Opioid Epidemic
Best practices

Dr. David Leszkowitz
Board Certified Addiction Medicine/Family Medicine
No Disclosures

Patient's Current Monthly Medications

Diazepam 5mg QID
Methadone 10mg QID
Oxycodone 10mg QID
Mirtazapine 30mg QHS
Methocarbamol 750mg BID
Baclofen 10mg TID

Never judge, takes all those that comes before you!

AN ESTIMATED 97 MILLION ADULTS IN THE UNITED STATES ARE OVERWEIGHT OR OBESE

WEIGHT MANAGEMENT IN PRIMARY CARE

We must treat the primary cause of the disease
OA, RA

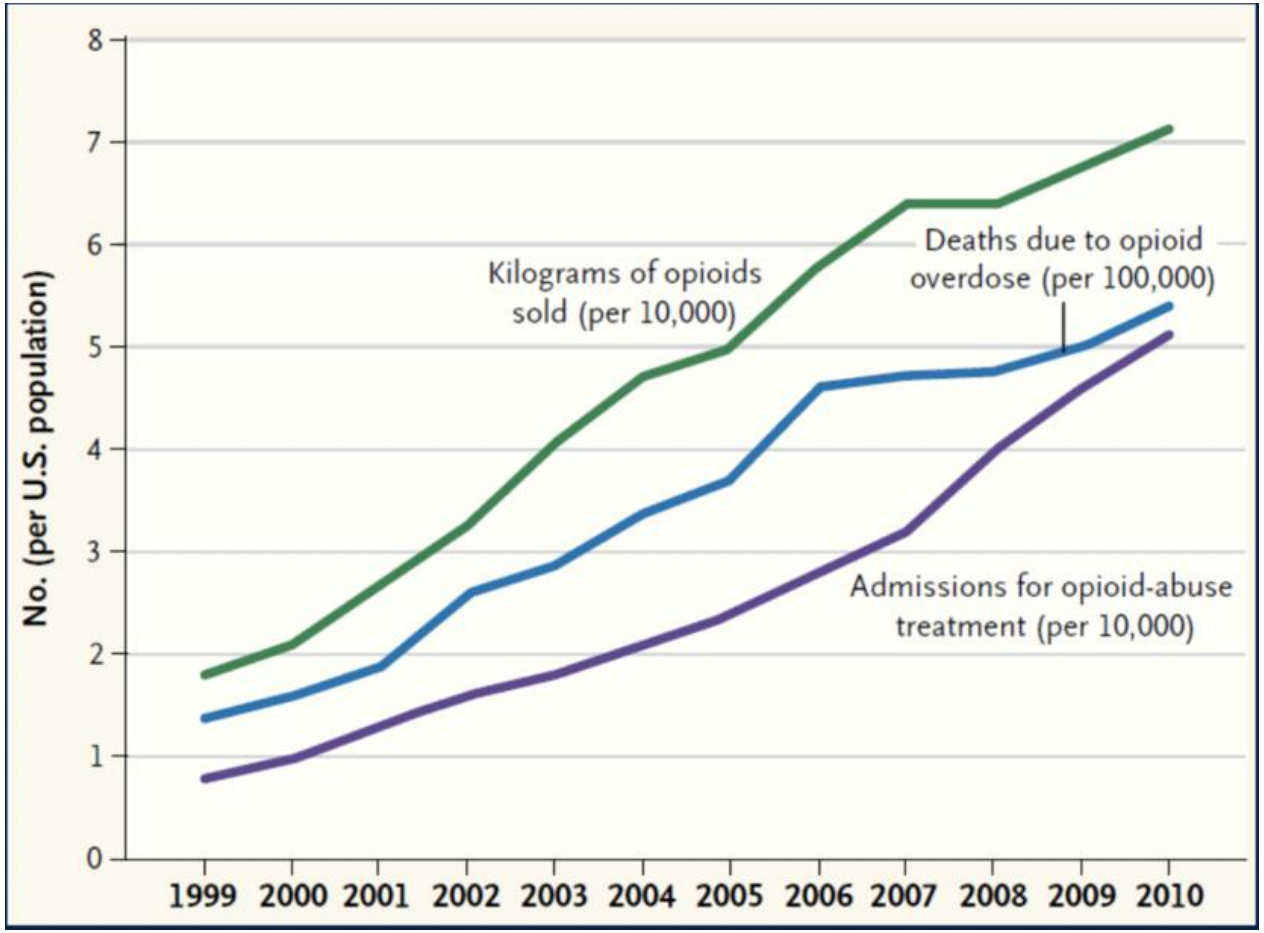
BAYER
PHARMACEUTICAL PRODUCTS.

Send for samples and Literature to

FARBENFABRIKEN OF ELBERFELD CO.

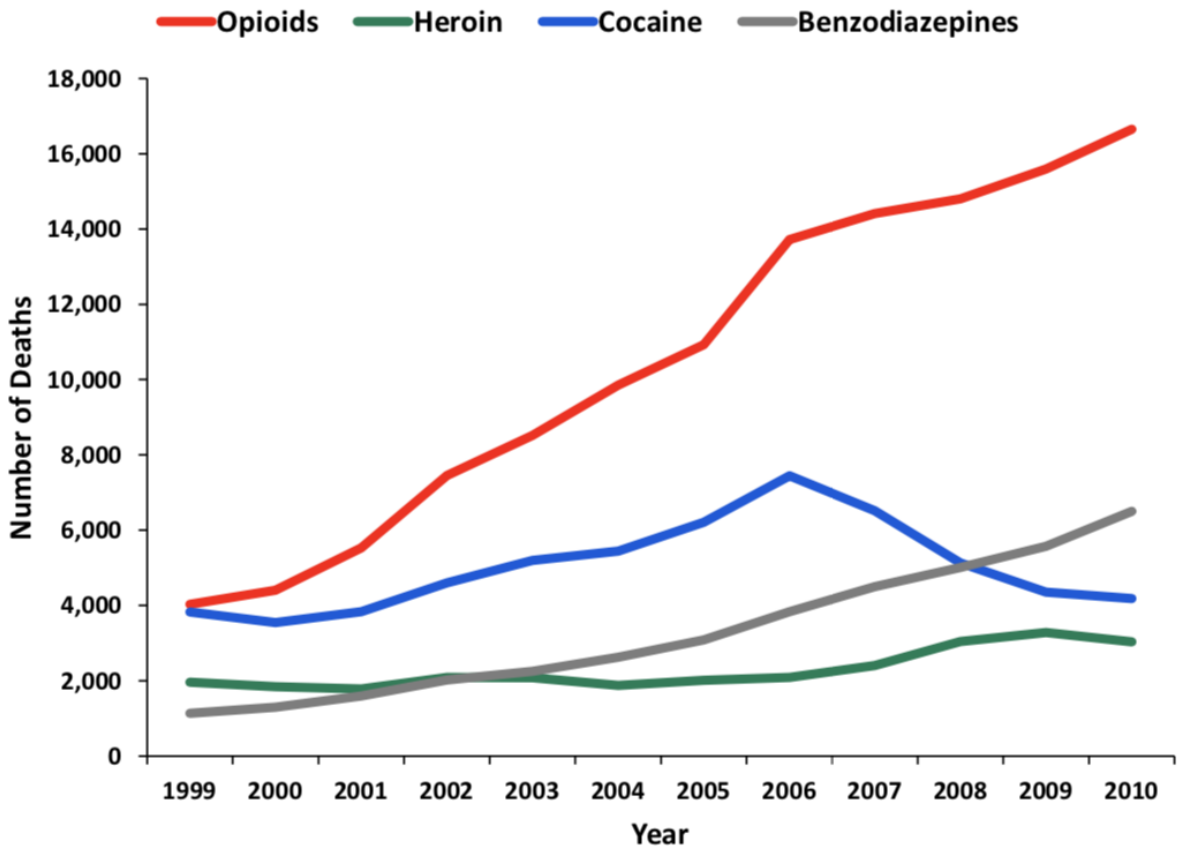
40 STONE STREET, NEW YORK.

Prescription Opioid Trends: 1999-2010

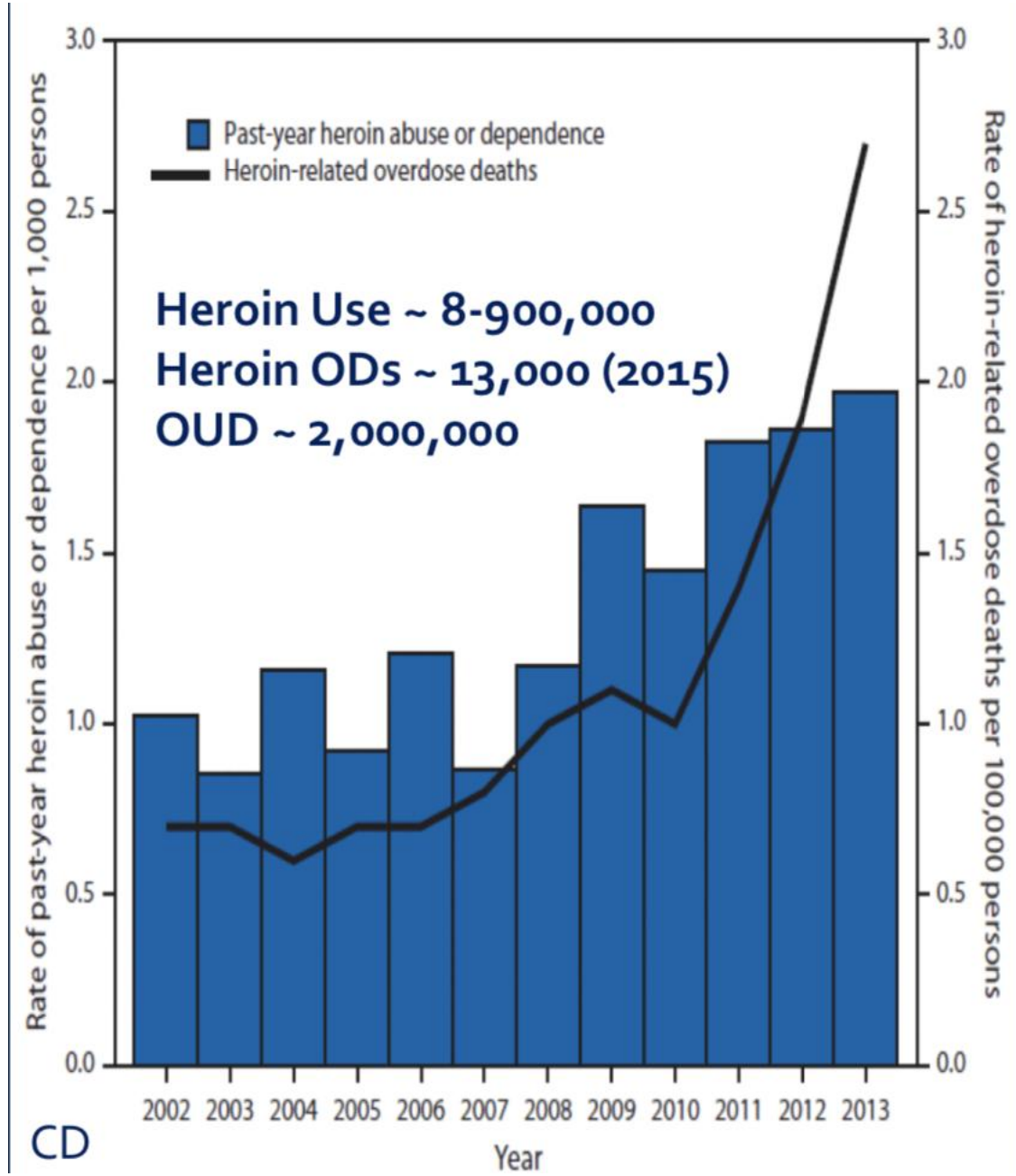


National Vital Statistics System, 1999-2008; Automation of Reports and Consolidated Orders System of the DEA; Treatment Episode Data Set

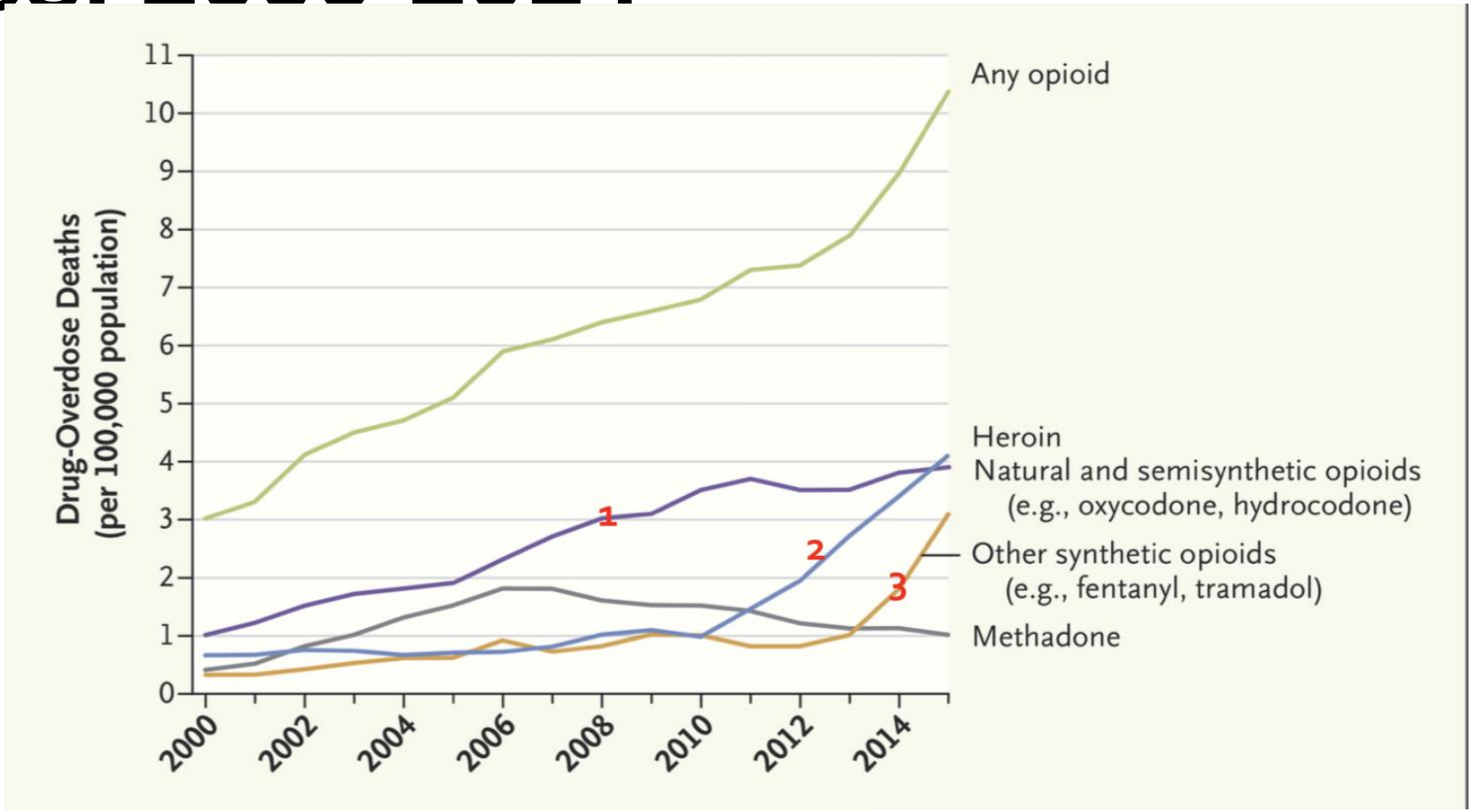
Drug Overdose Deaths by Major Drug Type, United States, 1999-2010



CDC, National Center for Health Statistics, National Vital Statistics System, CDC Wonder. Updated with 2010 mortality data.


Past-year heroin abuse or dependence
Heroin-related overdose deaths
Heroin Use ~ 8-900,000
Heroin ODs ~ 13,000 (2015)
OUD ~ 2,000,000
Rate of past-year heroin abuse or dependence per 1,000 persons
Rate of heroin-related overdose deaths per 100,000 persons
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013
Year
CD

Drug-Overdose Deaths Involving Opioids, by Type of Opioid, United States, 2000-2014



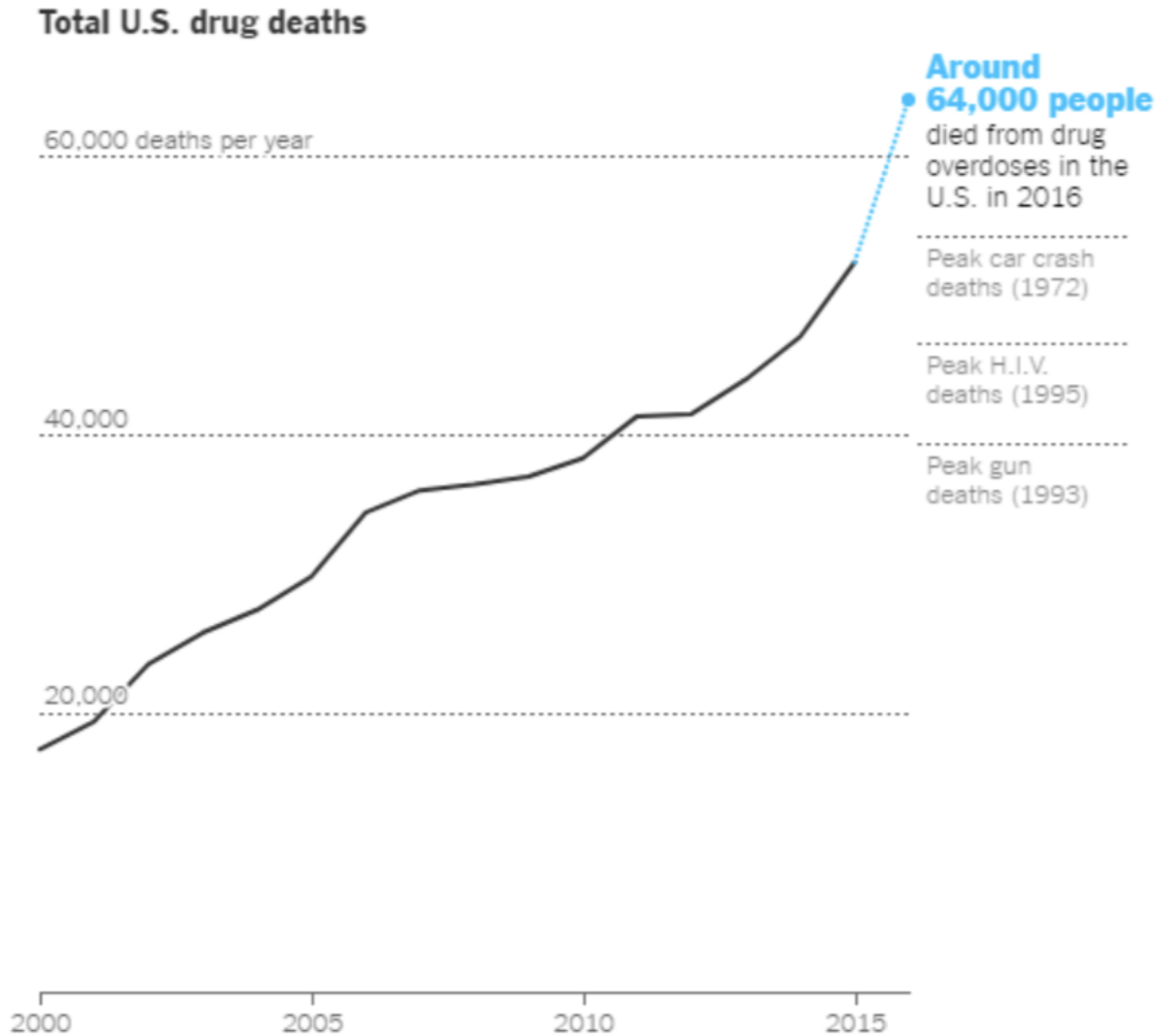
Frank RG, Pollack HA. N Engl J Med 2017;376.605-607

The NEW ENGLAND JOURNAL of MEDICINE

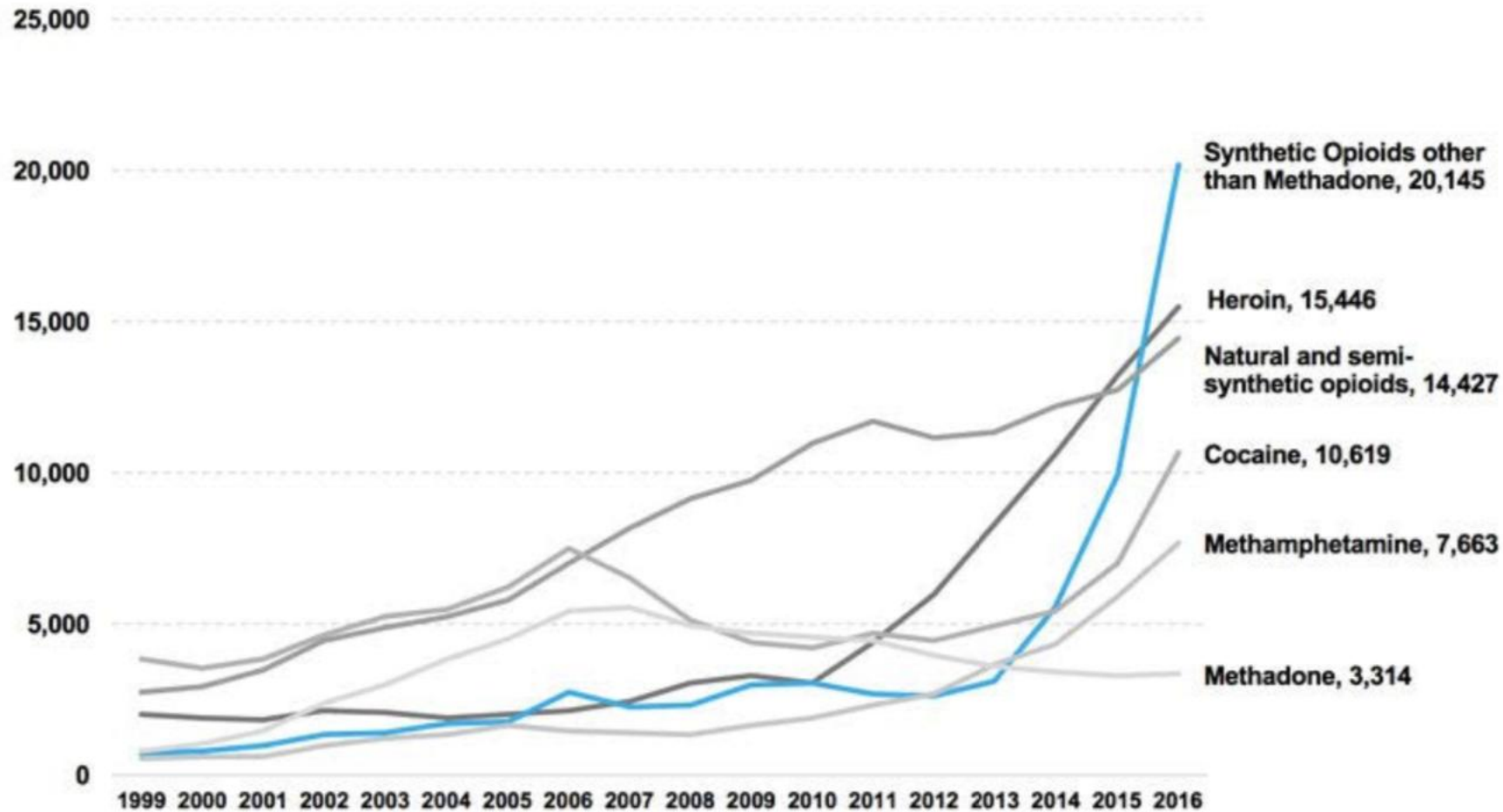
2 Minutes: $3A_4$

Synthetic opioids/fentanyl analogues/metabolites	A. All cases (N=100)	B. Acryl Fentanyl Positives (N=56)	C. Furanyl Fentanyl Positives (N=39)
Fentanyl	99 (99%)	56 (100%)	39 (100%)
Norfentanyl	64 (64%)	39 (70%)	26 (67%)
Acryl fentanyl	56 (56%)		25 (64%)
Despropionylfentanyl	46 (46%)	26 (46%)	32 (82%)
Furanyl Fentanyl	39 (39%)	25 (45%)	
Carfentanil	3 (3%)	2 (4%)	1 (2.6%)
Acetyl Fentanyl	2 (2%)	1 (2%)	1 (2.6%)
Butyryl/isobutyrylfentanyl	1 (1%)	0 (0%)	0 (0%)
Furanyl Norfentanyl	1 (1%)	1 (2%)	1 (2.6%)
U47700	1 (1%)	1 (2%)	1 (2.6%)

100 Accidental OD deaths 2017(3mos): 99% + FENTANYL Only 3 cases + HEROIN


Total U.S. drug deaths
Around 64,000 people
died from drug overdoses in the U.S. in 2016
60,000 deaths per year
40,000
20,000
Peak car crash deaths (1972)
Peak H.I.V. deaths (1995)
Peak gun deaths (1993)
2000
2005
2010
2015

Drugs Involved in U.S. Overdose Deaths, 2000 to 2016



Lethal Dose

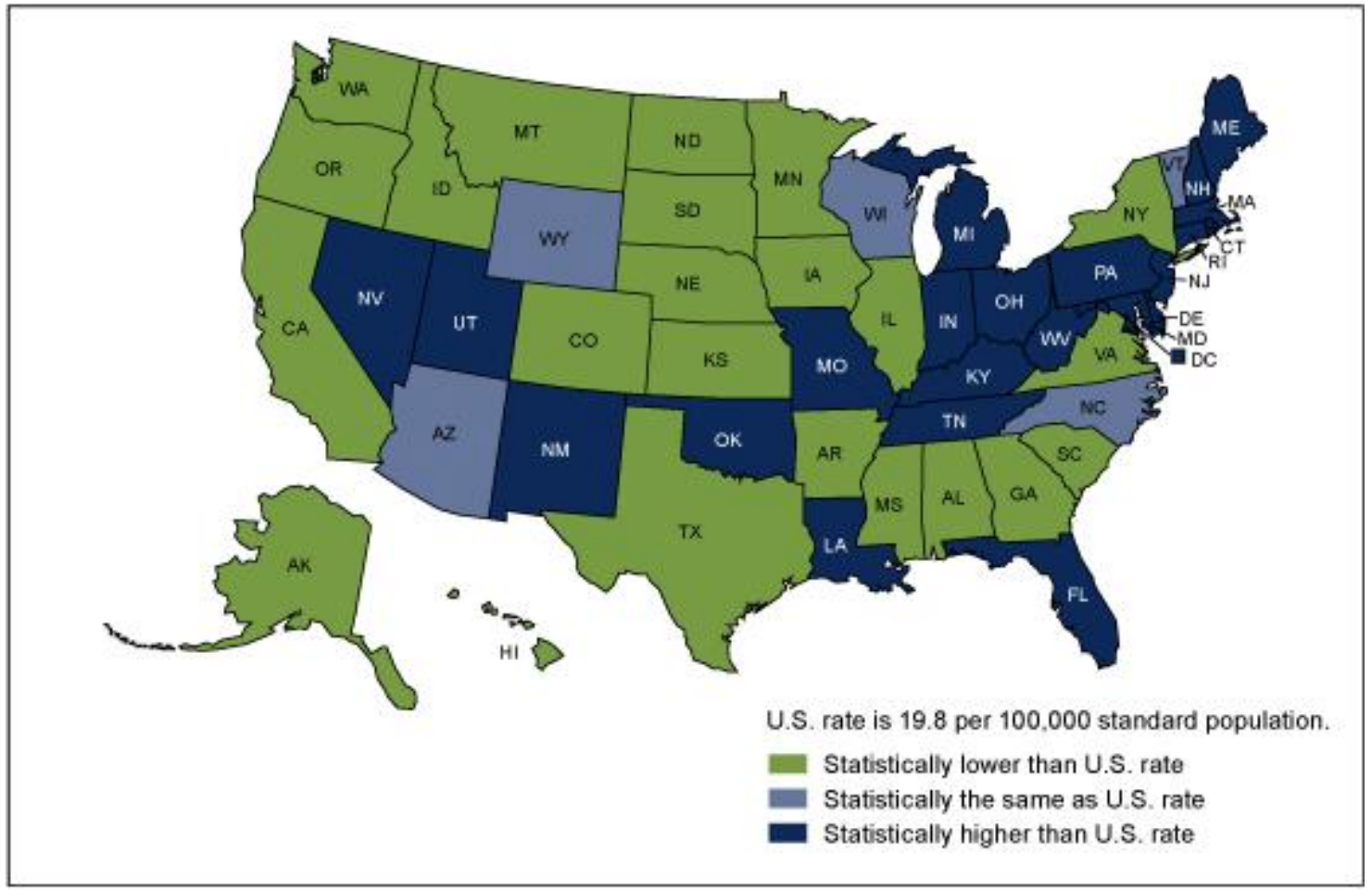
Morphine = 1X
Fentanyl = 100X
Carfentanil = 10,000X

Lethal doses of heroin compared to "synthetic" opioids.
New Hampshire State Police Forensic Lab

Patient Result Summary

Drug	Result	Prescribed
Consistent Positives - Prescribed		
Norbuprenorphine	26.1	YES
7-Aminoclonazepam	>1000	YES
Gabapentin	>10000	YES
Inconsistent Negatives - Prescribed		
Buprenorphine	Negative	YES
Inconsistent Positives - Not Prescribed		
Alprazolam	66.0	NO
Fentanyl	>60	NO
Norfentanyl	>200	NO
Morphine	649.4	NO
Codeine	55.1	NO
THC-COOH	48.6	NO

Drug Overdose Deaths - 2016



Hedegaard et al. Drug Overdose Deaths in the United States, 1999-2016. NCHS Data Brief No. 294. December 2017.

Addiction

- Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.
- Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.

American Society of Addiction Medicine (ASAM). 2011

Opioid Neurobiology and Pharmacology

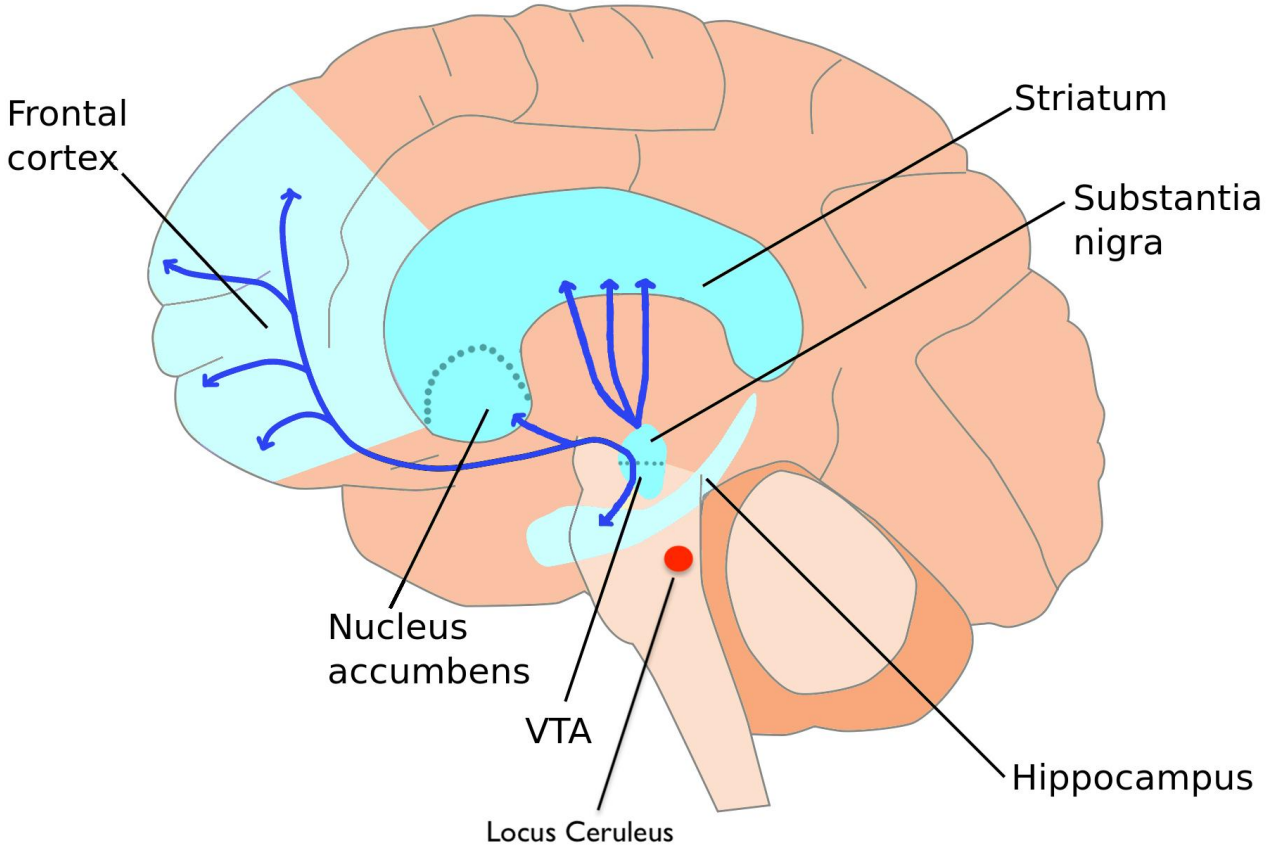
Opiates and Opioids

- **Opiates** are present in opium e.g., morphine, codeine, thebaine
- **Opioids** are manufactures as
  - **Semi-synthetic opioids** derived from an opiate e.g., heroin from morphine
  - **Synthetics opioids** completely synthesized to have function similar to natural opiates e.g., methadone

Opium poppy Plants

Reward/Reinforcement Pathway

- Reward/reinforcement is in part controlled by μ-receptors in the
- Reward pathway:
  - Ventral Tegmental Area (VTA)
  - Nucleus Accumbens with projections to Prefrontal Cortex
  - Dopaminergic system



Heroin and The Reward Pathway

- Heroin (di-acetyl-morphine)
  - Very lipophilic
  - Rapidly crosses the blood brain barrier in the reward pathway
- This is the reason heroin is preferred over morphine as a drug of abuse by injecting opioid users

Opioid Tolerance & Physical Dependence

- Both tolerance and physical dependence are physiological adaptations to chronic opioid exposure
- **Tolerance** 
  - Increased dosage needed to produce specific effect. Develops readily for CNS and respiratory depression
- **Physical Dependence** 
  - Sings and symptoms of withdrawal by abrupt opioid cessation, rapid dose reduction, administration of antagonist e.g., Narcan (Naloxone)

Opioid pharmacology

- Mu-opioid receptor
- G-protein coupled receptor
- Subtypes and > 100 polymorphisms to the mu-opioid receptor gene
- High affinity for beta-endorphin and enkephalins and low affinity for dynorphins
- Characterized by high affinity for morphine
- Acute changes in neuronal excitability via “disinhibition” of presynaptic release of GABA

Opioid Agonist Drug Effects

Acute Use Effects			
Euphoria	Nausea/vomiting	Miosis	Depressed respiration
Sedation	Analgesia	Itching	Decreased consciousness
Large Dose Acute Effects			
Non-responsive	Miosis	If severe anoxia Pupils may dilate	Bradycardia & hypotension
Skin cyanotic	Skeletal muscle flaccid	Pulmonary edema	Slow or absent respiration
Chronic Use Effects			
Physical dependence	Tolerance	Lethargy	Decrease bowel motility

Opioid-Induced Respiratory Depression

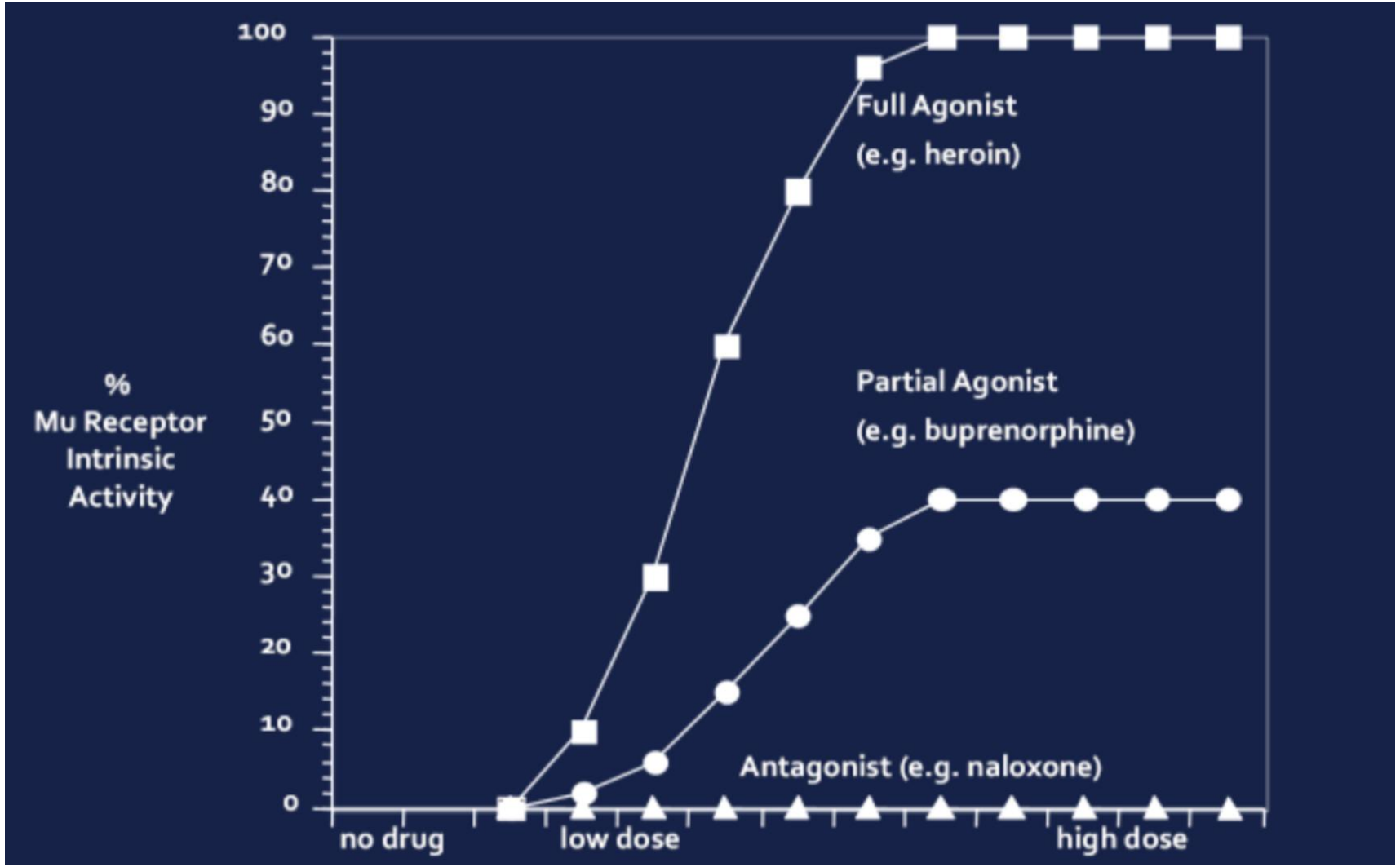
- Depression of the medullary respiratory center
- Decreased tidal volume and minute ventilation
- Right-shifted CO2 response
- Hypercapnea, hypoxia and decreased oxygen saturation
- Immediately life threatening
- Sedation occurs before significant respiratory depression and therefore is a warning sign

Dahan a et al. *Anesthesiology*. 2010.

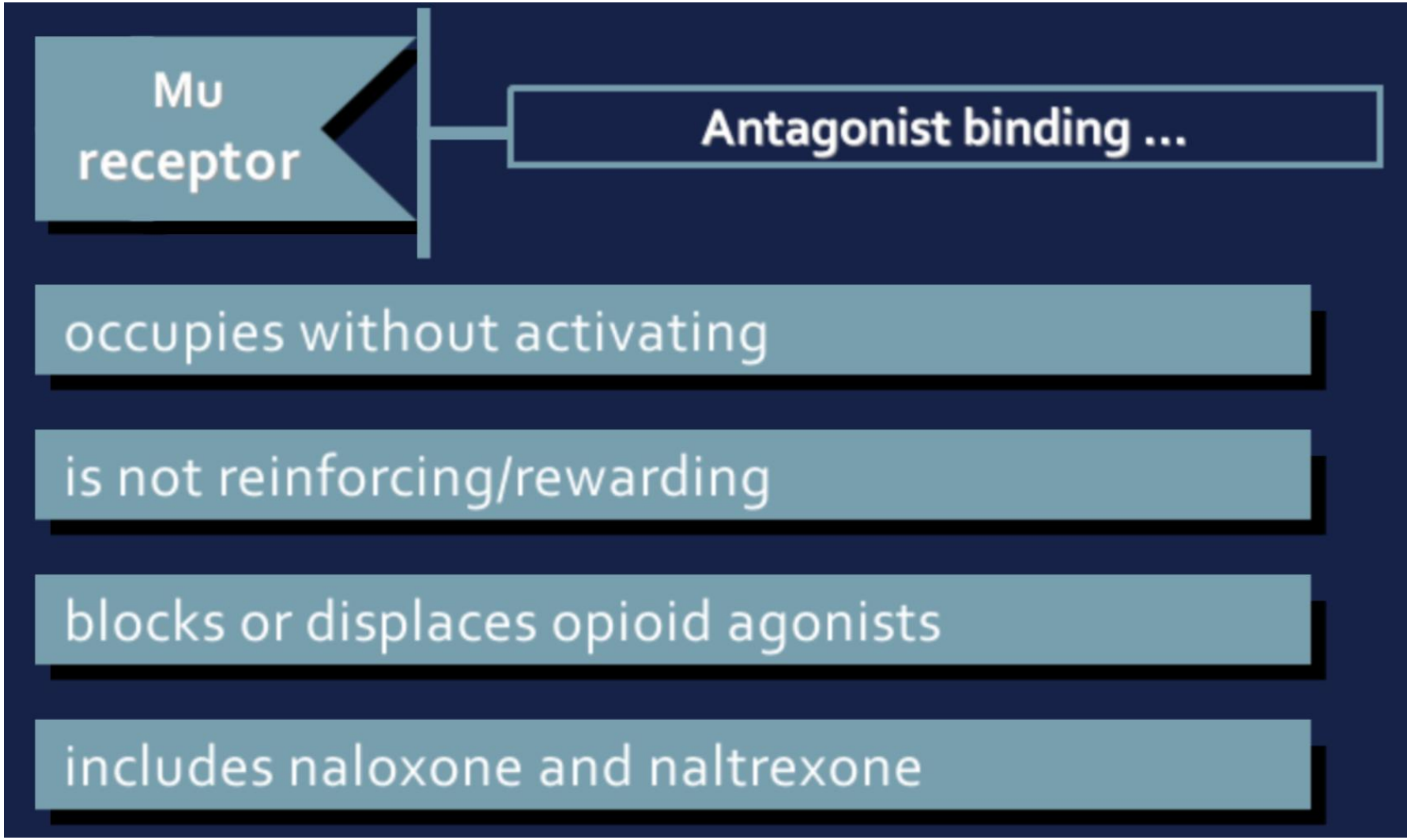
Opioid Characteristics that Increase Euphoria (reward)

- **Route of administration**
  - Faster route has a greater abuse potential
    - Injecting IV > Smoking > Injecting SQ > Oral/Intranasal
- **Drug half life**
  - Shorter half-life a greater abuse potential
    - Heroin > Methadone
- **Lipophilicity faster across blood brain barrier**
  - Higher lipophilicity has a greater abuse potential
    - Heroin > Morphine > Methadone

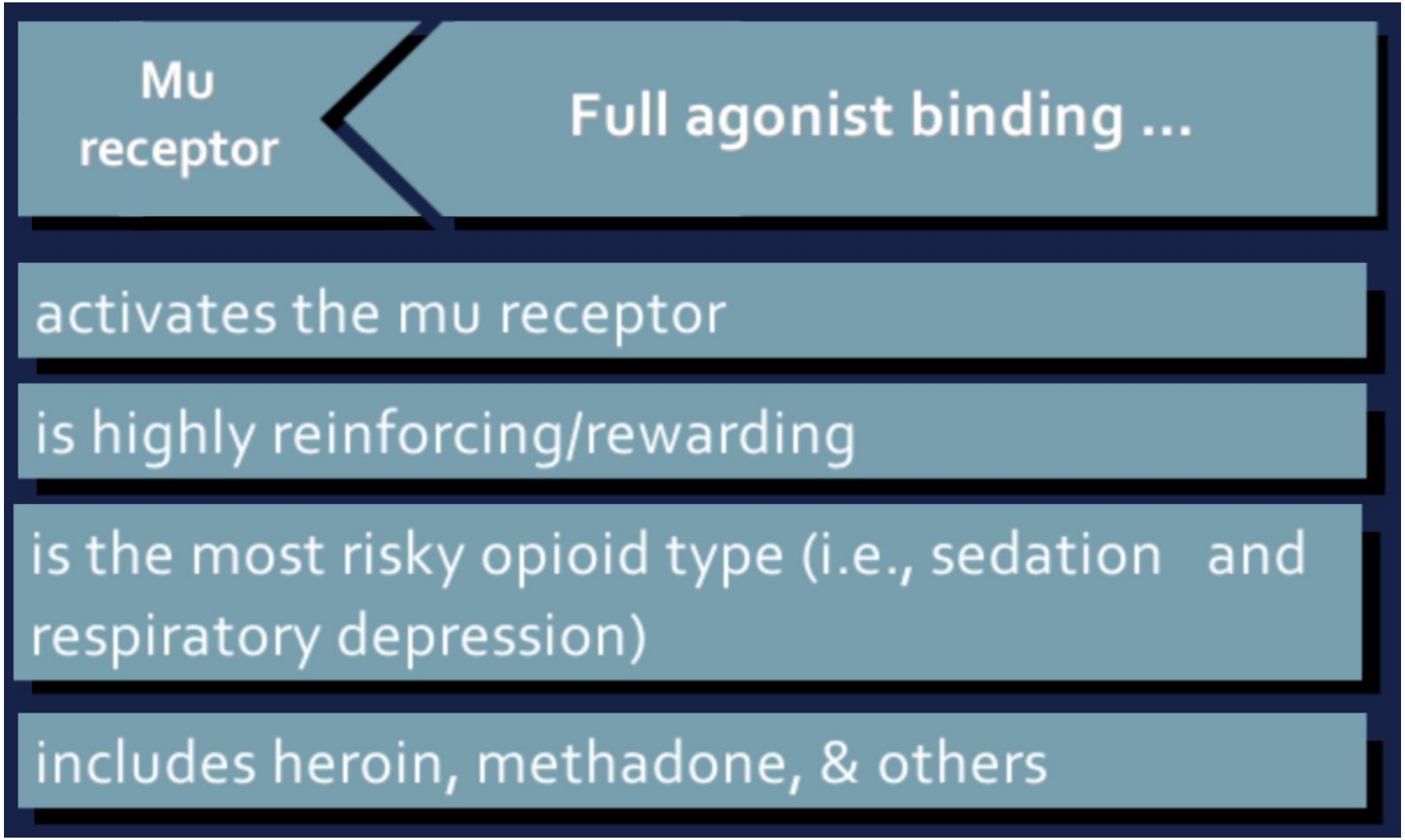
Opioid Agonists and Antagonists



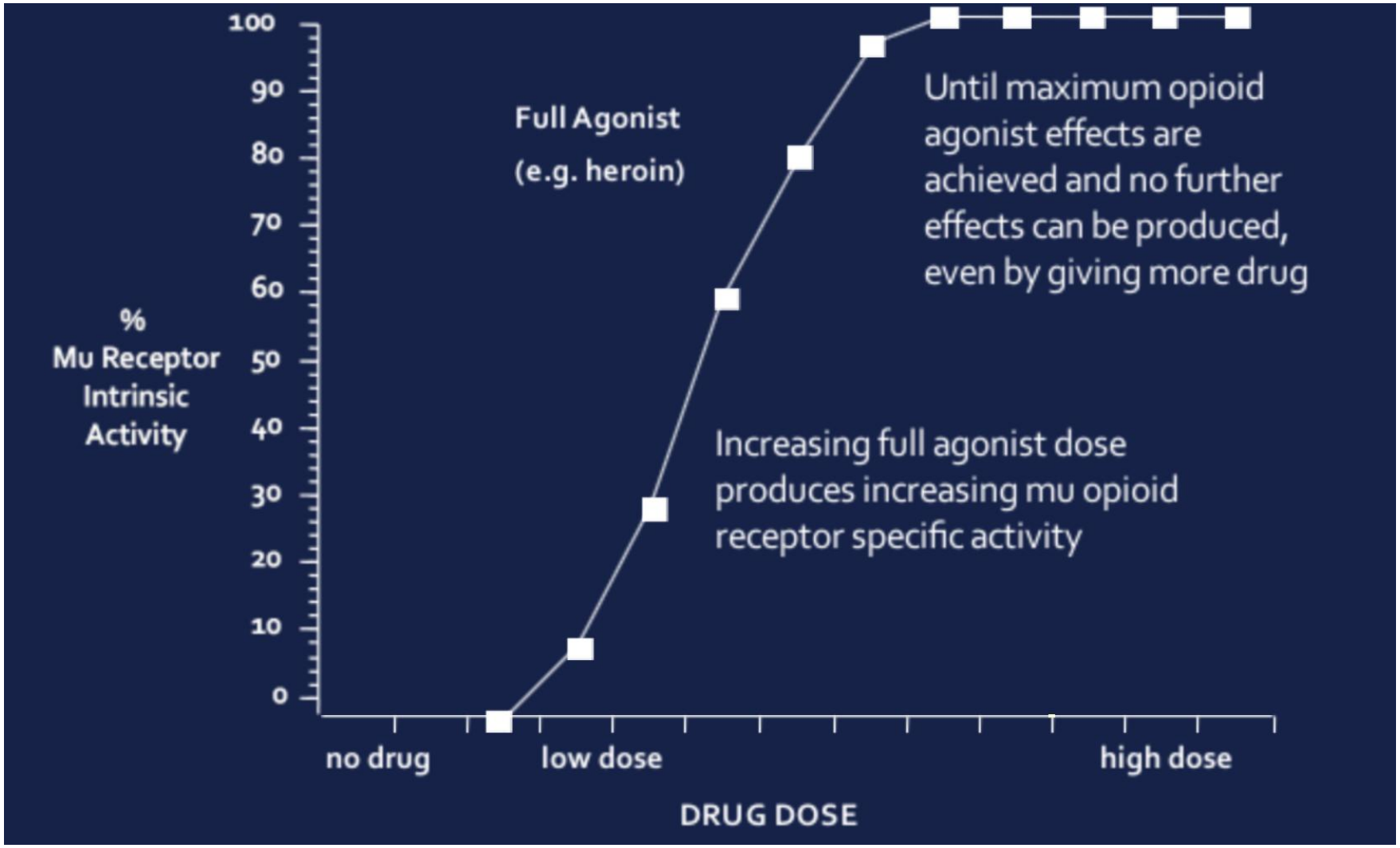
Full Opioid Antagonist



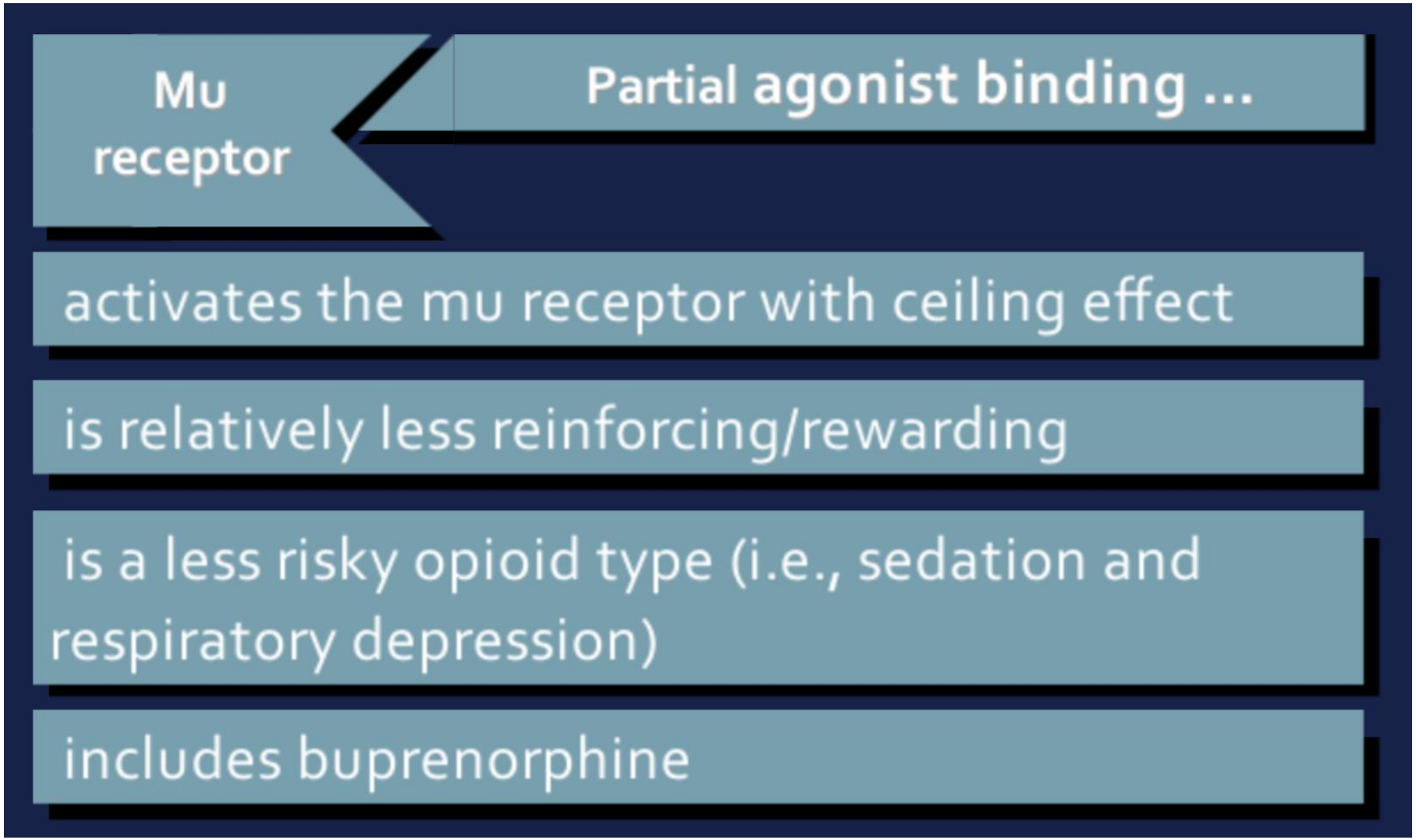
Full Opioid Agonists



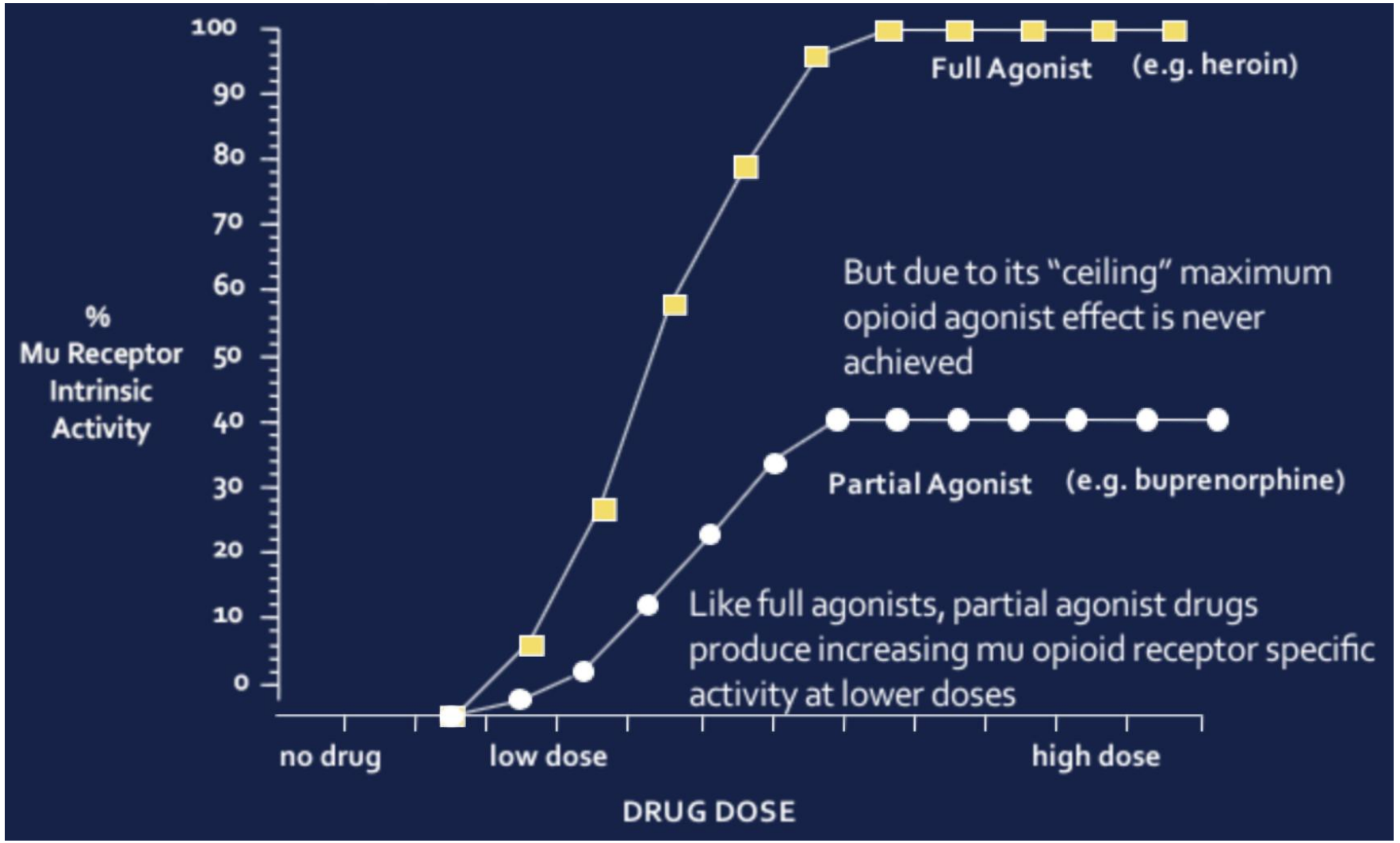
Full Agonist Activity Levels



Partial Opioid Agonists

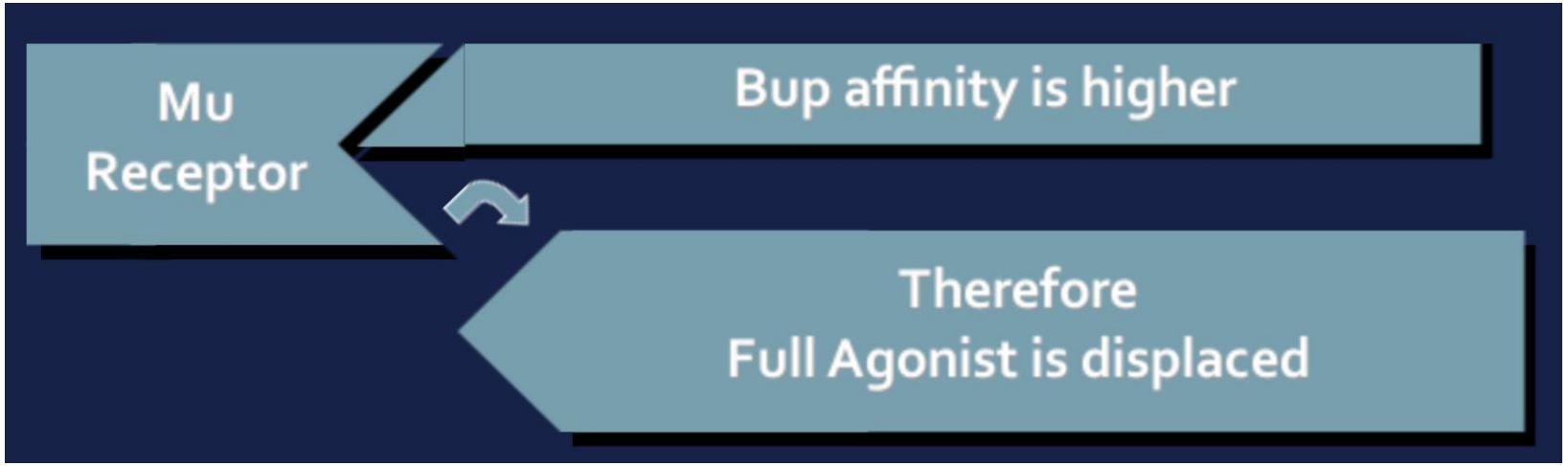


Partial Agonist Activity Levels



Receptor Affinity

- Affinity is the strength with which a drug physically binds to a receptor
  - Buprenorphine's affinity is very strong and it will displace full agonists like heroin and methadone
  - Note: receptor binding strength (strong or weak), is NOT the same as receptor activation (agonist or antagonist)



Receptor Dissociation

- Dissociation is the speed (fast or slow) of disengagement our uncoupling of a drug from the receptor
  - Buprenorphine's dissociation is slow
  - Therefore Buprenorphine stays on the receptor a long time and blocks heroin or methadone from binding

Medication Comparison

	Methadone	Buprenorphine	ER Naltrexone
Pharmacology	Full agonist	Partial agonist	Full antagonist
Dosing	Daily (but duration often longer)	Daily	*q4wks*
Setting	Specialty licensed OTP	Office-based or OTP, requires "X" waiver	Any medical setting, requires injection
Induction	No time restriction; start low, go slow	Mild-mod withdrawal: > 8-12 hrs after last opioid	>7 days after last opioid
Adherence	Intrinsically reinforcing	Intrinsically reinforcing	Long acting

Medication Comparison: Limitations and Benefits

	Methadone	Buprenorphine	ER Naltrexone
Side Effect/Safety	Sedation esp early in treatment, constipation, liver disease. Caution re: concurrent benzos/alcohol overdosing, drug-drug interactions	Lower extremity swelling, urinary hesitancy, constipation. Caution re: concurrent benzos/alcohol. Not recommended for patients with severe hepatic impairment.	Injection site rxns, nausea, malaise. Caution re: precipitated withdrawal if given before opioid free washout period. Risk of hepatoxicity.
Other advantages	Co-morbid pain, high potency, high structure of delivery setting.	Safety compared to methadone, co-morbid pain, dosing flexibility, lower burden of OBOT delivery, simple pharmacy availability	Low diversion, no dependence, verifiable dosing. Lower stigma in some settings compared to agonists.
Craving reduction	+++	++	+

Medication Comparison: Limitations and Benefits (Continued)

	Methadone	Buprenorphine	ER Naltrexone
Contraindications	Hypersensitivity, respiratory depression, severe bronchial asthma or hypercapnia, paralytic ileus	Hypersensitivity	Hypersensitivity reactions to naltrexone, or for injectable previous hypersensitivity reactions to polylactide-co-glycolide, carboxymethylcellulose, or any other constituent of the diluent. Patients currently physically dependent on opioids, including partial agonists. Patients receiving opioid analgesics. Patients in acute opioid withdrawal.
Pregnant women	Treatment with methadone should be initiated as early as possible during pregnancy.	Buprenorphine monoproduct is a reasonable and recommended alternative to methadone.	If a woman becomes pregnant while receiving naltrexone, it is appropriate to discontinue the medication if the patient and doctor agree the risk of relapse is low.
Diversion/misuse	Diversion and misuse are possible	Diversion and misuse are possible	No risk

Calculating Morphine Milligram Equivalents (MME)*			
Opioid	**Conversion Factor** (convert to MMEs)	**Duration (hours)**	**Dose Equivalent Morphine Sulfate (30mg)**
Codeine	0.15	4-6	200 mg
Fentanyl (MCG/hr)	2.4		12.5 mcg/hr**
Hydrocodone	1	3-6	30 mg
Hydromorphone	4	4-5	7.5 mg
Morphine	1	3-6	30 mg
Oxycodone	1.5	4-6	20 mg
Oxymorphone	3	3-6	10 mg
Methadone†			
1-20 mg/d	4		7.5 mg
21-40 mg/d	8		3.75 mg
41-60 mg/d	10		3 mg
≥61 mg/d	12		2.5 mg

Sample Case

Your patient is a 45-year-old man who is taking oxymorphone 10 mg 4 times a day for chronic pain. You have determined he is an appropriate candidate for a long-acting regimen and decide to convert him to extended release oxycodone.

1. Total daily dose of oxymorphone → 10 mg X 4 times /d = 40 mg/d
2. Convert to MMEs (oxymorphone conversion factor = 3) →40 X 3 = 120 MME
3. Determine MMEs of oxycodone (oxycodone conversion factor = 1.5) → 120/1.5 = 80 mg/d
4. Decrease dose by 25% → 25% of 80 = 20 → 80 – 20 = 60
5. Divide by interval (q 12 hours) → 60/2 = 30

The starting dose of extended release oxycodone is 30 mg q 12h.

Setting the Tone

- Empathic vs. unconcerned
- Unbiased vs. judgmental
- Supportive vs. dismissive
- Accepting vs. fault-finding
- Optimistic vs. skeptical

Before getting started…

- Make treatment goals and expectations clear to patient
- Know community referral sources to expediate referral when a patient needs more than your practice can offer
- Check Michigan Automated Prescription System (MAPS) to verify patient medication history
- Check urine drug test to confirm patient substance use history
- Use a Treatment Agreement that includes plan of care (e.g., medication management, monitoring) and informed consent (e.g., adverse effects)

RED FLAGS

- Strong preference for specific drug
- Multiple “allergies”
- Multiple Prescribers/Pharmacies
- Frequent visits to the ED
- “Eating”, injecting or snorting meds
- Refusing drug screen

MISUSE

Assessment Overview

- Establish diagnosis of opioid use disorder and current opioid use history
- Identify comorbid medical and psychiatric conditions; how, when, where they will be addressed
- Screen for and address communicable diseases
- Evaluate level of physical, psychological and social functioning or impairment
- Determine patient’s readiness to participate in treatment

Current Opioid Use History

- Quantity used per day
- Type: heroin, prescription opioids
- Routes: IV, IM, SC, PO, intranasal, inhaled
- Last used, date and time
- Previous attempts to discontinue
- Past treatment experience
  - Nonpharmacologic
  - Pharmacologic with agonist (methadone, buprenorphine) and antagonist (naltrexone) therapies

Co-morbidity?

- **Medical**
  - Past and present medical illness, hospitalizations, surgeries, accidents/injuries
  - Current medications, drug allergies
  - Is the patient taking other medications that may interact with buprenorphine, e.g., opioids, naltrexone, sedative-hypnotics?
- **Psychiatric**
  - History of inpatient and/or outpatient treatment
  - Is the patient psychiatrically stable?
  - Are the psychosocial circumstances of the patient stable and supportive?

Physical Examination

During a standard physical examination, pay attention to:

- Stigmata of injection drug use, e.g., needle tracks, skin and soft tissue infections
- Stigmata of chronic infections, e.g., HIV, hepatitis C
- Neurocognitive function
- Liver disease and dysfunction

Laboratory Evaluation

- Liver function tests
- Hepatitis and HIV serologies
- Pregnancy test for women
- Urine drug testing
  - Naturally occurring opiates (morphine, codeine)
  - Synthetic and semisynthetic opioids (methadone, oxycodone)
  - Other commonly used drugs (cocaine, amphetamines, benzodiazepines)

Are you ready to treat your patient?

- Are there resources available in the office to provide appropriate treatment? Medical or psychiatric care?
- On-call coverage?
- Are there treatment programs available that will accept referral for more intensive levels of service if needed?
- Words of wisdom
  - Don’t start with the most complicated
  - Start with 1, not 30
  - Know your limits
  - Don’t be afraid to consult and refer

Treatment

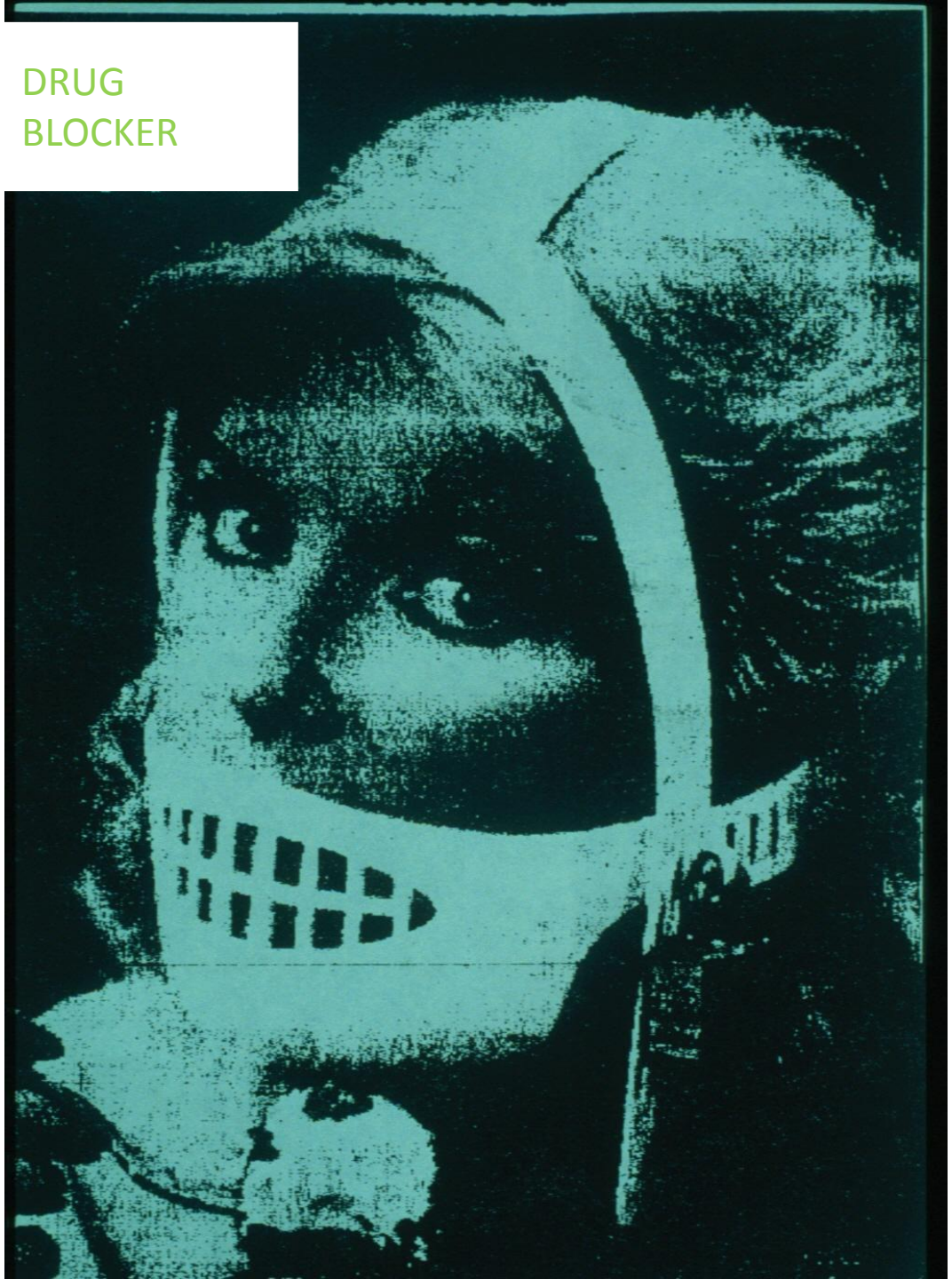
HARM

Street Values of Legal Drugs

Generic Name	Brand Name	Brand Cost/100	Street Value per 100
Tylenol w/ Codeine	Tylenol #3	$56.49	$800.00
Diazepam	Valium 10mg	$298.04	$1,000.00
Hydromorphone	Dilaudid 4 mg	$88.94	$10,000.00
Mehylphenidate	Ritalin	$88.24	$1,500.00
Oxycodone	Oxycontin 80 mg	$1,081.36	$8,000.00

Source: Kentucky All Schedule Prescription Electronic Reporting (KASPER). A Comprehensive Report on Kentucky's Prescription Monitoring Program Prepared by the Cabinet for Health and Family Services Office of the Inspector General, Verson 1~3/29/2006

DRUG
BLOCKER



Why use medications? Because they work….

- 80-89% relapse to drug use without medication assisted treatment (MAT)
- Increased treatment retention
- 80% decreases in drug use and crime
- 70% decrease all cause death rate

NIH Consensus Statement et al. *JAMA.* 1998.

Medication Assisted Treatment (MAT)

- "**All** Treatments Work for **Some** People/Patients."

- No One Treatment Works for **All** People/Patients."

Alan I. Leshner Ph.D

Former Director NIDA

Medication Assisted Treatment (MAT)

- Goals
  - Alleviate signs/symptoms of physical withdrawal
  - Opioid receptor blockade
  - Diminish and alleviate drug craving
  - Normalize and stabilize perturbed brain neurochemistry
- Options
  - Opioid antagonist
    - Naltrexone (full opioid antagonist)
  - Opioid agonist
    - Methadone (full opioid agonist)
    - Buprenorphine (partial opioid agonist)

Naltrexone

- Pure opioid antagonist
- Blocks opioids without agonist effects
  - Serum level of 2ng/ml blocks 25mg IV heroin effects
- No tolerance or physical dependence (withdrawal) develops
- Prevents impulsive drug use
- Protects against overdose, but discontinuation poses higher risk because of lost tolerance

Oral Naltrexone Efficacy

- Oral Naltrexone
  - Duration of action 24-48 hours
  - FDA approved in 1984
- 10 RCTs ~ 700 participants to naltrexone alone or with psychosocial therapy compared with psychosocial therapy alone or placebo
  - No clear benefit in treatment retention or relapse at follow up
- Benefit in highly motivated patients
  - Impaired physicians > 80% abstinence at 18 months

Cochrane Database of Systematic Reviews. 2006.

Oral Naltrexone Safety

- Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses
- Naltrexone does not appear to be hepatotoxic at the recommended doses
- Contraindicated in hepatitis or liver failure

Oral Naltrexone Dosing

- 50mg daily,
- 100mg every 2 days,
- 150 mg every third day
- Adherence has limitation on effectiveness
- Induction requires 5-7 days of abstinence from heroin or short-acting opioid, 7-10 days from buprenorphine or methadone

Sigmon S et al. *American Journal of Drug and Alcohol abuse.* 2012.

Injectable Naltrexone (XR-NTX)

- Multicenter (13 sites in Russia) Funded by Alkermes
- DB RPCT, 24 weeks, n = 250 w/opioid dependence
- X—NTX vs. placebo, all offered biweekly individual drug counseling
- Weeks of confirmed abstinence (90% vs 35%)
- Patients with confirmed abstinence (36% vs 23%)
- Craving (-10 vs +0.7)

Krupitsky E et al. *Lancet.* 2011.

Injectable Naltrexone Dosing

- Monthly XR-NTX 380mg for opioid dependence
- IM injection (w/customized needle) once/month
- FDA approved 2010
- Patients must be opioid free for a minimum of 7-10 days before treatment

Sigmon S et al. *American Journal of Drug and Alcohol abuse.* 2012.

Methadone Maintenance Treatment

- Highly regulated – *Narcotic Addict Treatment Act 1974*
  - Created Opioid Treatment Programs (OTPs)
  - Separate system not involving primary care or pharmacists
- Treatment (methadone dispensing) for opioid use disorder limited to licensed OTPs
- It is illegal for a physician to prescribe methadone for the treatment of opioid use disorders in an office-based practice

Methadone Maintenance in OTP

- Highly structured
  - Daily nursing assessment
  - Weekly individual and/or group counseling
  - Random supervised drug testing
  - Psychiatric services
  - Medical services
  - Methadone dosing
    - Observed daily → ”take homes” based on stability and time in treatment. Max: 27 take homes. Varies by state, county and individual clinic.

Methadone Maintenance Treatment Benefits

- Increase overall survival
- Increases treatment retention
- Decreases illicit opioid use
- Decreases hepatitis and HIV seroconversion
- Decreases criminal activity
- Increases employment
- Improves birth outcomes

Methadone Maintenance Treatment Limitations

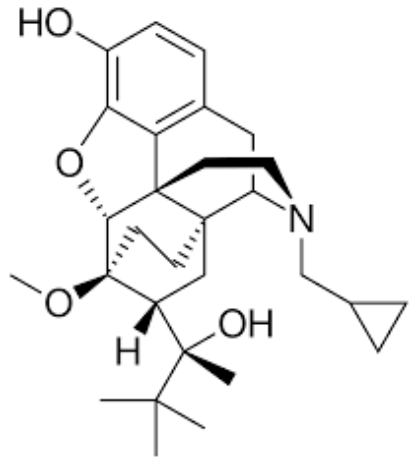
- Limited access
- Inconvenient and highly punitive
- Mixes stable and unstable patients
- Lack of privacy
- No ability to “graduate” from program
- Stigma

Methadone Safety

- Long, variable, unpredictable half-life
  - Serum t ½ 20-120 hours
- QTc prolongation, risk of torsades de pointes
  - Generally does related; > 100mg daily
  - Multifactorial; ↓ K; ↓ Mg, other drugs ↑ QTc
  - CYP450: 3A4, 2D6 interactions
  - QTc > 500 msec > Torsades de Pointes

Wedam E et al. *JAMA Internal Medicine.* 2007.

Buprenorphine



- Partial mu-opioid agonist
- Schedule III (*vs. Methadone: schedule II*)
- **Metabolism**
  - In liver with N-dealkylation by cytochrome P450 3A4 enzyme system into an active metabolite norbuprenorphine
    - Norbuprenorphine undergoes further glucuronidation
- **Elimination**
  - Excreted in feces (70%) and urine (30%)
    - Mean elimination half-life = 37 hours
  - Commercial screening urine drug test for parent compound and metabolite
  - Does NOT show as opiate positive on standard screen

Cytochrome P450 3A4 interactions

- Buprenorphine is metabolized by CYP3A4. Clinically significant drug/drug interactions are uncommon
- Elevated Buprenorphine levels have bene reported with co-administration of atazanavir/ritonavir
- Decreased buprenorphine levels have been reported with co-administration of rifampin

McCace-Katz et al. *The American Journal of Addictions.* 2009.

Buprenorphine Formulations

- Approved for moderate to severe OUDs, can be used OFF LABEL for pain
  - Sublingual forms (tablets and films)
  - **“Combo”** (buprenorphine/naloxone)
  - **”Mono”** (Buprenorphine only) generic tablets only
- Approved for pain and NOT OUDs
  - Parenteral form
  - Transdermal Patch (7-day)

Sublingual Use & Bioavailability

- Sublingual tablets/film strip must be held under tongue for several minutes to dissolve
  - Instruct to:
    - Not talk
    - Keep dissolving liquid under tongue
    - Don’t swallow till entire tablet dissolved
    - Considerable variability between patients in Bup Bioavailability of tablets/film strip
    - Buccal film – able to talk and swallow

Purpose of Naloxone in “Combo”

- Naloxone has limited bioavailability orally or sublingually, but is active parenterally, e.g., injected SQ, IM or IV
- The combo product, if crushed, dissolved and injected the:
  - Naloxone may cause initial withdrawal if the person is physically opioid dependent
    - Decreasing diversion and misuse
  - Naloxone will block, or attenuate, the opioid agonist effect of the buprenorphine
    - Therefore safer if diverted

Comer S et. al. *Addiction.* 2010.

Buprenorphine/Naloxone Bioavailability

- If dissolved sublingually
  - Buprenorphine is active
  - Naloxone is not active
- If swallowed
  - Buprenorphine not active (minimal oral bioavailability)
  - Naloxone not active (no oral bioavailability)
- If injected
  - Buprenorphine active, but
  - Naloxone active x 20 minutes so attenuates the parenteral “rush”

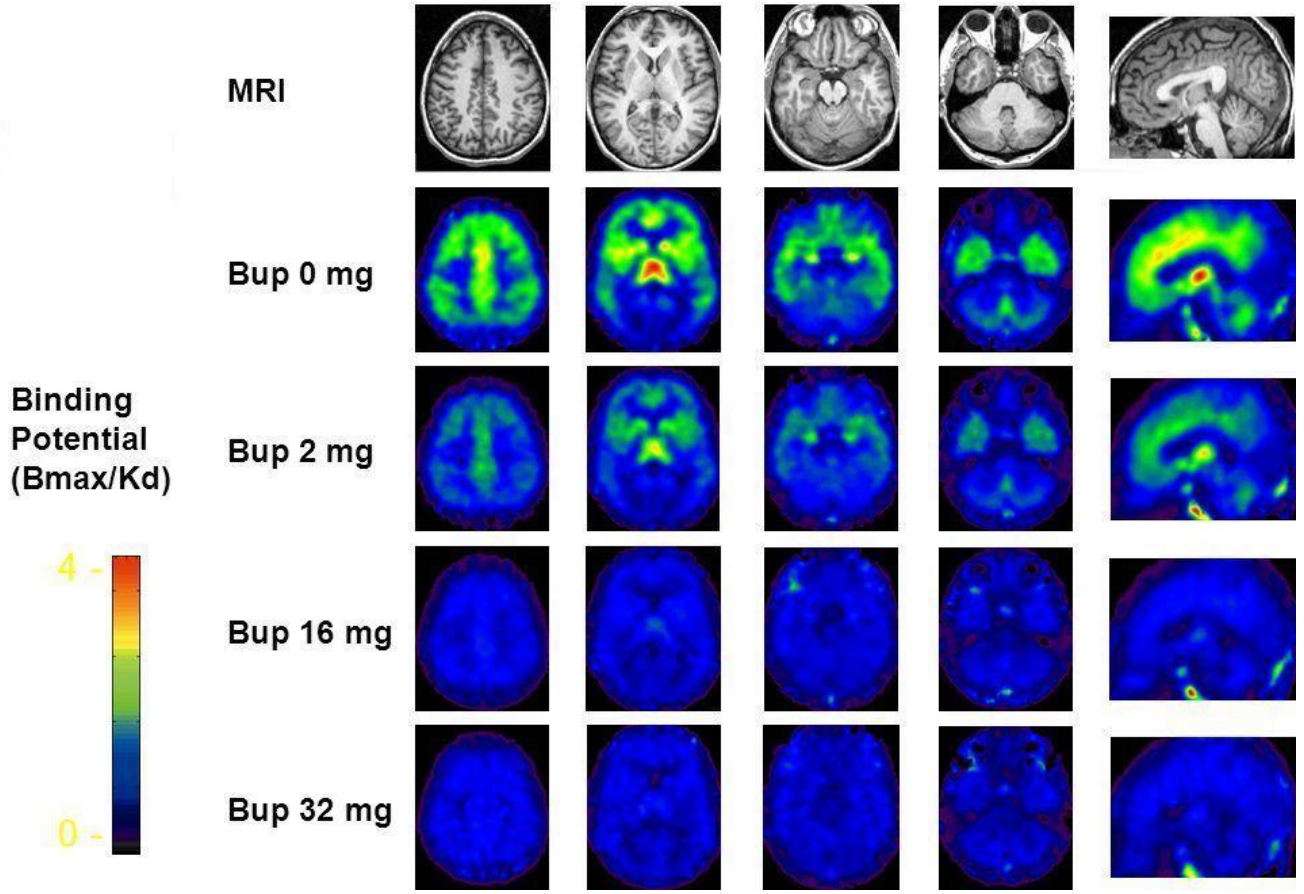
- Not time released so tablets/film strip can be split

  (splitting tablets or film is considered “off-label” use)

How Does Buprenorphine Work?

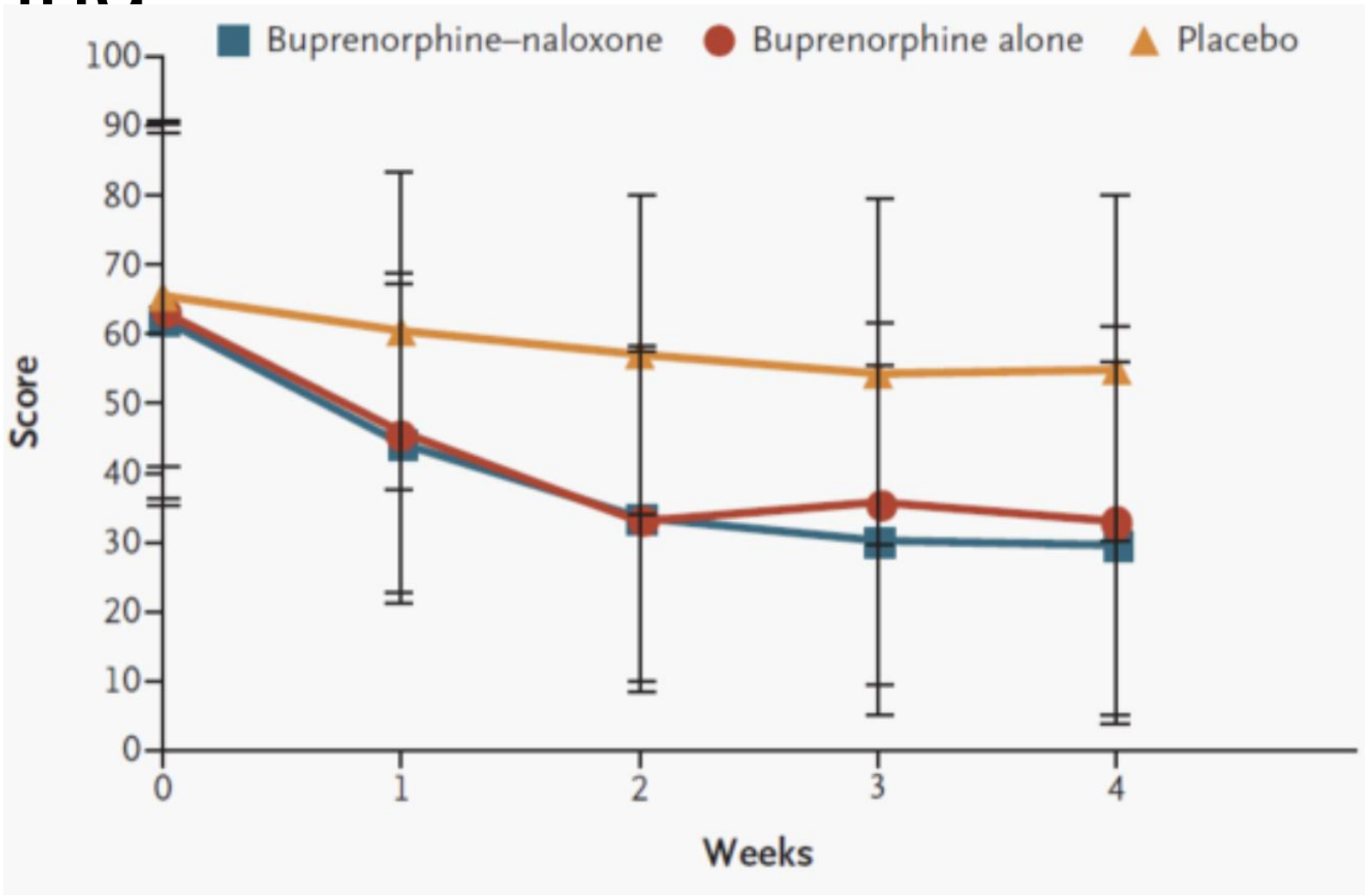
- Buprenorphine may reduce the effects of other opioids taken due to its high affinity for, and slow dissociation from, the mu receptor
- However, buprenorphine is unlikely to block *ALL* effects from an opioid taken after initiation of buprenorphine treatment
- This is because the availability of mu receptors is a dynamic process; while effects may be less, they are not likely to be completely eliminated

Effects of Buprenorphine Dose on mu opioid receptor availability in subjects



Zubieta et al. *Neuropsychopharmacology.* 2000; 23:326-334.

Buprenorphine Decreases Opioid Craving



Fudala P et al. *NEJM*. 2003.

Clinical Uses of Buprenorphine

- Induction
- Stabilization/Maintenance
- Tapering off Maintenance (Discontinuation)
- Buprenorphine for Opioid Withdrawal Management

Unobserved “Home” Inductions

- Numerous studies demonstrate that unobserved “home” inductions are both effective and safe
- Should be performed in properly selected patients
- Providers and patient/significant other should be able to communicate during the induction
- Same protocol as in office-based induction

Alford DP et al. *J Gen Intern Med.* 2007.
Lee JD et al. *J Gen Intern Med.* 2008. Cunningham CO et al. *J Subst Abuse Treat.* 2011. Sohler NL et al. *J Subst Abuse Treat.* 2011.
Lee JD et al. *J Addict Med.* 2014.

Buprenorphine: “The First Prescription”

- The amount of buprenorphine prescribed for induction and stabilization depends on many factors:
- How reliable is the patient?
- Is there a significant other who can secure and dispense the medication: particularly important with younger patients
- How are co-pays managed? Is it reasonable to fill prescriptions every few days?
- Prior authorizations

Bioequivalence of Buprenorphine Formulations

Available Dosage Strengths	
Buprenorphine sublingual tablets, including generic equivalents:	2 mg buprenorphine 8 mg buprenorphine
Buprenorphine and naloxone sublingual tablets, including generic equivalents:	2 mg buprenorphine/ 0.5 mg naloxone 8 mg buprenorphine / 2 mg naloxone
Zubsolv® (Buprenorphine and naloxone sublingual tablets):	1.4 mg buprenorphine / 0.36 mg naloxone 2.9 mg buprenorphine / 0.7 mg naloxone 5.7 mg buprenorphine / 1.4 mg naloxone 8.6 mg buprenorphine / 2.1 mg naloxone 11.4 mg buprenorphine / 2.6 mg naloxone
Suboxone® sublingual film (Buprenorphine and naloxone sublingual film):	2 mg buprenorphine / 0.5 mg naloxone 4 mg buprenorphine / 1 mg naloxone 8 mg buprenorphine / 2 mg naloxone 12 mg buprenorphine / 3 mg naloxone
Bunavail® (Buprenorphine hydrochloride and naloxone hydrochloride buccal film):	2.1 mg buprenorphine / 0.3 mg naloxone 4.2 mg buprenorphine / 0.7 mg naloxone 6.3 mg buprenorphine / 1 mg naloxone

How Long Should Buprenorphine Maintenance Continue?

- No data to provide guidance on how long to treat a patient with buprenorphine/naloxone maintenance
- Studies as long as 16 weeks show high relapse rates with medical withdrawal (Weiss et al., 2011)
- Patients can be retained long term; showed approximately 75% retention at one year with maintenance (Kakko et al., 2003)
- Continue maintenance as long as patient is benefitting from treatment (opioid/other drug use, employment, educational goals pursued, improvement in relationships, improvement in medical/mental illnesses, engaged in psychosocial treatment)

HHS guidance for tapering patients off opioids

- The new HHS guide recommends tapering off opioids at a rate "slow enough to minimize opioid withdrawal symptoms and signs," and moving more slowly the longer patients have been using opioids.

- Common tapers range from reducing opioids dosage between 5% and 20% every four weeks, but HHS recommends reducing dosage by 10% per month or slower for patients who have used opioids for more than a year.

Options to treatment chronic pain

- **Buprenorphine**
  - Belbuca
  - Butrans patches
  - Buprenorphine/Naloxone (Suboxone; Zubsolv, Bunavail)
  - Probuphine (6 months implant)
  - Sublocade (monthly injections)

NSAIDs

NSAIDs approved in the United States

- Ibuprofen (Motrin, Advil)
- Celecoxib (Celebrex)
- Diclofenac (Cambia, Cataflam, Voltaren-XR, Zipsor, Zorvolex)
- Diflunisal (Dolobid)
- Indomethacin (Indocin)
- Ketorolac (Toradol)
- Naproxen (Aleve, Anaprox, Naprelan, Naprosyn)
- Tolmetin (Tolectin)
- Piroxicam (Feldene)
- Oxaprozin (Daypro)

Analgesics

- Acetaminophen (PO, IV)

Cymbalta

Duloxetine

Brand name: Cymbalta

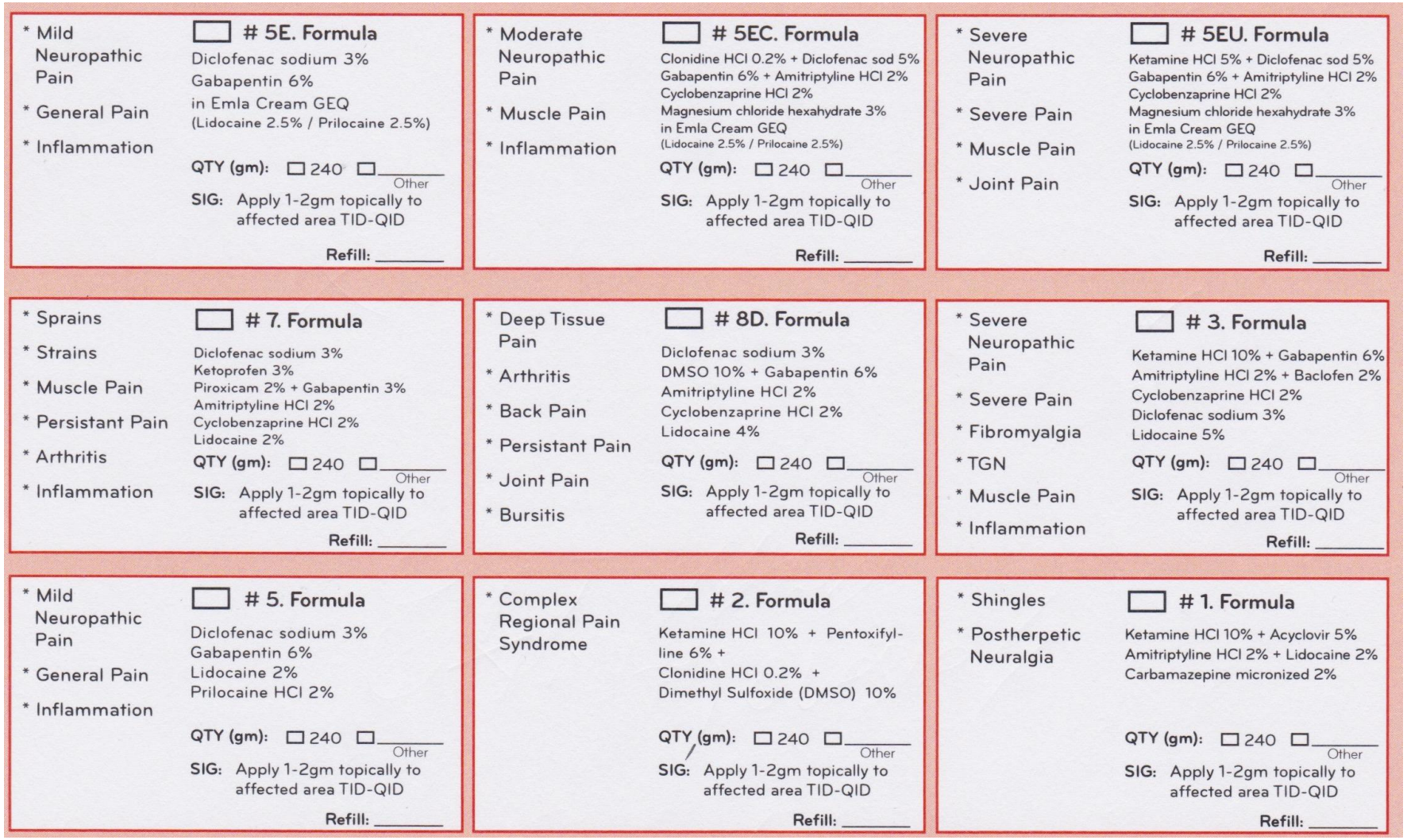
Nerve pain medication and antidepressant

It can treat depression, anxiety, diabetic peripheral neuropathy, fibromyalgia, and chronic muscle or bone pain.

DEPRESSION

SSRIs

Creams and lotions



* Mild Neuropathic Pain
* General Pain
* Inflammation

☐ # 5E. Formula

Diclofenac sodium 3%
Gabapentin 6%
in Emla Cream GEQ
(Lidocaine 2.5% / Prilocaine 2.5%)

QTY (gm): ☐ 240 ☐ _____ Other

SIG: Apply 1-2gm topically to affected area TID-QID

Refill: _____

* Moderate Neuropathic Pain
* Muscle Pain
* Inflammation

☐ # 5EC. Formula

Clonidine HCl 0.2% + Diclofenac sod 5%
Gabapentin 6% + Amitriptyline HCl 2%
Cyclobenzaprine HCl 2%
Magnesium chloride hexahydrate 3%
in Emla Cream GEQ
(Lidocaine 2.5% / Prilocaine 2.5%)

QTY (gm): ☐ 240 ☐ _____ Other

SIG: Apply 1-2gm topically to affected area TID-QID

Refill: _____

* Severe Neuropathic Pain
* Severe Pain
* Muscle Pain
* Joint Pain

☐ # 5EU. Formula

Ketamine HCl 5% + Diclofenac sod 5%
Gabapentin 6% + Amitriptyline HCl 2%
Cyclobenzaprine HCl 2%
Magnesium chloride hexahydrate 3%
in Emla Cream GEQ
(Lidocaine 2.5% / Prilocaine 2.5%)

QTY (gm): ☐ 240 ☐ _____ Other

SIG: Apply 1-2gm topically to affected area TID-QID

Refill: _____

* Sprains
* Strains
* Muscle Pain
* Persistant Pain
* Arthritis
* Inflammation

☐ # 7. Formula

Diclofenac sodium 3%
Ketoprofen 3%
Piroxicam 2% + Gabapentin 3%
Amitriptyline HCl 2%
Cyclobenzaprine HCl 2%
Lidocaine 2%

QTY (gm): ☐ 240 ☐ _____ Other

SIG: Apply 1-2gm topically to affected area TID-QID

Refill: _____

* Deep Tissue Pain
* Arthritis
* Back Pain
* Persistant Pain
* Joint Pain
* Bursitis

☐ # 8D. Formula

Diclofenac sodium 3%
DMSO 10% + Gabapentin 6%
Amitriptyline HCl 2%
Cyclobenzaprine HCl 2%
Lidocaine 4%

QTY (gm): ☐ 240 ☐ _____ Other

SIG: Apply 1-2gm topically to affected area TID-QID

Refill: _____

* Severe Neuropathic Pain
* Severe Pain
* Fibromyalgia
* TGN
* Muscle Pain
* Inflammation

☐ # 3. Formula

Ketamine HCl 10% + Gabapentin 6%
Amitriptyline HCl 2% + Baclofen 2%
Cyclobenzaprine HCl 2%
Diclofenac sodium 3%
Lidocaine 5%

QTY (gm): ☐ 240 ☐ _____ Other

SIG: Apply 1-2gm topically to affected area TID-QID

Refill: _____

* Mild Neuropathic Pain
* General Pain
* Inflammation

☐ # 5. Formula

Diclofenac sodium 3%
Gabapentin 6%
Lidocaine 2%
Prilocaine HCl 2%

QTY (gm): ☐ 240 ☐ _____ Other

SIG: Apply 1-2gm topically to affected area TID-QID

Refill: _____

* Complex Regional Pain Syndrome

☐ # 2. Formula

Ketamine HCl 10% + Pentoxifylline 6% +
Clonidine HCl 0.2% +
Dimethyl Sulfoxide (DMSO) 10%

QTY (gm): ☐ 240 ☐ _____ Other

SIG: Apply 1-2gm topically to affected area TID-QID

Refill: _____

* Shingles
* Postherpetic Neuralgia

☐ # 1. Formula

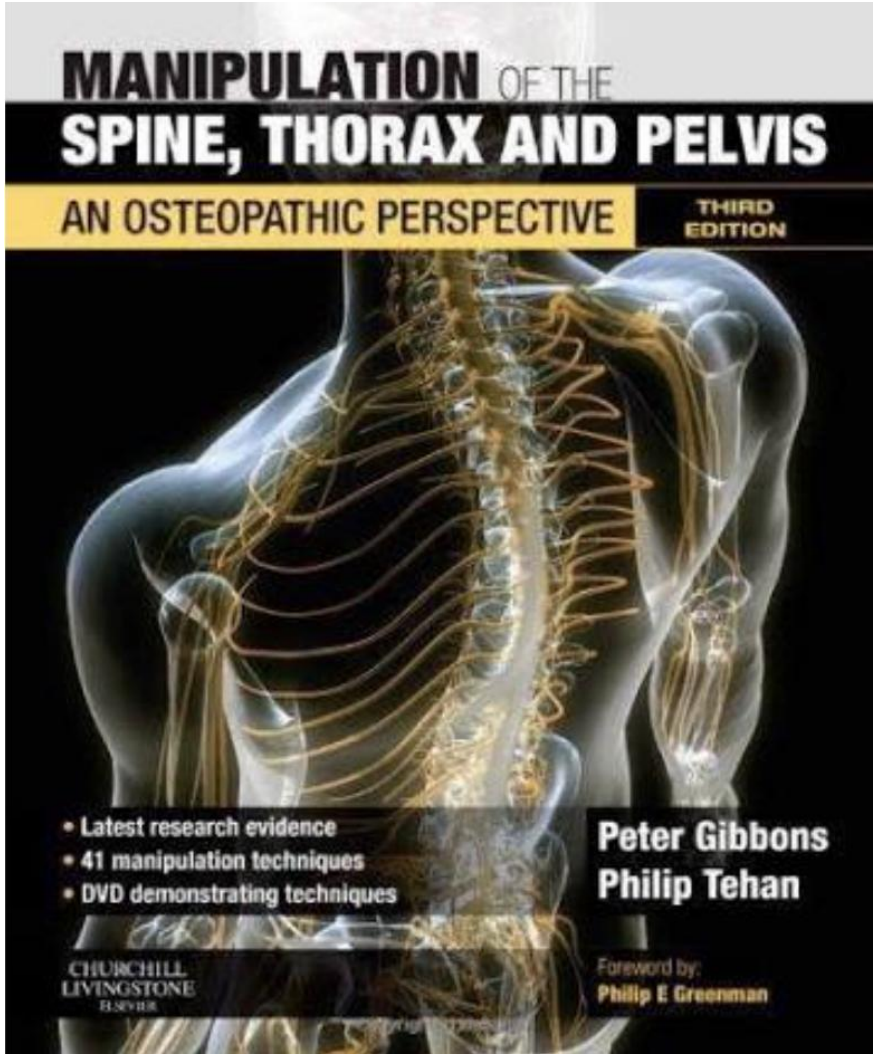
Ketamine HCl 10% + Acyclovir 5%
Amitriptyline HCl 2% + Lidocaine 2%
Carbamazepine micronized 2%

QTY (gm): ☐ 240 ☐ _____ Other

SIG: Apply 1-2gm topically to affected area TID-QID

Refill: _____

Osteopathic Manipulative Medicine



Other acceptable treatments

- Hot/Cold packs
- Physical therapy
- Message therapy
- TENS unit
- Hydrotherapy
- Chiropractic therapy

Alternative Medicine

- CBD oils
- Acupuncture
- Hypnosis

Legislation

Drug Addiction Treatment Act (DATA) of 2000

- Signed by President Clinton in October 2000
- Allows prescription of an opioid to an opioid addicted person for the treatment of addiction, with certain restrictions.
- Prior to this Act, only licensed methadone treatment programs

DATA 2000, obtaining Buprenorphine waiver

- MD/DO must have 8 hours of training in opioid by AMA, AAAP, ASAM, AOA, APA
- PA/NP must complete an additional 16 hours of training
- Providers must submit notification to Secretary of HHS of intent to prescribe and obtain a new DEA number. The regular DEA is retained for other scheduled substances. The new “X” DEA is used only for buprenorphine prescriptions.

DATA 2000, restrictions: Medication allowed

- Drug must be approved by FDA for use in treating addiction
- Medication must be DEA schedule III, IV, or V (*Methadone is schedule II*)
- Buprenorphine and Buprenorphine/naloxone sublingual tablets and film strips approved October 2002, are schedule III, and are the only the only medications fitting these restrictions

DATA 2000, restrictions: number of patients

- 30 patients per provider during the first year of the waiver
- After the first year 100 patients per provider – a new waiver must be obtained
- Patient remains on your census until the last prescription has run out
- Hospitalized patients with a primary diagnosis of other than opioid dependence can be ordered buprenorphine by a non-waivered provider

UDT: Detection Windows in Urine

Drug/Medication	Primary Metabolite	Ave. Detection Time (days)
Opiates (heroin, morphine)	Morphine	2-3
Semisynthetic Opioids (oxycodone, hydrocodone)	Variable Must be tested specifically	2-3
Methadone	EDDP	2-3
Buprenorphine	Nor-buprenorphine	2-3
Cocaine	benzoylecgonine	2-3
Amphetamines		2-3
Benzodiazepine	Varies by medication type	Variable with half life Unreliable immunoassays
Marijuana Occasional Marijuana Chronic	THC	1-3 Up to 30

Prescription Drug Monitoring Program (PDMP)

- State-wide system tracking prescriptions
  - Decreasing or preventing misuse of medications
  - Improving clinical decision making
- Pharmacies report information to state
- Information varies:
  - Schedule II, II and III, II-IV, II-V
  - Some selected non-scheduled medications with abuse potential: e.g. gabapentin, ephedrine
- Data availability
  - Format/eligibility vary by state

RED FLAGS

- Strong preference for specific drug
- Multiple “allergies”
- Multiple Prescribers/Pharmacies
- Frequent visits to the ED
- “Eating”, injecting or snorting meds
- Refusing drug screen

WHIZZINATOR

EVIDENCE OF MISUSE

- Multiple early refill requests
- Refill requests after hours
- Multiple reports of lost/stolen Rx
- Rx from multiple sources w/o your knowledge
- Intoxication (observed or reported)
- Pressuring or threatening behavior
- Injecting or snorting
- Pattern of behavior that suggests recurring misuse
  - Unsanctioned dose escalations
  - Deteriorating function
  - Failure to comply (recs or screens)
- Demands prompt intervention

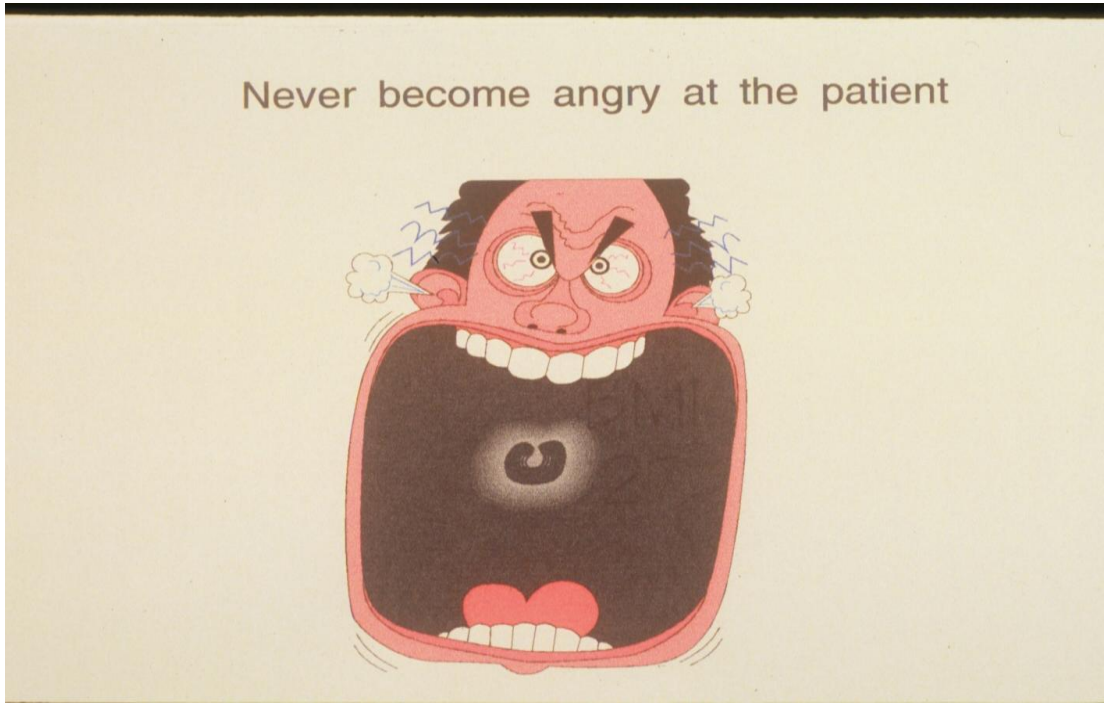
Relapse: Prevention and Management

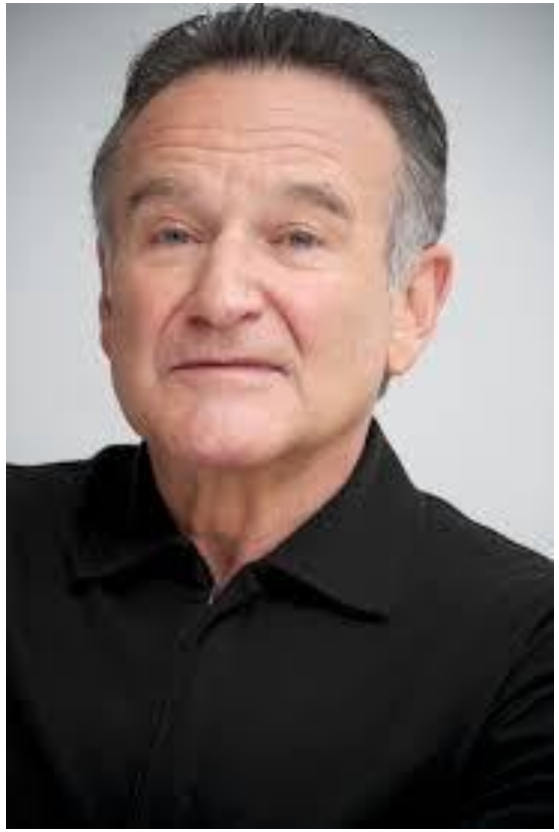
- Relapse is a process in which return to substance use results from maladaptive responses to stressors and stimuli
- Relapse precipitants
  - Negative affect (anger, fatigue, boredom, family conflict)
  - Cravings/cues (people, places and things)
  - Social pressure (social functions)
- Education patients about how to anticipate/avoid/cope with these precipitants
- After initial use (a lapse), patients may experience guilt, shame resulting in return to heavy use
- Recovery is a learning process, lapses provide valuable lessons
- Return to substance use requires prompt evaluation and possible referral to additional or higher level of care

Doyle TJ, Friedmann PD, Zywiak WH. Addressing Unhealthy Alcohol Use in Primary Care, 2013.

Never judge, takes all those that comes before you!

- Never become angry at the patient
- Offer easier goals if necessary
- Praise even with moderate improvement
- Manage the patient’s entire care
- Encourage support groups and material
- Encourage the use of different tools





Robin William 1951 - 2014

Seymour Hoffman 1967 - 2014

Questions?