Most commonly overdosed prescription opioids:
  - Methadone
  - Oxycodone
  - Hydrocodone

Epidemiology

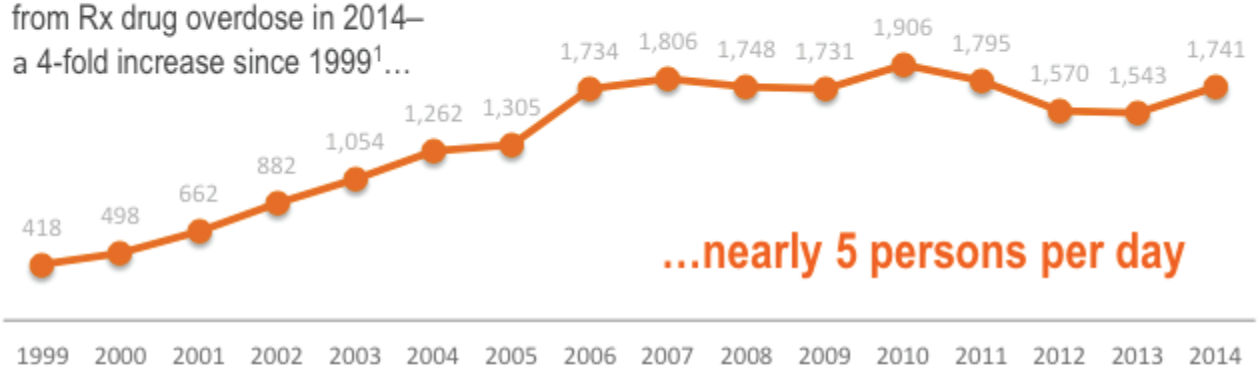
- Overdose deaths from prescription opioids from 1999 to 2014:
  - Overdose rates were highest among people aged 25 to 54 years.
  - Overdose rates were higher among non-Hispanic whites and American Indian or Alaskan Natives, compared to non-Hispanic blacks and Hispanics.
  - Men were more likely to die from overdose, but the mortality gap between men and women is closing.

Epidemiology

- Additional Risks of Prescription Opioids
  - In 2014, almost 2 million Americans abused or were dependent on prescription opioids.
  - As many as 1 in 4 people who receive prescription opioids long term for non-cancer pain in primary care settings struggles with addiction.
  - Every day, over 1,000 people are treated in emergency departments for misusing prescription opioids.

CONSEQUENCES

More than 1,700 young adults, ages 18-24, died from Rx drug overdose in 2014– a 4-fold increase since 1999[1]…



…nearly 5 persons per day

Among young adults, for every death due to Rx drug overdose, there were:

119 Emergency Room Visits[6]

&

22 Treatment Admissions[7]

Epidemiology

- Additional Risks of Heroin Use
  - More than nine in 10 people who used heroin also used at least one other drug.
  - Among new heroin users, approximately three out of four report having abused prescription opioids prior to using heroin.
  - 70% of heroin addicts who smoke marijuana return to using heroin.

Epidemiology

% Increase from Previous Year	2014	2015	2016	2017
Total Overdose Deaths	47,055	52,404 11.4%	63,632 21.4%	70,237 10.4%
Total Opioid Overdose Deaths	28,647	33,091 15.5%	42,429 28.2%	47,600 12.2%
Heroin Overdose Deaths	10,000	12,989 29.9%	15,469 16.0%	15,482 ----
Synthetic Opioid Overdose Deaths		9,580	19,413 102.6%	28,466 46.6%

Epidemiology

% of Total Deaths	2014	2015	2016	2017
Total Overdose Deaths	47,055	52,404	63,632	70,237
Total Opioid Overdose Deaths	28,647 60.9%	33,091 63.1%	42,429 66.7%	47,600 67.8%
Heroin Overdose Deaths	10,000 21.2%	12,989 24.8%	15,469 24.3%	15,482 22.0%
Synthetic Opioid Overdose Deaths		9,580 18.3%	19,413 30.5%	28,466 40.5%

Epidemiology

- From 2015 to 2016:
  - Overall drug deaths increased 21.5%.
  - Overdose death rate from non-MTD synthetic opioids more than doubled.
  - Overdose death rate from prescription opioids increased 10.6%.
  - Overdose death rate from heroin increased 19.5%.

Epidemiology

- Overdose death rate from cocaine increased 52.4%.
- Overdose death rate from psycho-stimulants increased 33.3%.

What is Methadone?

- Full synthetic opiate agonist active at the mu opiate receptor.
- Schedule II
- Used for severe pain, opioid detoxification, and opioid maintenance therapy.
- Metabolized by the Cytochrome P450 – CYP3A4, CYP2B6, and CYP2D6* isoforms.

What is Methadone?

- Half-life is 8-59 hours. For practical purposes, this can generally be considered to be 24-36 hours.
- Peak effect is 3-8 hours after administration.
- Analgesic effects generally last 4-6 hours, regardless of how much is given.
- Incomplete cross-tolerance.

Why Opioid Maintenance Therapy?

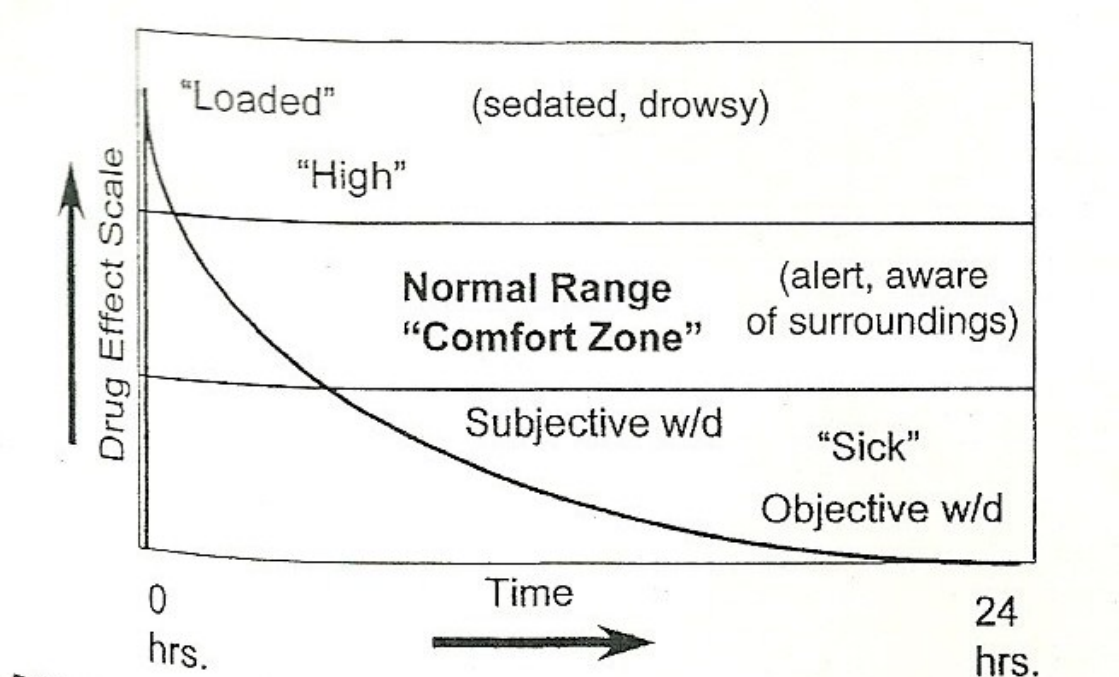


FIGURE 49.1. Heroin-simulated 24-hour dose-response.

Why Opioid Maintenance Therapy?

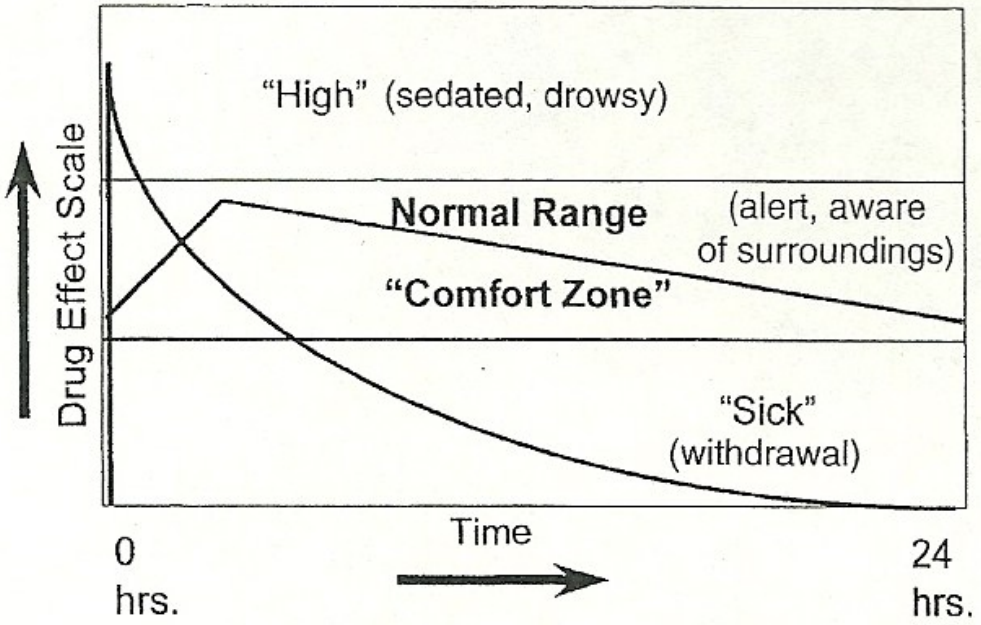
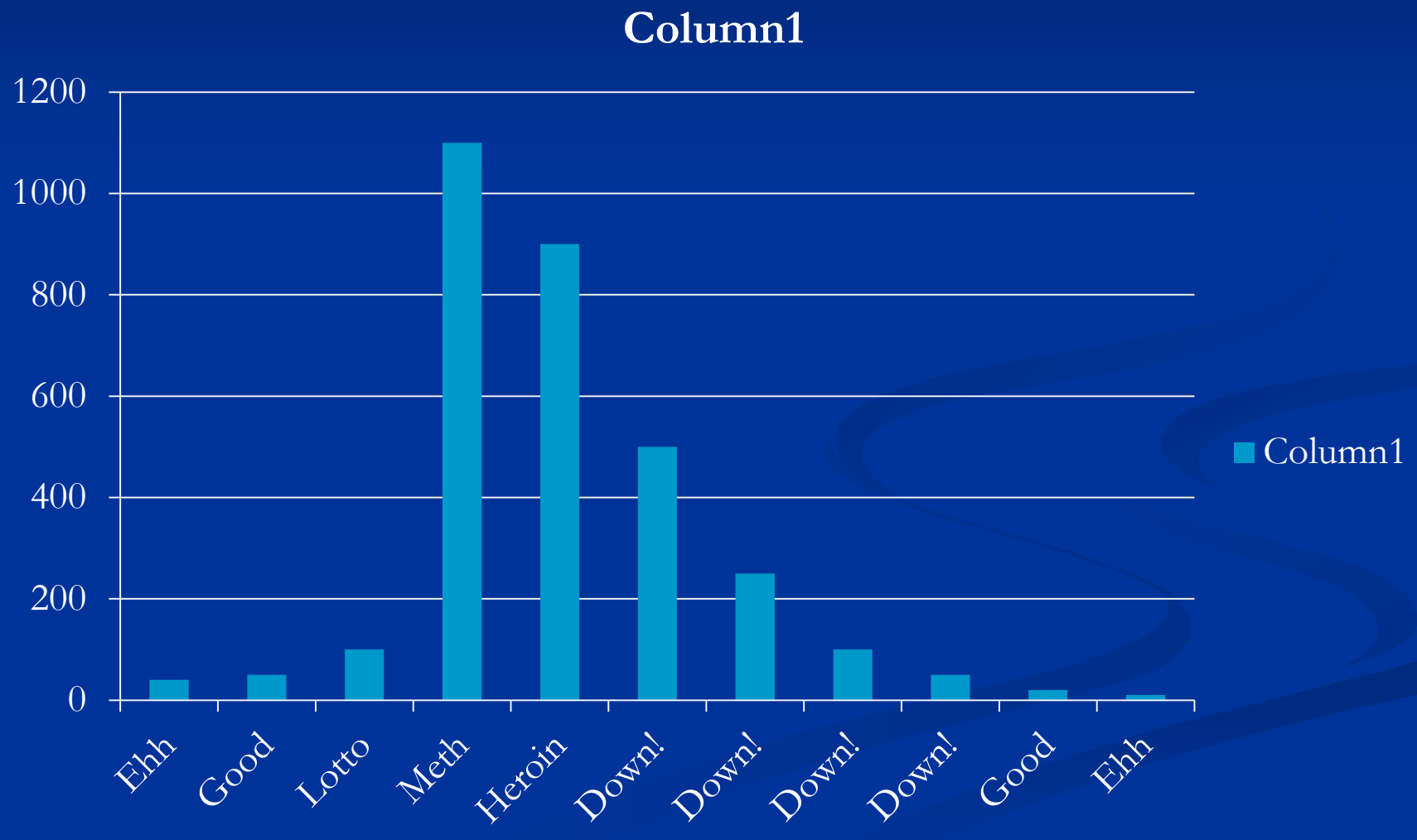


FIGURE 49.2. Methadone 24-hour . . . at steady-state.

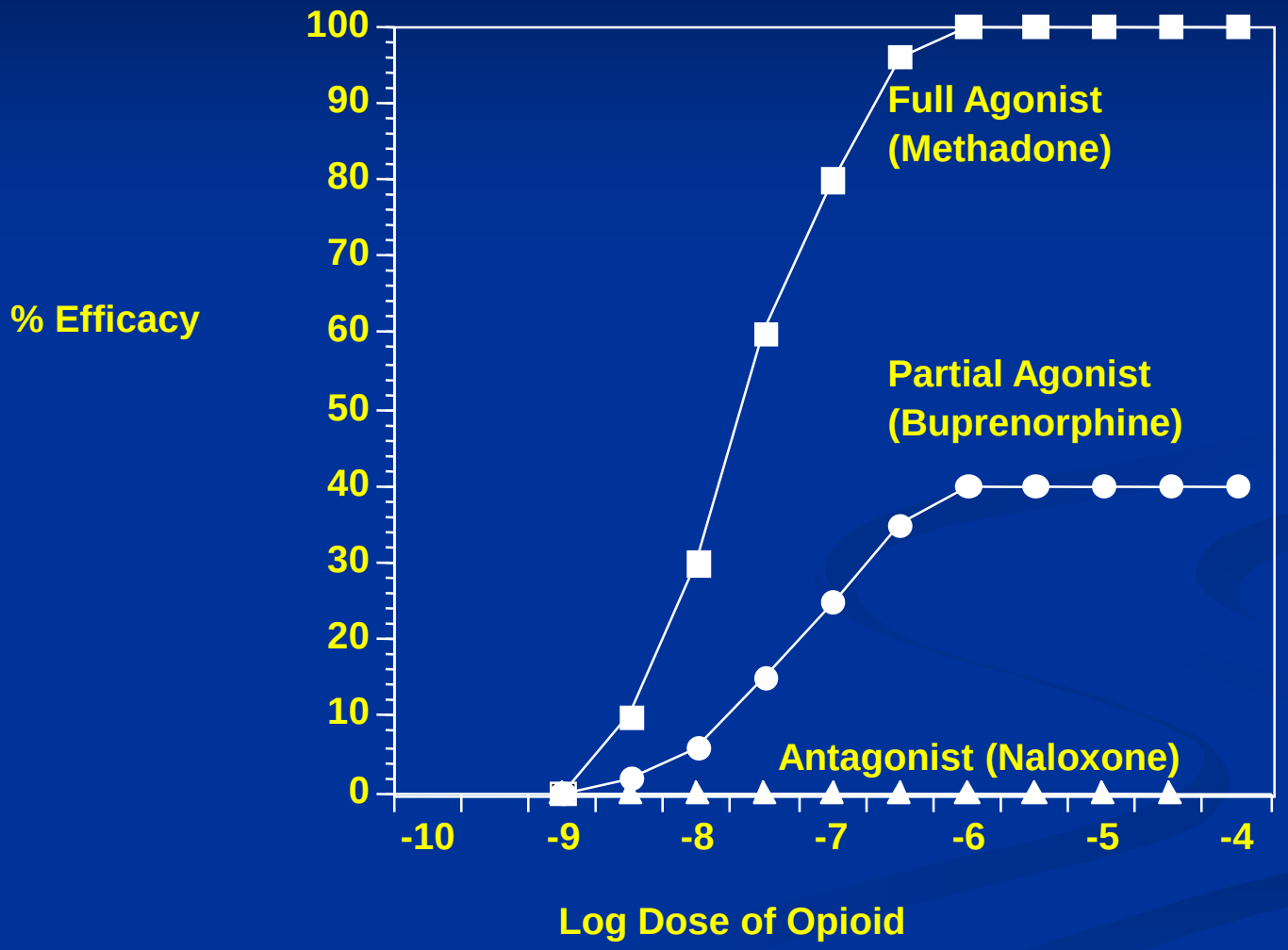
What's the Key?

- It is all about Dopamine!

Dramatization of Dopamine Levels in the Brain

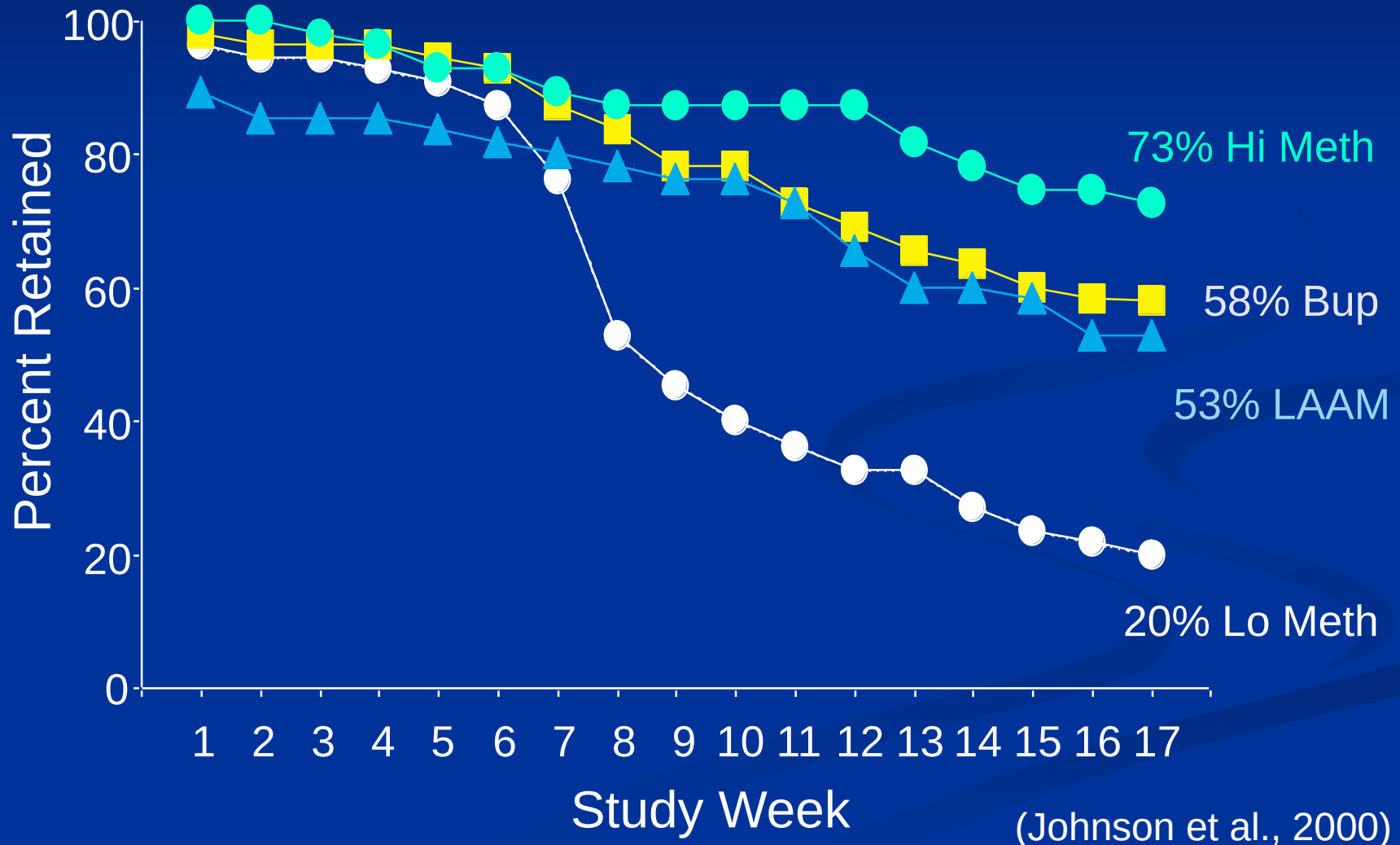


Efficacy: Full Agonist (Methadone), Partial Agonist (Buprenorphine), Antagonist (Naloxone)



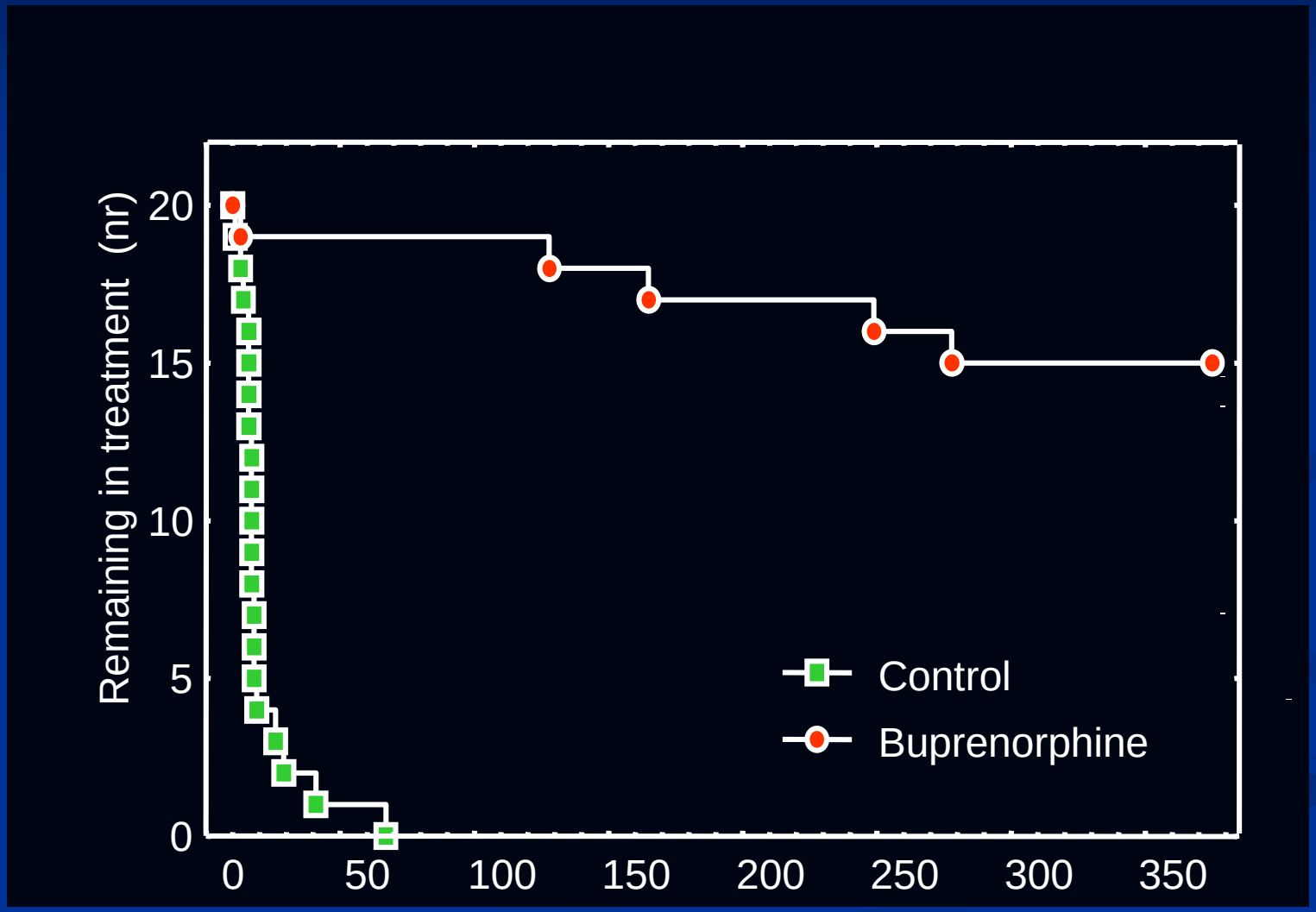
Bup, Methadone, LAAM Comparison

Treatment Retention



(Johnson et al., 2000)

Buprenorphine Maintenance/Withdrawal: Retention

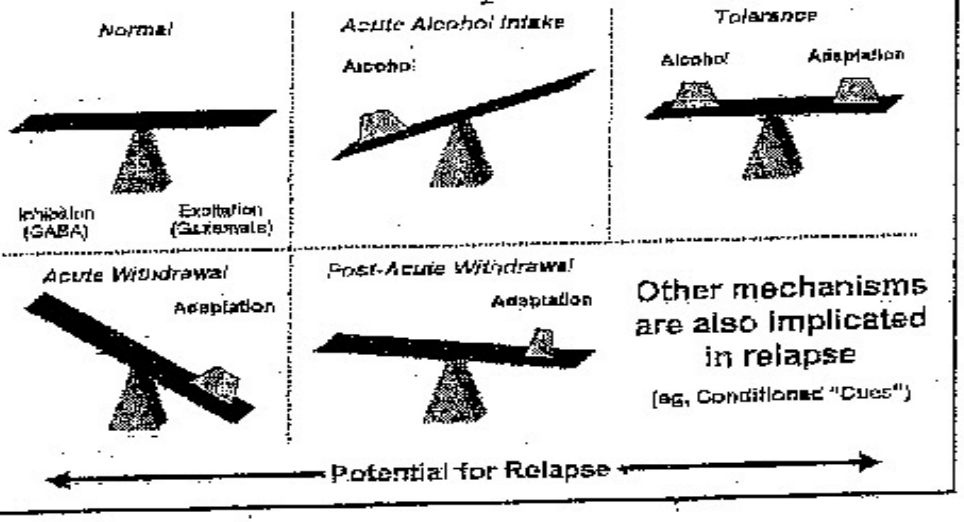


(Kakko et al., 2003)

Kakko et al, Lancet Feb 22, 2003
Buprenorphine Maintenance/Withdrawal: Mortality

	Placebo	Buprenorphine	Cox regression
Dead	4/20 (20%)	0/20 (0%)	$\chi^2=5.9$; p=0.015

Neuroadaptation: Potential for Relapse



Methadone vs. Buprenorphine Selection Criteria

- Substance used: Oral opioids, particularly hydrocodone, demonstrate a better outcome with Suboxone than injected opioids (especially heroin).
- Length of use: Less than 5 years of addictive use is more amenable to treatment with Suboxone.

Methadone vs. Buprenorphine Selection Criteria

- Physical Factors:
  - Age
  - Previous treatment
    - How many treatment episodes.
    - What has been used.
    - How long was treatment.
    - How successful was treatment.
  - Pregnancy – what they are using already.

Methadone vs. Buprenorphine Selection Criteria

- Psycho-social Factors:
  - Family pressures – e.g. resistance to Methadone.
  - Peer pressures – e.g. what recovering friends use.
  - Employment – time considerations for dosing.
  - Funding – what insurances will cover.
  - Monetary – what the patient can afford.

Medication for Opioid Use Disorder After Nonfatal Opioid Overdose and Association With Mortality: A Cohort Study

- Annals of Internal Medicine (June 19, 2018)
  - 17,568 Massachusetts adults without cancer who survived an opioid overdose between 2012 and 2014.
  - In the 12 months following a non-fatal opioid overdose:

Cont.

- 2040 persons (11%) enrolled in MMT for a median of 5 months.
- 3022 persons (17%) received buprenorphine for a median of 4 months.
- 1099 persons (6%) received naltrexone for a median of 1 month.

Cont.

- Among the entire cohort, all-cause mortality was 4.7 deaths per 100 person-years.
- Opioid-related mortality was 2.1 deaths per 100 person-years.
- MMT group demonstrated 60% lower mortality rate.
- Buprenorphine group demonstrated 40% lower mortality rate.
- Naltrexone group showed no significant difference.

Maternal Drug Addiction

- Approximately every 15 minutes, a baby is born with opioid withdrawal.
- Opioid withdrawal:
  - In the first trimester increases risk of miscarriage.
  - In the third trimester increases risk of premature labor and premature separation of the placenta.

Maternal Drug Addiction

- Risks of Opioid Use During Pregnancy
  - Neonatal Abstinence Syndrome/Neonatal Opioid Withdrawal Syndrome (NAS/NOWS).
  - Intrauterine growth restriction.
  - Preterm labor.
  - Fetal seizures.
  - Fetal death.

Maternal Drug Addiction

- Other Indirect Risks to the Fetus
  - Increased risk of maternal infection.
  - Malnutrition.
  - Poor prenatal care.
  - Associated damage from drug-seeking behavior.

Maternal Drug Addiction

- Methadone is currently the treatment of choice.
- Maternal dose does not determine presence or severity of NAS symptoms.
- MAT Dosing Considerations:
  - In the third trimester –
    - Body mass increases.
    - Extracellular fluid volume increases 50% over normal.
    - Increased rate of metabolism of the medication.
    - Doses frequently need to be increased.

Maternal Drug Addiction

- Nursing During MAT
  - Minimal amount of methadone gets into the milk.
  - Nursing can reduce length of stay of the infant.
  - Nursing can reduce the need for morphine treatment in the infant.

Maternal Drug Addiction

- Benefits of Treatment During Pregnancy
  - Stabilizing fetal levels of opioids, reducing repeated prenatal withdrawal.
  - Linking mothers to treatment for infectious diseases.
  - Improved long-term health outcomes for mother and baby.

Maternal Drug Addiction

- Compared to Untreated Pregnant Women, Infants Demonstrate:
  - Lower risk of NAS/NOWS.
  - Less severe NAS/NOWS.
  - Shorter treatment time.
  - Longer gestational age.
  - Greater weight and head circumference.

Psychosocial Considerations

- Who are these people?
  - People with abysmal childhoods – trying to numb the painful feelings and memories.
  - People who became physically dependent after legitimate medical use and progressed to addiction.
  - People who began using recreationally as adolescents and became dependent and progressed to addiction.

REMEMBER

THIS IS NOT A CAREER CHOICE!!!

Considerations in Treatment

- Common objections to treatment with Methadone:
  - Just trading one drug for another.
  - It's a crutch.
  - It causes: weight gain, soft bones, bad teeth, liver damage, opiate-dependent babies in pregnant women.

Considerations in Treatment

- Many people feel a sense of normalcy or increased energy when they use.
- Psycho-social development stops when patient begins abusing substances.
- Many patients are tired of using and terrified of stopping.
- Many patients live in homes where at least one other significant person continues to use some form of substance.

Considerations in Treatment

- Many opiate addicts have a decreased tolerance to pain (hyperalgesia).
- Many opiate addicts appear to possess a limited concept of time. There are only two times:
  - Now
  - Not now

Considerations in Treatment

- Most addicts are filled with guilt and shame around their use.
- Addicts *cannot* be shamed into stopping.
- The best approach in dealing with addicts is to be positive and respectful while holding them accountable for their behaviors.

Summary

- Opioid dependence/addiction is a significant problem and getting worse.
- Methadone helps support the brain as it re-adjusts to an opiate-free state.
- Methadone is a positive alternative to illicit opioids.
- Methadone is a safer alternative to illicit opioids.

Summary

- Team approach to the treatment will improve outcomes.
- Stopping the use of opiates is only the first step in the recovery process.
- Recovery takes a lifetime.